SOCIEDAD ARGENTINA DE COLOPROCTOLOGÍA

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OFFICIAL REPORT

UPDATE ON COLON CANCER TREATMENT

AUTHOR

Hugo A. Amarillo, MAAC, MASCP, FACS
Surgery and Coloproctology Sector, Sanatorio Modelo, San Miguel de Tucumán, Tucumán, Argentina

CONTRIBUTORS

Romina Bianchi, MAAC, MASCP, FACS
Coloproctology Sector, Hospital Juan A. Fernández and Coloproctology Sector, Favaloro Foundation, Ciudad Autónoma de Buenos Aires, Argentina

Alejandro Moreira Grecco, MAAC, MSACP
Gastrointestinal Surgery Service, Hospital de Cínicas, Ciudad Autónoma de Buenos Aires, Argentinal

Pablo Jorge, MAAC, MASCP
Surgery and Coloproctology Service, Hospital Pablo Soria, San Salvador, Jujuy, Argentina

Lucía Daniela Lamas, MAAC
Surgery and Coloproctology Service, Hospital Pablo Soria, San Salvador, Jujuy, Argentina

Vicente Borquez, MAAC, MASCP
Coloproctology Service, Hospital San Bernardo, Salta, Argentina

Walter Martín García, MAAC, MASCP
Coloproctology Service, Nuevo Hospital del Milagro, Salta, Argentina

Alejandro Sanchez Ruiz, MAAC, MASCP
Coloproctology Service, Hospital San Bernardo, Salta, Argentina

Pablo A. Tacchi, MAAC, MASCP
Coloproctology Service, Hospital San Bernardo, Salta, Argentina

María S. Bruzzi, MAAC, MASCP
Coloproctology Service, Hospital Centro de Salud, San Miguel de Tucumán, Tucumán, Argentina

Paula Casares, MAAC
Surgery and Coloproctology Service, Sanatorio Modelo, San Miguel de Tucumán, Tucumán, Argentina

Audel Closas, MAAC
Coloproctology Service, Hospital Centro de Salud, San Miguel de Tucumán, Tucumán, Argentina

Marcelo Viola Malet
Department of Surgery, Médica Uruguaya (MUCAM), Montevideo, Uruguay

Marcelo Laurini Zanola
Department of Surgery, Médica Uruguaya (MUCAM), Montevideo, Uruguay

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FOREWORD

Being designated as an official speaker at the Argentine Congress of Coloproctology marks a turning point in the academic career of a surgeon dedicated to colorectal surgery in a professional manner. It not only represents the academic culmination within the scientific activity of a National Congress that brings together the most important experts in the specialty, but also a challenge that allows the expression of his past with regard to the pre- and postgraduate training process. This challenge is particularly greater if it is a surgeon and coloproctologist whose care activity is carried out only in one province of the Argentine interior. This story will reflect the individuality of the speaker and all the aspects related to his professional career from recently graduated doctor to specialist surgeon.

The treatment of colon cancer together with the treatment of rectal cancer, are probably the two emblematic topics of the specialty, due to the constant changes and the current complexity of this pathology that affects an increasingly younger population. The frequency with which colon cancer occurs in daily practice, the variability of its clinical presentation, the multiplicity of professionals involved in the therapeutic approach and the complex situation of the different realities in our country, motivate the interest of scientific societies in generating therapeutic recommendation guidelines on this relevant topic of the specialty.

It is difficult to briefly address the topic given the encyclopedic nature of the available bibliography. The extent and diversity of published studies, reviews and guidelines make it necessary to decide on the format of the approach, as well as the specific topics to be addressed.

The development of this report will cover the current global and national epidemiology and the basic aspects of diagnosis and histological classification that allow defining the concepts necessary for treatment. It is essential to present the latest update on colon cancer staging, since it is the pillar for establishing treatment.

The therapeutic approach will be carried out in stages, covering all the techniques described, although highlighting the topic of this report regarding the update. Among the various topics covered, endoscopic techniques for the treatment of early colon cancer, the definition and management of invasive cancer and the risk factors that mark the different prognosis and treatment of advanced locoregional cancer stand out. Regarding metastatic cancer, its initial general approach will be discussed, without going into depth on the management of the metastases of each individual organ.

Controversial topics are updated, such as total excision of the mesocolon, the type of lymph node dissection and the indication for extended or segmental colectomy.

The current therapeutic recommendations for complicated colon cancer and the postoperative care that favorably affects postoperative outcome are described. The report concludes with a brief mention of the surgical technique..

Finally, the results of a national and regional survey of specialists are detailed and the experience obtained in health centres in 3 provinces in northwestern Argentina is presented.

However, let us remember that this report will try to be brief and directed to surgeons, especially those with an interest in colorectal diseases.

Hugo A. Amarillo, MD, PhD, MAAC, MASCP, FACS
San Miguel de Tucumán, Tucumán, Argentina

ACKNOWLEDGEMENTS

First of all, I would like to thank the authorities of the SACP who, on the occasion of the Argentine Congress of Coloproctology held in Mar del Plata in 2023, invited me to participate as a candidate for official speaker at the 47th Argentine Congress of Coloproctology. Having been subsequently chosen by opposition has the merit of having achieved this long-awaited goal for any academic surgeon. Being able to do so in the same year in which I turn 50 years old and 27 as a doctor, together with the 25th anniversary of the Official Report on Hemorrhoidal Pathology by another Tucumán surgeon, in this case my father, honors me personally, as well as the entire Tucuman surgical community and the history of surgery and coloproctology in Tucumán.

This choice as a speaker creates an enormous responsibility for me, not only because of the magnitude of the topic to be discussed, but also because it is in the hands of a surgeon from the smallest province in our country. For this reason, I thank those who participated in my selection process and also those who participated in my training process since my graduation as a doctor. I thank my high school teachers who obviously identified my taste for chemistry and biology in a school with a commercial baccalaureate, and warned that something particularly unusual was happening, that I was training in accounting sciences to end up choosing a career like medicine.

My thanks to my professors from the basic cycle of the Medicine Degree at the National University of Tucumán, whose names, classes and exams I remember as if it were today. To the professors of the clinical and surgical cycle of the degree and to those who allowed me to carry out my final internship entirely in an operating room. My thanks to my professors from the basic cycle of the Medicine course at the National University of Tucumán, whose names, classes and exams I remember as if it were today. To the professors from the clinical and surgical cycle of the course and to those who allowed me to carry out my final internship entirely in an operating room.

I would like to express my gratitude to Drs. Martín Mihura, Claudio Irribarren†, Eduardo Porto, Roberto Cerutti and so many others that I could not name, both from the Surgery Service and from the entire British Hospital of Buenos Aires. I would also like to thank all my senior residents, especially my colleagues Drs. Daniel Pirchi and Rafael Maurette, from whom I learned daily during our residency year. I would also like to thank all the doctors of the Coloproctology Service of the British Hospital of Buenos Aires, who during my fellowship in the specialty under the direction of Dr. Eduardo Donnelly and later of Dr. Mario Salomón, directed me and progressively trained me in all the care, academic and human practice of the specialty. My training in laparoscopic colorectal surgery and colonoscopy, practices that at that time caused constant debate in the meetings of this society, was fundamental for my professional life.

During those years I was able to finish and defend my doctoral thesis at the University of Buenos Aires, for which I would like to thank my thesis director, Prof. Dr. Pedro Ferraina, who generously advised and accompanied me throughout the years of my career. I would also like to extend my gratitude to Dr. Martín Mihura, who helped me define the research topic of my thesis, which was carried out entirely within the British Hospital of Buenos Aires.

My initial training in the specialty was carried out abroad, for which I would like to thank other admired professionals in the specialty with whom I shared rotations and specialized conferences, especially Prof. Dr. Alfredo Reis Neto, from Campinas, Brazil and Dr. Steven Wexner, from the Cleveland Clinic in Weston, Florida, USA. After this training, upon returning to Tucumán, my career in university teaching began. For this reason, I would like to thank my friends and colleagues from the unfortunately discontinued III Chair of Pathology and Surgical Clinic of the Faculty of Medicine of the National University of Tucumán, faculty where I developed my entire teaching career for more than 23 years, in addition to having completed the course between 1992 and 1998. I would also like to deeply thank my colleagues, friends and members of the Tucumán Association of Coloproctology, a society for which I have fought for a long time, initially as a partner and then as a member of the board of directors, with the aim of promoting its growth and extension towards the professional community, generating at the same time an academic link between all coloproctologists in northwest Argentina. My healthcare career links me directly to the Sanatorio Modelo in the city of Tucumán, an institution where I have been since my early years until today. I would like to thank my colleagues on the Executive Committee and the Board of Directors, whose help makes the task that involves long hours of daily healthcare management easier for me. I would also like to thank all the doctors, surgeons and residents, as well as the nursing and administrative staff who link me to this institution every day.

My gratitude would not be complete if I did not dedicate a few words to the Journal Committee, authorities and members of the Revista Argentina de Coloproctología, an organization to which I have been linked for almost 10 years and which constitutes one of the main objectives of my academic life and a source of pride for my professional life. To them, thank you for being the best possible group to accompany me in this hard and difficult task.

As Leiro says, a story consists of a narrative genre composed of literary works that tell stories in a brief and compact manner. In my understanding and following certain principles, one is a slave to one's words and master of one's silence, so one should only interrupt it if what one is going to say is more beautiful. Likewise, it is said that there are three filters for a story. The first is truth, so one should try to say only something true. The second is kindness, what one says must be true and good. The third is usefulness, so a story must be true, good and useful, otherwise it will be meaningless. We will try to honor this concept.

Finally, I would like to dedicate this report to all surgeons in the interior, especially those with an interest in colorectal pathology. Being a doctor graduated from a public university in the interior of our country and with complete postgraduate training in Buenos Aires, I decided to practice my profession in the interior, where work is generally more isolated, which makes everything a little more difficult. I made this decision despite understanding the difficulty of carrying out any academic task away from training centers and academic excellence centers. However, carrying out a task like this allows one to achieve a double reward.

I leave for the end my recognition to those who participated, corrected and collaborated in the writing of this report, either by supporting or participating objectively. For this I would like to thank mainly Drs. Pablo Jorge and Daniela Lamas from Jujuy, Drs. Borquez, García, Tachi and Sánchez from Salta, Drs. Romina Bianchi, Mariano Laporte and Alejandro Moreira Grecco from Buenos Aires, Drs. Marcelo Viola and his team from Uruguay, Drs. Paula Cassares, Julieta Pereyra, Susana Bruzzi and Drs. Audel Closas from Tucumán. I am particularly grateful for the effort made in the correction by Drs. Juan Pablo Campana, Carlos Vaccaro and Rita Pastore.

I dedicate and thank my patients who generously tolerate and demand my medical care. They are the custodians of all my knowledge and dedication.

Finally, hoping to have thanked all those who contributed in one way or another to this report, I offer my apologies to those whom I may have inadvertently omitted and who deserve to be on this list. Thank you all very much!

My father taught me many things, including respect for surgery and the specialty, but my main memory is that he almost demanded that I have fun doing what I had chosen and that is what I do, enjoying my work every moment. This was probably his greatest and best lesson. Today I can say that I like nothing more than being in an operating room and if I could add something I would tell those who come after me not to set a limit for themselves, not to let anything or anyone tell them that they cannot do something. Any goal is possible; you just have to work hard to achieve it. The only limit will be the one you set for yourself. Be brave, work hard and have fun along the way.

Finally, I recognize that in order to dedicate enough time to this goal, it was necessary to put my affections aside for more than a year. For this reason, I especially thank and dedicate this report to those who always teach me that moments together make us forget our absences, my three reasons to smile, Facundo, Agustina and Victoria.

OBJECTIVES

The objectives of the different guidelines and the evidence consulted on which this report is based are:

- To review fundamental and concise concepts on incidence, epidemiology, initial evaluation, histology and staging of colon cancer.
- To analyze the evidence on the treatment of colon cancer in general and by stage.
- To analyze the results of colon cancer treatment in the NOA in the last 5 years
- To evaluate the main issues surrounding the management of colon cancer in Argentina through a survey directed to surgeons in our country.

ABBREVIATIONS

AFL: Aflibercept
AJCC: American Joint Committee on Cancer
ASA: American Society of Anesthesiologists
ASCO: American Society of Cancer Oncology
ASRCS: American Society of Colon and Rectal Sugeons
Bev: Bevacizumab
BLI: Blue Laser Imaging
Cape: Capecitabine
CRC: Colorectal Cancer
ECC: Early Colon Cancer
CEA: Carcinoembryonic Antigen
Cetu: Cetuximab
CIN: Chromosomal Instability
DEIS: Directorate of Health Statistics and Information
DFS: Disease Free Survival
EGFR: Epidermal Growth Factor Receptor
EIAS: ERAS Interactive Audit System
EMR: Endoscopic Mucosal Resection
ERAS: Enhanced Recovery after Surgery
ESD: Endoscopic Submucosal Resection
ESMO: European Society for Medical Oncology
FDG PET/CT: Fluorodeoxyglucose Positron Emission Tomography
FICE: Flexible Spectral Imaging Color Enhancement
5FU: 5 Flourouracil
FOLFIRI: 5FU + leucovorin + irinotecan
FOLFIRINOX or FOLFOXIRI: 5FU + leucovorin + oxaloplatin + irinotecan
HIPEC: Hyperthermic Intraperitoneal Chemotherapy
HNPCC: Hereditary Nonpolypoid Colorectal Cancer
IARC: International Agency for Research on Cancer
INC: National Cancer Institute
IP: Pedunculated protruding
IPS: Subpedunculated
Iri: Irinotecan
IS: Sessile protruding
LCI: Linked color imaging
LV: Leucovorin
MCC: Merkel Cell Carcinoma
MSI: Microsatellite Instability
MMR: Mismatch Repair
NBI: Narrow Band Imaging
NCCN: The National Comprehensive Cancer Network
NSABP: National Surgical Adjuvant Breast And Bowel Project
OXA: Oxaliplatin
OS: Overall Survival
Pani: Panitumumab
Pembro: Pembrolizumab
pTNM: Pathological Staging of the Tumor According to Size, Nodes and Metastasis
PECA: Estimated Percentage of Annual Change
MBC: Mechanical Bowel Preparation
Ram: Ramurizumb
Reg: Regorafenib
RELARC: Radical Extent of Lympadenectomy LAparo-scopic Right Colectomy for Right-Sided Colon Cancer
EFTR: Endoscopic Full-Thickness Resection
SBRT: Stereotactic Body Radiation Therapy
OS: Overall Survival
SIVER- Ca: Epidemiological Surveillance And Report-ing System For Cancer
DFS: Disease-Free Survival
Sm: Submucosal
AAR: Age-Adjusted Rate
Tis: Tumor In Situ
TNM: Tumor (T), Node (N), Metastasis (M)
UICC: International Union for Cancer Control
VEGF: Vascular Endothelial Growth Factor

CHAPTER 1
Epidemiology of colon cancer

Incidence and epidemiology

Colorectal cancer (CRC) is the third most common cancer in men (10.2%) and the second in women (9.2%) Accounts for 10% of all tumors and the fourth cause of cancer-related death worldwide.(1,2) Worldwide, colon cancer was estimated at 1.1 million new cases (6.1%) and 551,000 (5.8%) deaths.[2–5]

The highest incidence of colon cancer is found in Europe, Australia, New Zealand and East Asia, China, Japan, South Korea and the female population of Singapore.[6]

The mortality rate in the European Union is 15 to 20 per 100,000 men and 9 to 14 per 100,000 women and has decreased over time, especially in the female sex. The 5-year survival rate ranges from 28.5 to 57% in men and 30.9 to 60% in women, with an overall estimate of 46.8 and 48.4%, respectively.[4,7]

The American Cancer Society estimated that approximately 105,000 Americans would be diagnosed with colon cancer and 53,200 would die from it by 2020. The risk of developing colon cancer is approximately 4%, with the highest risk occurring in people with a family history of CRC. In the United States, colon cancer is a leading cause of cancer-related death, being the third most common cause of cancer, with more than 100,000 Americans diagnosed annually.[8]

Age is considered a major non-modifiable risk factor for sporadic colon cancer. It occurs at an age greater than 65 years in 70% of patients and is rare in those under 40, although recent data from the West have reported an increase in incidence in the 40-44 age group.[6,9]

According to a recent study of over 920,000 patients with colon adenocarcinoma, the average age was 68±13 years, 50.5% were female, 83% were white, and the majority (85.3%) lived in metropolitan areas.[10]

Analysis of a cohort in the United States showed a 5-year survival rate of 90% in localized cancer, 70% when there is regional involvement, and 14% in distant involvement.[4,8]

Surgery remains the most important primary treatment for most patients with colon cancer, while chemotherapy is most frequently used as adjuvant treatment. However, neoadjuvant therapy for locally advanced tumors is currently a relevant new therapeutic perspective, as is immunotherapy for metastatic tumors.

Colon cancer in Argentina

The Instituto Nacional del Cancer (INC) published in 2022 the incidence of the various types of cancer in our country, according to data from Siver-Ca, an agency dependent on the Ministry of Health of the Nation. CCR was the second most common in both sexes.[11]

In 2022, breast cancer had the highest incidence, accounting for 16.2% (21,631) of all new cases, and was the leading cancer in women. In second place was CRC with 11.9% (15,863 cases) and in third place was lung cancer. In men, the main sites of cancer were prostate (19.7%), CRC (13.3%) and lung (13.2%). In women, breast cancer predominated (31.6%) followed by CRC (10.6%) and cervical cancer (6.9%) (Table 1.1).

Colon cancer mortality

The distribution of deaths by sex and topographic location is shown in Table 2.2. As in the previous period and considering both sexes, lung cancer caused the highest number of deaths, with 8,438 (14.3%) cases, followed by colorectal cancer (12.2%) and breast cancer (9.9%).[12]

Lung cancer caused the highest mortality from malignant tumors in men (18.2/100,000), followed by CRC (13.1/100,000), prostate cancer (10.2/100,000), pancreatic cancer (6.9/100,000) and gastric cancer (5.8/100,000). In women, breast cancer was the most frequent (16.4/100,000), followed by lung cancer (8.8/100,000), CRC (8.5/100,000), cervical cancer (7.4/100,000) and pancreatic cancer (5.6/100,000).

CRC mortality over the period 2002-2022 is shown in Fig. 1.1. A different trend was observed according to sex. In men, a significant upward trend was recorded between 2002 and 2006, with an estimated annual percentage change (PECA) of 1.5%. Between 2006 and 2016, the rate of increase slowed to a value of 0.04% per year, and in the last 4 years a statistically significant decrease was observed, at a rate of -3.2% per year. In contrast, in women, a constant downward trend was observed at an average rate of -0.2% per year.

The age-adjusted mortality rate (TAE) for CRC in both sexes in Argentina is presented in Fig. 2.2, according to distribution quintiles. In men, the province of Neuquén was in the highest mortality quintile (125.5 deaths per 100,000 inhabitants). The province of San Juan was in the lowest quintile (73.3 deaths per 100,000). In women, La Pampa was in the highest quintile (95.2 deaths per 100,000), while the province of Catamarca was in the lowest quintile (62 deaths per 100,000 women).

Table 1.1. Absolute and relative distribution of incident cancer cases estimated by IARC for Argentina in 2022, by most frequent tumor location and sex. (N=133,420). With permission from the Instituto Nacional del Cancer.

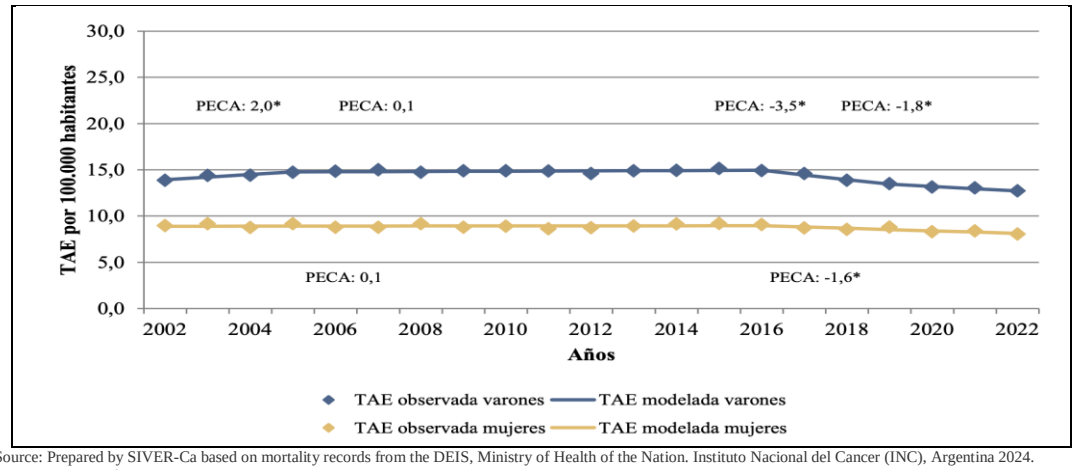
Sites	Total, n	%	Men, n	%	Women, n	%
Breast	21,631	16.2	,,,	...	21,631	31.6
Colon-Rectum	15,863	11.9	8,633	13.3	7,230	10.6
Lung	13,016	9.8	8,587	13.2	4,429	6.5
Prostate	12,836	9.6	12,836	19.7	,,,	...
Pancreas	5,554	4.2	2,704	4.2	2,85	4.2
Kidney	4,908	3.7	3,409	5.2	1,499	2.2
Cervix	4,696	3.5	,,,	...	4,696	6.9
Stomach	4,460	3.3	2,870	4.4	1,590	2.3
Thyroid	4,229	3.2	645	1	3,584	5.2
Non-Hodgkin lymphoma	3,838	2.9	2,019	3.1	1,819	2.7
Bladder	3,713	2.8	2,827	4.3	886	1.3
Leukemia	2,998	2.2	1,691	2.6	1,307	1.9
Uterus	2,686	2	,,,	...	2,686	3.9
Liver and intrahepatic bile ducts	2,504	1.9	1,538	2.4	966	1.4
Ovary	2,191	1.6	,,,	...	2,191	3.2
Esophagus	2,142	1.6	1,433	2.2	709	1
Testicle	2,054	1.5	2,054	3.2	,,,	...
Brain, central nervous system	2,012	1.5	1,059	1.6	953	1.4
Skin melanoma	1,603	1.2	954	1.5	649	0.9
Larynx	1,266	0.9	1,074	1.7	192	0.3
Lips, oral cavity	1,236	0.9	798	1.2	438	0.6
Multiple myeloma	1,059	0.8	576	0.9	483	0.7
Hodgkin lymphoma	873	0.7	555	0.9	318	0.5
Gallbladder	810	0.6	225	0.3	585	0.9
Penis	470	0.4	470	0.7	,,,	...
Oropharynx	436	0.3	323	0.5	113	0.2
Vulva	343	0.3	,,,	...	343	0.5
Salivary glands	309	0.2	194	0.3	115	0.2
Mesothelioma	248	0.2	136	0.2	112	0.2
Kaposi sarcoma	246	0.2	213	0.3	33	0
Nasopharynx	153	0.1	111	0.2	42	0.1
Vagina	106	0.1	,,,	...	106	0.2
Hypopharynx	86	0.1	73	0.1	13	0
Others	7,552	5.7	4,339	6.7	3,213	4.7
Unspecified	5,293	4	2,694	4.1	2,599	3.8
Total	**133,420**	**100**	**65,040**	**100**	**68,380**	**100**

Source: Prepared by SIVER/INC based on Globocan 2022 data. Argentina, 2024.
IARC: International Agency for Research on Cancer.

Table 2.2 Distribution of cancer deaths by topographic site according to sex. Argentina, 2022. With permission from the Instituto Nacional del Cancer.

Sites	Men		Women		Total	
	n	%	n	%	n	%
Lung	5.190	17.5	3.248	11.1	8.438	14.3
Colon-Rectum	3.916	13.2	3.301	11.3	7.217	12.2
Breast	81	0.3	5.750	19.6	5.831	9.9
Pancreas	2.094	7.1	2.272	7.8	4.366	7.4
Prostate	3.443	11.6		0	3.443	5.8
Stomach	1.692	5.7	997	3.4	2.689	4.6
Uterus-neck		0	2.222	7.6	2.222	3.8
Kidney and other urinary	1.494	5	651	2.2	2.145	3.6
Liver	1.111	3.7	706	2.4	1.817	3.1
Esophagus	1.026	3.5	503	1.7	1.529	2.6
Brain and other CNS	784	2.6	628	2.1	1.412	2.4
Gallbladder and extrahepatic bile ducts	573	1.9	697	2.4	1.270	2.2
Bladder	920	3.1	344	1.2	1.264	2.1
Ovary		0	1.179	4	1.179	2
Non-Hodgkin lymphoma	631	2.1	463	1.6	1.094	1.9
Uterus-body		0	842	2.9	842	1.4
Myeloma	329	1.1	299	1	628	1.1
Larynx	504	1.7	90	0.3	594	1
Soft tissues	268	0.9	297	1	565	1
Tumors with frequency < 1%*	2.322	7.8	1.679	5.7	4.001	6.8
Poorly defined and metas-tasis	2.376	8	2.371	8.1	4.747	8.1
Total	**29.667**	**100**	**29.264**	**100**	**58.931**	**100**

*Includes: lips and oral cavity, skin: melanoma and non-melanoma, bone, other thoracic organs, thyroid, testicle, mesothelioma, pharynx, penis, other genitals, small intestine, anus, vulva, parotid glands, salivary glands, other endocrine glands, vagina, nasal cavity, paranasal sinuses and others, eye, Kaposi sarcoma and other malignant tumors.
Source: Prepared by SIVER-Ca based on mortality records from the DEIS, Ministry of Health of the Nation. Instituto Nacional del Cancer (INC), Argentina 2024.



Source: Prepared by SIVER-Ca based on mortality records from the DEIS, Ministry of Health of the Nation. Instituto Nacional del Cancer (INC), Argentina 2024.
*Statistically significant (p<0.005).

Figure 1.1 *Trend and estimated percentage of annual change (PECA) in colorectal cancer mortality in men (blue line) and women (orange line). Age-adjusted rates (TAE) per 100,000 inhabitants. Argentina, 2002-2022. With permission from the Instituto Nacional del Cancer.*

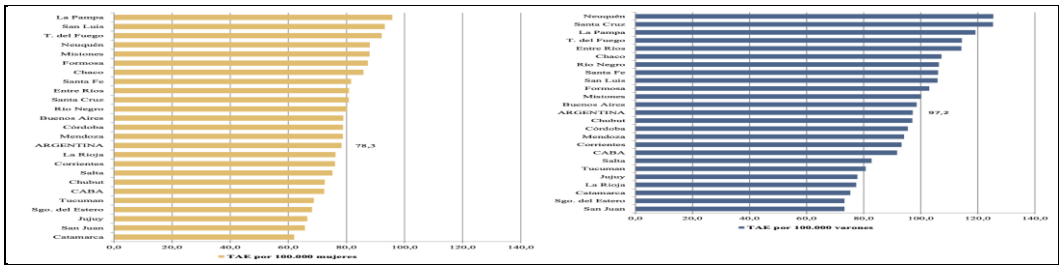
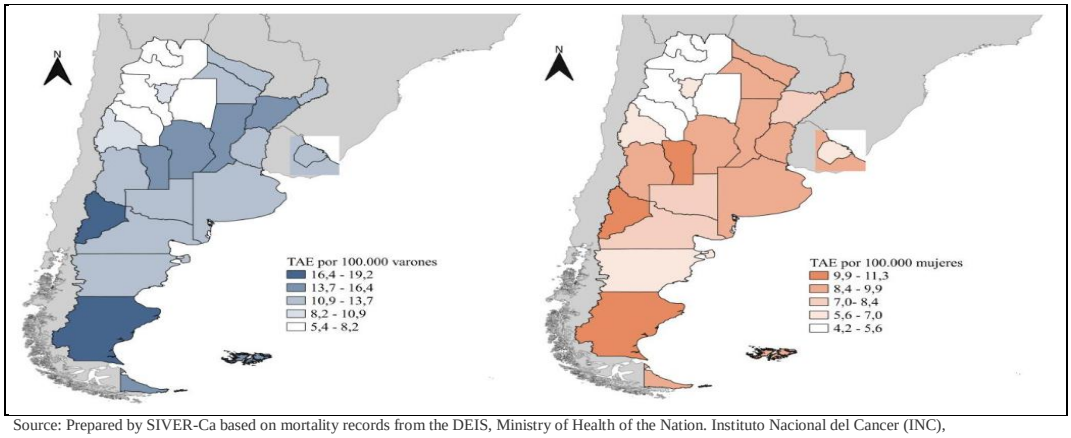


Figure 2.2. *Cancer mortality in women (orange bar chart) and men (blue bar chart). All sites. Age-adjusted rates (TAE) per 100,000 inhabitants grouped into quintiles. Argentina and its jurisdictions, 2022. With authorization from the Instituto Nacional del Cancer.*

In most jurisdictions of the country, male mortality due to this tumor location was higher than female mortality, with the exception of Río Negro, where the difference by sex increased compared to what was observed in 2019. Excess male mortality ranged between 0.8/100,000 inhabitants in Salta and La Pampa and 14.6/100,000 in Santa Cruz, while the average difference at the country level between male and female mortality was 4.8/100,000. In Salta, men and women had similar mortality rates (5.8/100,000 men and 5.7/100,000 women) (Fig.3.3).



Source: Prepared by SIVER-Ca based on mortality records from the DEIS, Ministry of Health of the Nation. Instituto Nacional del Cancer (INC), Argentina 2024.

Figure 3.3. *Colorectal cancer mortality by jurisdiction. Age-adjusted rates (TAE) per 100,000 inhabitants. Argentina, 2022. (blue: men, orange: women). With permission from the Instituto Nacional del Cancer.*

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CHAPTER 2
Diagnosis and initial evaluation

Risk factors

Risk factors for colon cancer include genetic factors such as ethnicity, age, sex, and family history, as well as lifestyle factors. In Asian countries and specific regions, high incidences are related to economic development, urbanization, and a Western lifestyle.[1–4]

Individuals with any of the following history are considered to be at high risk for colon cancer and should be actively screened. In addition, those with inherited syndromes should be referred for genetic counseling:

- Personal medical history of adenoma, colon cancer or inflammatory bowel disease, such as Crohn's disease or ulcerative colitis.
- Family history of adenoma or colon cancer.
- Hereditary syndromes (2-5%): Lynch syndrome or hereditary non-polyposis colon cancer (2-4%), familial adenomatous polyposis and its variants (1%), Turcot syndrome, MUTYH-associated polyposis syndrome, Peutz-Jeghers disease.

Diagnosis

Because of the specific topic of this treatment update report, we will not address the basics of screening, specific diagnosis, or symptoms of uncomplicated colon cancer. However, we cannot define the current treatment of colon cancer without first establishing the basic principles of its staging.

Following the diagnosis of a colon tumor, a clinical examination and laboratory tests are necessary to correctly assess the patient's general condition and characteristics before defining the definitive therapeutic approach. Evidence IIA.

It is essential to perform a cancer-related history analysis, including specific symptoms, personal clinical history, family history, physical examination, and perioperative risk, before planning treatment. Evidence IB.[1]

An objective way to assess preoperative risk is to analyze the general condition according to the Eastern Cooperative Oncology Group.[2]

In addition to the complete physical examination, the humoral examination includes general laboratory tests, coagulation tests, liver function, kidney function, and proteinogram. Evidence IIA. Likewise, carcinoembryonic antigen (CEA) should be evaluated before surgery and during postoperative follow-up for early detection of metastatic disease. Evidence IIIA.[1]

The preoperative CEA level is important to define the oncological prognosis of each case. A level >5 ng/ml suggests a worse outcome.[5]

According to a multivariate analysis of over 130,000 patients included in the National Cancer Database, preoperative CEA is an independent predictive factor of overall survival (OS) in patients with stage I, II, and III colon cancer. Patients with elevated CEA have a 62% increased risk of death compared with patients with normal CEA. Although CEA is considered an important predictor, there is no complete consensus on the cutoff value. In stage IV patients, decreased CEA in response to chemotherapy has been associated with improved survival.[5–10]

Histological classification of colon carcinoma

Approximately 95% of malignant neoplasms of the colon are adenocarcinomas.[11–13] According to their histological characteristics, carcinomas are classified as:

a) Adenocarcinoma: the usual form of malignant neoplasia originating in the colonic glandular epithelium.
b) Mucinous or colloid adenocarcinoma: more than 50% of the lesion is made up of lakes of extracellular mucin containing malignant epithelium forming acini, epithelial strips or loose cells. It is frequently associated with microsatellite instability.
c) Signet ring cell adenocarcinoma: more than 50% of the neoplastic cells show abundant intracellular mucin and the nucleus is located peripherally in a characteristic ring shape, regardless of the presence of extracellular mucin lakes. Some show microsatellite instability.
d) Adenosquamous carcinoma: features of squamous carcinoma and adenocarcinoma coexist in separate areas of the same tumor or are intermingled. More than an occasional focus of squamous differentiation is required to define this subtype.
e) **e)** Medullary carcinoma: characterized by a covering of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, surrounded by an intense lymphocytic infiltrate. It is a rare variant that is invariably associated with microsatellite instability and has a better prognosis than poorly differentiated and undifferentiated carcinoma.
f) f) Undifferentiated carcinoma: malignant epithelial tumor without any type of cellular olodifferentiation (glandular, squamous or neuroendocrine), beyond the epithelium itself. These tumors are genetically different and are typically associated with microsatellite instability.

Histologic grade of differentiation

According to the degree of histological differentiation, adenocarcinoma can be:

- Well differentiated (G1): more than 95% of the tumor forms glands.
- Moderately differentiated (G2): 50 to 95% of the tumor forms glands.
- Poorly differentiated (G3): less than 50% of the tumor forms glands.

It is necessary to determine the level of infiltration of the colonic wall (affectation of the submucosa, muscularis propria, perivisceral fat, serosa, or other organ by contiguity), the presence of lymph node metastasis (regional disease) and distant metastasis (disseminated disease).[1,2,14]

Histological prognostic factors

Histopathological factors that have been definitively proven to be prognostic are pTNM, the presence of residual tumor after a curative procedure (R1 or R2 resection), and vascular and/or lymphatic invasion. Histological grade, margin status (radial, distal, and deep), and the presence of residual tumor after neoadjuvant therapy are also sufficiently proven.

Promising, but not yet sufficiently proven in the clinical context, are the histological characteristics associated with microsatellite instability (MSI): peritumoral lymphoid response, mucinous and medullary histological type, high MSI grade, and tumor border configuration (infiltrative vs. expansive).[1,2,14]

Histological evaluation and report

Histopathology reports non-mucinous adenocarcinoma in 89.2%, mucinous adenocarcinoma in 9.3%, and signet ring cells in 1.5%. The histology report is of particular importance and should be performed immediately after surgery to determine lymph node involvement and tumor extension into the colon wall and adjacent structures, as well as to establish the need for biopsies due to suspected distant invasion (e.g. liver, peritoneum).

Although the analysis of this aspect exceeds the objectives of this report, it is important to define a correct histological report because the choice of postoperative treatment will depend on it. A standard histological evaluation should include:[1,2,4,14]

- Morphological description of the specimen
- Type of surgery performed
- Location and size of the tumor
- Presence of macroscopic or microscopic tumor perforation
- Histological grade and type
- Definition of T stage (extension of the tumor into the colon wall and involvement of adjacent structures)
- Distance of the tumor to the resection margins (proximal, distal and radial)
- Presence of tumor deposits
- Perineural and/or lymphovascular invasion
- Presence of tumor budding
- Evaluation of N stage (site and number of resected regional nodes and their tumor involvement)
- Evaluation of M stage (involvement of other distant organs, e.g. peritoneum, liver, lung, defining whether metastases were biopsied or resected)
- Tumor status with respect to mismatch repair (MMR) and microsatellite instability (MSI).

Pathologic stage should be reported according to the 8th edition of the Union for International Cancer Control (UICC) classification.

According to the American Society of Colon and Rectal Surgeons (ASCRS) practice parameters, a standard histologic surgical report should include a description of the type of surgery, tumor morphology (size, location and integrity), histologic grade and type, penetration into the wall of the colon and adjacent organs, description of margins, tumor deposits, perineural and lymphovascular invasion, tumor budding, description of lymph nodes, distant organ involvement, and MMR/MSI status. Evidence 4A.[1]

Genomic and chromosomal instability in colon cancer

There are two main types of genomic instability in CRC: MSI and chromosomal instability (CIN). MSI leads to a high rate of point mutations, while CIN refers to an increased rate of accumulation of chromosomal disorders.[15-17]

Microsatellites are very short regions of DNA that are repeated in tandem and that can be located within genes and constitute non-coding regions of the genome. MSI occurs in 15% of CRCs and is the result of the inactivation of the MMR system, either by mutations in these genes or by hypermethylation of the promoter of the MLH1 gene, one of the genes of this system. The main function of the post-replication mismatch repair system is to eliminate base-base pairings and insertion/deletion bonds that arise as a consequence of DNA polymerase dysfunction during DNA synthesis.[16]

Defective MMR facilitates malignant transformation by allowing rapid accumulation of mutations that inactivate genes that perform key functions in the cell. Defective MMR genes, by failing to produce the proteins responsible for correcting nucleotide mismatches during DNA replication, also promote mutations in other genes. But genes that have microsatellites in their own coding sequence are also involved. There is a hereditary form of colorectal cancer, hereditary non-polypoid colorectal cancer (HNPCC) or Lynch syndrome, which accounts for 3 to 5% of all CRC and is the most frequent entity within the hereditary CRC syndrome. In this syndrome, MSI is due to mutations in the MMR genes.

The predisposition to cancer observed not only in HNPCC but also in other cancer syndromes caused by germline mutations in genes regulating DNA fidelity [e.g., Li-Fraumeni syndrome (TP53, CHK2), Nijmegen syndrome (NBS1), Bloom syndrome (BLM), and ataxia telangiectasia (ATR/ATM)] demonstrates that inactivation of mechanisms regulating genomic stability constitutes a primary event in carcinogenesis. MMR-deficient cells display a mutator phenotype in which the spontaneous mutation rate is very high and can be 100- to 1000-fold higher than in normal cells.[17,18]

Virtually all CRCs exhibit either MSI or CIN, suggesting that genomic instability is not only common but also fundamental in the genesis of CRC.

CIN is the most common type of instability in CRC and occurs in approximately 85% of colon tumors. Aneuploidy, characterized by changes in the structure and number of chromosomes, is considered a hallmark of CIN, although more precise information is still lacking.[18]

Evaluation of tumor extension

Before evaluating tumor extension, the macroscopic and microscopic type of the lesion, location, initial resectability, and association with polyps or second tumors should be evaluated. Evidence IA.[1]

The colon should be evaluated with a complete colonoscopy to rule out synchronous tumors, which are present in 4% of patients with Stage I and II. The incidence of synchronous adenomas is 30% to 50%.[1]

Proximal and distal endoscopic tattooing of early tumors should be performed routinely to facilitate their intraoperative localization, particularly during minimally invasive surgery. In patients with obstructive colon cancer, where proximal endoscopic evaluation is impossible, virtual colonoscopy is highly effective (sensitivity 94%) in detecting synchronous tumors or adenomas, which affect the surgical plan in 2% to 21% of patients.[14]

High histological grade and poor cell differentiation have been shown to be predictors of poor outcome and should therefore be taken into consideration before recommending any type of treatment.

The histological diagnosis of malignancy should be confirmed whenever possible before treatment. Methods for diagnosis and preoperative confirmation of malignancy are beyond the scope of this report and their approach could be considered a topic in itself.

The outcome of colon cancer is strongly related to the stage of the disease. Early-stage colon cancer is potentially curable and is associated with excellent OS, unlike what occurs in patients with metastatic disease. Approximately 20% of new colon cancers present synchronous metastases at the time of diagnosis, with the most frequently affected organs being the liver (17%), peritoneum (5%), lung (5%) and lymph nodes (3%).[19]

Preoperative assessment of tumor extent is essential to determine whether resection of the primary tumor alone will be necessary and, if there are distant metastases, whether they will be amenable to resection or systemic therapy.

Computed tomography of the chest, abdomen and pelvis with oral and intravenous contrast is the preferred method for initial staging. It allows for the assessment of the locoregional extension of the tumor and its possible complications (obstruction, perforation, fistula or abscess), as well as distant metastases. However, the sensitivity for peritoneal metastases is relatively low. Evidence IIB.[1,20–23]

Magnetic resonance imaging may replace computed tomography in patients with iodine allergy or renal failure with a glomerular filtration rate less than 30 ml/min. It is also useful for better definition of peritumoral soft tissues when CT results are inconclusive. Abdominal MRI may also

be combined with chest CT for initial staging. Evidence 2A.[1] Fluorodeoxyglucose positron emission tomography (FDG PET/CT), used in selected nonmetastatic cases, has a negative predictive value of 93% for advanced adenomas and 100% for tumors. However, neither NCCN nor ESMO recommend staging with PET/CT. Another option to rule out synchronous lesions is intraoperative colonoscopy, or postoperative colonoscopy in a period close to surgery.[24,25]

For ESMO, PET/CT does not add relevant information in the routine initial evaluation for staging localized colon tumors. It should be reserved for patients who initially present with distant metastases and for decision making in surgical treatment of those with Stage IV. Evidence IIA.[14] Table 2.1 shows the different studies available for staging colon cancer and their level of evidence, according to ESMO.

Table 2.1. Levels of evidence and grades of recommendation in the staging of colon cancer.

Test	Level of evidence. Grade of recommendation
Complete colonoscopy	I. A
Imaging studies	
Computed tomography	
- Lung	I. B
- Abdomen	I. B
- Pelvis	I. B
Virtual colonoscopy	I. A
Magnetic resonance imaging	II. A
Laboratory	
Cell count	II. A
Coagulation	II. A
Liver function	II. A
Kidney function	II. A
Albumin	III. A
CEA	III. A

CEA: Carcinoembryonic antigen.

Recommendations

- Preoperative evaluation should include a complete physical examination, complete laboratory tests, CEA determination, abdominal, chest, and abdominopelvic CT with oral and intravenous contrast. Evidence III A.
- In the absence of an indication for urgent tumor resection, a complete colonoscopy is recommended to confirm the diagnosis and rule out synchronous tumors. If a complete colonoscopy is not possible, an alternative is to combine a left-sided colonoscopy with a CT-guided colonoscopy. Evidence IA.
- In the event that colonoscopy cannot be performed before the surgical procedure, a complete colonoscopy should be performed between 3 and 6 months after tumor resection. Evidence IVC.

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CHAPTER 3
TNM staging

Colon cancer staging is performed according to the American Joint Committee on Cancer (AJCC) classification: AJCC/TNM, in its 8th edition (Tables 3.1 and 3.2). Evidence IB.[1–3] Below are only a few mentions regarding staging that are relevant to treatment. The current edition (8th) includes the M1c category for peritoneal implants, clarifies the concept of tumor deposits (N1c), and highlights the importance of perineural and lymphovascular invasion, MSI, tumor budding, and mutations in the K-RAS, N-RAS, and BRAF genes, which have an impact on therapeutic decisions (Fig. 3.1 and Tables 3.1 and 3.2).[1]

Staging system for colon cancer. TNM, AJCC, 8th edition, 2017.

TNM		Description
T		Primary tumor
Tx		Primary tumor cannot be evaluated
T0		No evidence of primary tumor
Tis		Carcinoma in situ, intramucosal carcinoma (involvement of the lamina propria without extension through the muscularis mucosae
T1		Tumor invades the submucosa (through the muscularis mucosae but not into the muscularis propria)
T2		Tumor invades the muscularis propria
T3		Tumor invades through the muscularis propria into pericolic tissue
T4		Tumor invades the visceral peritoneum or invades or adheres to neighboring organs or structures
	T4a	Tumor invades through the visceral peritoneum (includes gross perforation of the colon through the tumor or continued invasion of the tumor through areas of inflammation on the surface of the visceral peritoneum)
	T4b	Tumor invades or adheres to adjacent organs or structures
N		Regional lymph node
Nx		Regional lymph node not evaluable
N0		No evidence of lymph node metastasis
N1		1 to 3 positive regional lymph nodes (tumor in lymph node ≥ 0.2 mm) or any number of deposits Tumor present and identifiable if nodes are negative
	N1a	1 regional lymph node is positive
	N1b	2 or 3 regional lymph nodes are positive
	N1c	No positive lymph nodes, but tumor deposits are present in the subserosa, mesentery, or nonperitoneal pericolic tissue or mesocolic tissues
N2		4 or more positive lymph nodes
	N2a	4 to 6 positive lymph nodes
	N2b	7 or more positive lymph nodes
M		Distant metastasis
M0		No distant metastasis, no evidence of tumor in distant sites or organs
M1		Distant metastasis in 1 or more organs or sites or peritoneal
	M1a	Distant metastasis in 1 site without peritoneal metastasis
	M1b	Distant metastasis in 2 or more sites without peritoneal metastasis
	M1c	Peritoneal metastasis alone or associated with other organs or sites with metastasis

Table 3.2. Estadificación por estadios del cáncer de colon. TNM, AJCC, 8va edición, 2017.

Stage	T	N	M
0	Tis	N0	M0
I	T1 T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1 T2	N1 N1c	M0
	T1	N2a	M0
IIIB	T3 T4a	N1 N1c	M0
	T2 T3	N2a	M0
	T1 T2	N2b	M0
IIIC	T4a	N2a	M0
	T3 T4a	N2b	M0
	T4b	N1 N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

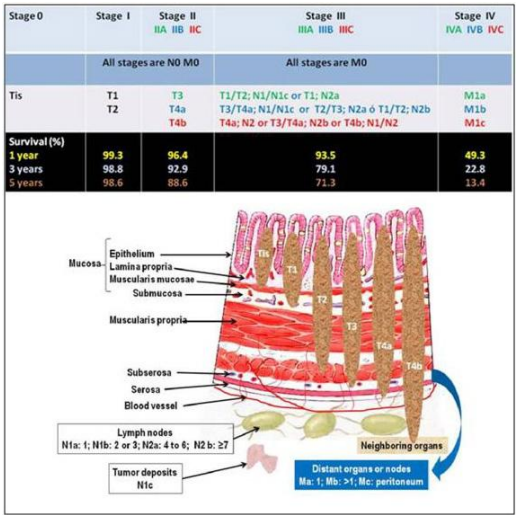

Figure 3.1. *Comparative analysis of stages. Adapted from AJCC, 8th edition, 2017.*

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CHAPTER 4
Treatment

Surgical treatment depends on the degree of invasion of the colon wall and the involvement of lymphatics or adjacent organs. Therefore, we will address early CRC and colon tumors with local or locoregional infiltration.

Treatment of early colon cancer (ECC)

A TCC is considered to be a lesion that affects only the mucosa and submucosa of the colon, without invading the muscularis propria. It is known that the doubling time of tumors that affect only the mucosa is longer than that of those that affect the submucosa (31 versus 25 months, respectively).[1]

Polyp is a morphological concept and is defined as a lesion in the mucosa that protrudes into the lumen of the intestine. Polyps can be characterized by the presence or absence of a pedicle, size or number. According to their histological type, they are divided into two groups: neoplastic (tubular, tubulovillous and villous adenomas, serrated polyps) and non-neoplastic (hyperplastic, inflammatory, juvenile, lipoma).[2,3]

Basis of microvascular architecture of colon lesions

Normal colonic mucosa: The capillary network of the mucosa is arranged in a cryptic pattern in the gland and is made up of arterioles and subepithelial capillaries that drain into veins that join together to form the submucosal veins. The diameter of the vessels is 8.6 ± 1.8 µm to 12.4 ± 1.9 µm (range: 6.4 - 20.9 µm). This capillary network is observed throughout the large intestine, from the cecum to the rectum.
Hyperplastic polyps: The vessel diameter in hyperplastic polyps is not significant compared to normal mucosa. The thickness of the intratumoral microinvasion is greater than in hyperplastic polyps and also greater than in normal mucosa.
Adenomas: In small adenomas (< 3 mm in diameter), the microvascular organization is similar to that of the normal colon. The vascular network is provided by arterioles and capillaries of the submucosa that drain into venules, only in the luminal lining. The capillary network on the tumor surface is preserved. The greatest difference from normal mucosa is based on an elongation of capillaries and venules and a moderate increase in microvascular diameter, which is measured at 13.1 ± 3.3 µm. Adenomas >3 mm in diameter have an elongation of microvessels. The microvascular structure of adenomas is similar to that of normal vessels, but is adapted to the configuration of the adenoma.
Carcinomas: the microvasculature of colon carcinomas is characterized by structural disorganization and a marked increase in density. However, vascular proliferation within tumors frequently results from an increase in the number and thickness of microvessels between tumor cells and a disorganization of vascular structure. Vessel diameter ranges from 18.3 ± 0.1 µm to 19.8 ± 7.6 µm (range: 2.2 - 84.5 µm).

Morphological classification or Paris classification

Macroscopically, superficial gastrointestinal lesions are classified as type 0 lesions to distinguish them from advanced tumors (types 1 to 4). The Roman numeral I is added if they are elevated more than 2.5 mm from the adjacent mucosa, II if they are elevated or depressed less than 2.5 mm, and III if they are clearly depressed (more than 2.5 mm).

Early colon tumors are classified by their morphology as protruding or polypoid and superficial or flat (Fig. 4.1). Protruding or type 0-I lesions may be pedunculated (0-Ip), subpedunculated (0-Ips), or sessile (0-Is). Superficial or type 0-II lesions may be elevated, flat, and depressed. They are subdivided into 0-IIa (slightly elevated < 2.5 mm), 0-IIb (strictly flat) and 0-IIc (slightly depressed < 1.2 mm). Type 0-III lesions (ulcer with depth > 1.2 mm) are not found in the colon. This classification allows combinations of subtypes, the most frequent being IIa + IIc and IIc + IIa (Table 4,1).[1,3-6]

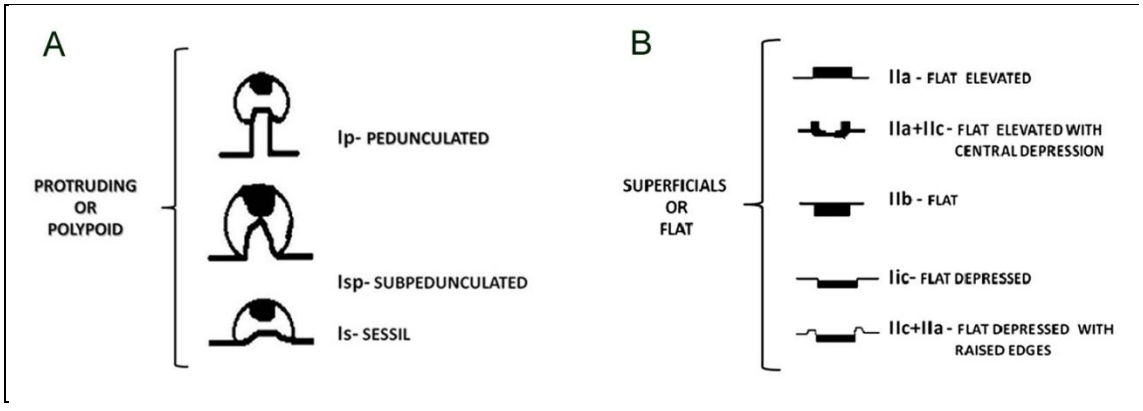


Figure 4.1. *Morphologic classification of early tumors.* ***A.*** *Protruding or polypoid lesions.* ***B.*** *Superficial or flat lesions. Adapted from the Japanese Research Society for CRC.*

Table 4.1 Paris endoscopic classification of superficial lesions type 0

Type of superficial tumoral lesion	Endoscopic appearance
0-I Polypoid	
0-Ip 0-Is	Protruded pedunculated Protruded sessile
0-II Flat: not polypoid, not excavated	
0-IIa 0-IIb 0-IIc	Flat elevated Flat Flat depressed
Mixed 0-IIc + 0-IIa Mixed 0-IIa + 0-IIc	Mostly depressed with raised borders Central depression in an elevated lesion
0-III Excavated	
Mixed 0-III + IIc o 0-IIC+III	Excavated and depressed lesions

Adapted from: Endoscopic Classification Review Group.[5]

Degree of invasion of the submucosal layer

The depth of submucosal invasion is an important prognostic factor in malignant polyps. Early tumors that invade the submucosal layer are classified according to the degree of invasion. In early polypoid tumors, the classification proposed by Haggitt et al.,[6] divides invasion into 4 levels, related to the prognosis. For sessile lesions, submucosal invasion is always level IV (Fig. 4.2).

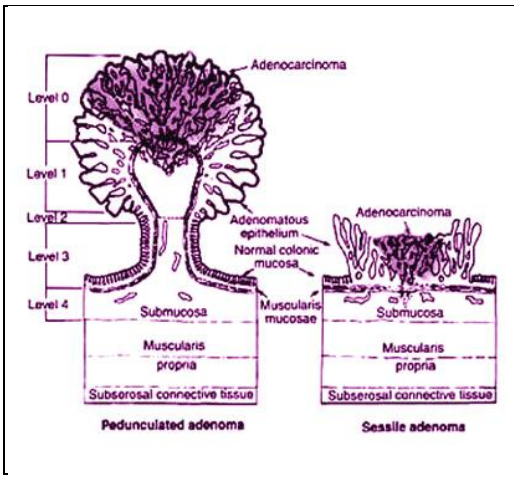


Figure 4.2. *Haggitt levels of carcinomatous invasion in polypoid lesions of the colon. Level 0: Noninvasive carcinoma, located above the muscularis mucosa. Level 1: Invasion of the mucosa and submucosa, but limited to the polyp head. Level 2: Involvement of the polyp neck (limited area between the head and the pedicle). Level 3: Invasion of the submucosa in the pedicle. Level 4: Invasion of the submucosa of the colon wall below the pedicle. Adapted from Haggitt, R. et al. Gastroenterology 1985.*[6]

Another classification for sessile lesions was proposed by Kikuchi et al.,[7] which divides the degree of vertical and horizontal invasion of the submucosa. The levels of invasion of the submucosa in depth are the upper third (Sm1), middle (Sm2) and lower third (Sm3). In turn, the upper third (Sm1) is subdivided into 3 according to the involvement or horizontal extension in relation to the size of the tumor. The Sm1a subtype invades the submucosa horizontally to an extent less than ¼ of the total tumor thickness, Sm1b invades horizontally between ¼ and ½ of the thickness and in Sm1c the horizontal invasion is greater than ½ of the tumor thickness (Fig. 4.3).

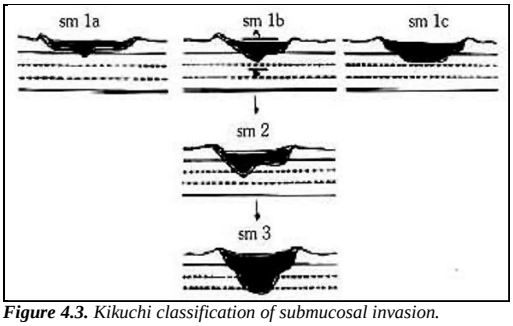


Figure 4.3. *Kikuchi classification of submucosal invasion.*

Prognostically, Sm1 is equivalent to Haggitt level 1, Sm2 is similar to Haggitt levels 2 and 3, while Sm3 may represent Haggitt level 4. A Sm1a or Sm1b lesion without vascular invasion has a zero rate of lymph node metastasis. Lesions with deeper or more extensive involvement have the capacity to metastasize, which determines the need to add surgical treatment after endoscopic treatment in these cases.

It is also possible to measure invasion depth in microns (µm) in 3 thirds: invasion < 500 µm, 500 -1000 µm, or > 1000 µm.[8]

In 2013, a systematic review revealed that the depth of invasion Sm1, Sm2 and Sm3 was associated with positive lymph nodes in 3.4, 8.5 and 22.6%, respectively.[9]
Thus, the depth of invasion greater than 1000 µm or Sm3 is currently used for the indication of an oncological surgical resection.

Haggitt classification can also be used to stratify the risk of presenting positive lymph nodes. As Haggit et al.[6] published in 1985, in pedunculated polyps with invasion limited to the head, neck, or stem (levels 1, 2, or 3), no metastatic lymph nodes were found and only 1% of patients died of colon cancer. In contrast, in patients with level 4 invasion, defined as invasion of the base of a pedunculated polyp or a sessile polyp, 25% of patients were diagnosed with positive lymph nodes or distant metastasis, supporting the indication for surgery in these cases. Other studies have shown a 13% positive lymph node rate in Haggitt level 4.[8]

Diagnosis of polypoid or flat ECC is crucial in order to decide on its treatment based on the location, morphological type, depth of invasion and degree of histological differentiation.

The diagnosis of deep invasion can be suspected at endoscopy by signs such as erosion, ulceration, fold convergence, retraction, deformity and rigidity. Better endoscopic evaluation can be achieved by chromoendoscopy or with enhanced imaging systems such as Narrow Band Imaging (NBI), Blue Laser Imaging (BLI), magnified endoscopy, etc.[10–12]The introduction of electron chromoscopy represented a new possibility in the endoscopic study of colorectal polyps by allowing the observation of the mucosal and vascular pattern.

The two most important electron chromoscopy systems are NBI and the computerized virtual chromoendoscopy system (FICE). The latter has also been modified by new endoscopy towers that allow it to be associated in real time with Blue Laser Imaging (BLI) and Linked Color Imaging (LCI), improving the observation of the vascular pattern and the inflammatory process of the mucosa. FICE is considered to have an excellent diagnostic capacity for the mucosal pattern and less for the vascular pattern. However, the definitive endoscopic diagnosis of the histological type of the polyp remains controversial.

Kudo et al.,[13] establish in their classification the degree of malignancy of colorectal lesions according to the patterns that configure the openings of the crypts and the microvasculature (*Pitt patterns*) (Table 4.2).

Table 4.3 details the histological classification proposed by the Vienna group for gastrointestinal intraepithelial neoplasias, with recommendations for treatment and follow-up.[14]

Treatment of malignant polyp

This section will address the treatment of early colon lesions (Tis and T1), to determine which are amenable to endoscopic resection and which to surgical resection.

The standard treatment of a colon polyp, when its morphological structure allows it, is complete endoscopic resection en bloc.[1] Endoscopic resection is sufficient for hyperplastic or adenomatous polyps with noninvasive adenocarcinoma or pTis (intraepithelial/intramucosal adenocarcinoma).[1,15–18]

For invasive or pT1 adenocarcinoma, management is determined by the morphology of the polyp and the presence of histological factors associated with adverse prognosis:

- Venous or lymphatic invasion
- Grade 3 or 4 cell differentiation
- Significant tumor budding (> grade 1)

For NCCN, unfavorable histologic findings are defined as grade 3 and 4 tumors, comparable to undifferentiated or poorly differentiated tumors, positive lymphovascular invasion, and positive resection margin.[19]

In the Japanese guidelines, the pathological finding of deep submucosal invasion (greater than 1000 µm) and tumor budding grade 2 or 3 are considered an indication for an additional surgical procedure with lymph node dissection, since the risk of lymph node metastasis is higher than in lesions without these risk factors.[20]

Risk levels in malignant polyps

Low-risk malignant polyp

A low-risk malignant polyp, pedunculated or sessile, can be defined as a polyp with well or moderately differentiated adenocarcinoma, without vascular or lymphatic invasion, without perineural invasion, without tumor budding or with low-grade budding, with negative resection margin, submucosal invasion less than 1 mm (1000 µm) and Haggitt invasion level 1, 2 or 3 in pedunculated polyps. Endoscopic resection is considered a definitive treatment in these patients with a minimal risk of residual disease or lymph node involvement.

High-risk malignant polyp

When a polyp, whether sessile or pedunculated, presents poorly differentiated adenocarcinoma, positive or indeterminate margin, submucosal invasion greater than 1 mm (1000 µm), vascular, lymphatic or perineural invasion, high-grade tumor budding and Haggitt level 4 invasion, oncologic surgical resection should be guaranteed because the risk of recurrence in the colon wall or regional lymph nodes is unacceptably high.

Table 4.2. Kudo classification describing the different patterns ofcolonic glandular crypts observable with chromoendoscopy.

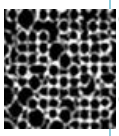
Pattern	Characteristics of crypt openings	Size (mm)	Diagram	Histology
I	Regular round	0.02		Normal colon
II	Stellated or papillary	0.02		70% Hyperplastic polyps 30% Adenomas
III S (short)	Round tubular, smaller than those of pattern I	0.01		86% Adenomas 13% Carcinomas
III L (large)	Long tubular	0.09		93% Adenomas 4.2% Carcinomas
IV	Grooves or turns (encephaloid)	0.032		75% Adenomas 22% Carcinomas
V	(Vi= irregular) (Vn= non-structured)			61% Carcinomas 39% Adenomas 93% Carcinomas 7% Adenomas

Table 4.3. Revised Vienna histological classification of gastrointestinal superficial epithelial neoplasms and treatment recommendations.

Category	Consequence	Recommendation
1. Negative for neoplasia	Normal, reactive, regenerative, hyperplastic, atrophic and metaplastic epithelium	Optional follow-up
2. Indefinite for neoplasia	Doubt about origin	Follow-up
3. Low-grade dysplasia: noninvasive neoplasia	Noninvasive neoplasia No risk of metastasis	Endoscopic resection and follow-up
4. High-grade dysplasia: noninvasive neoplasia 4.1 Adenoma with high-grade dysplasia 4.2 Carcinoma in situ 4.3 Suspected invasive carcinoma 4.4 Intramucosal carcinoma	Noninvasive neoplasia No risk of metastasis	Endoscopic resection and follow-up
5. Carcinoma with submucosal invasion	Invasive neoplasia Risk of metastasis	Endoscopic resection/Surgical treatment (According to histological risk factors)

Endoscopic treatment of malignant colon polyp

Endoscopic techniques include mucosal resection, endoscopic submucosal dissection, or a combination of endoscopic and laparoscopic techniques to avoid segmental colectomy in patients with low-risk polyps.[21] A complete endoscopic en bloc resection (not piecemeal resection), generally guarantees cure in more than 80% of patients.[22]

The definition of a negative margin after a polypectomy is a matter of debate. Initially, the need for a margin of more than 2 mm was maintained.[22] Subsequently, in 2012 in the United States, a review of 143 colectomized patients found residual cancer at the polypectomy site in 0, 9, and 16% and in regional nodes in 5, 21, and 7%, when the resection margin was ≥1 mm, <1 mm, or intermediate, respectively. [23]

In 2013, an analysis from the Northern Colorectal Cancer Study Group in England determined that endoscopic resection margins of 0 and >0 mm resulted in residual cancer at the polypectomy site or in regional nodes in 34% and 15% of cases, respectively.[15]

In 2018, the Scottish National Study found a 7% incidence of residual cancer in lymph nodes after polypectomy. In patients with incomplete polypectomy, residual cancer at the site was 29% and in regional nodes 9%. This study also demonstrated that a margin ≥ 1 mm does not reduce the risk of cancer when compared with a safety margin ≥ 0 mm.[2]

In 2013, a systematic review and meta-analysis of patients with pT1 CRC who did not undergo surgery demonstrated an incidence of lymph node involvement of 11%. It also showed that when associated with lymphovascular invasion, submucosal invasion ≥ 1 mm, poorly differentiated cancer, and tumor budding, lymph node involvement was 22%, 12%, 24%, and 21%, respectively.[24]

Fig. 4.4 shows the treatment scheme for an early polyp-cancer with and without histological risk factors for metastasis, according to ESMO guidelines.[25]

Surgical treatment of malignant colon polyp

The treatment strategy for early colon tumor, published by the Japanese guidelines, can be seen in Fig. 4.5. The presence of pT1 invasive cancer in a polyp requires review by the pathologist and the surgeon or endoscopist.[1,19,25,26]

For pedunculated polyps with pT1 adenocarcinoma confined to the head, neck, or stem, i.e., Haggitt 1-3, endoscopic resection with adequate endoscopic follow-up is sufficient, even in the presence of submucosal invasion if there are no other unfavorable prognostic factors at the time of resection. Evidence 4B.[25]

On the other hand, the presence of any unfavorable factor, or of a flat or sessile polyp according to the Paris classification with pT1 adenocarcinoma, determines the need for surgical resection in patients with adequate operative risk. Evidence 4B.[25]

The goal of surgical treatment is complete resection of the lesion including removal of lymph nodes for optimal postoperative outcome. Evidence 4B.[25]

The finding of positive resection margins, i.e. less than 1 mm, constitutes only a risk of local recurrence and can be managed by a new endoscopic resection, or by strict endoscopic follow-up.

High-risk findings in a polyp with pT1 invasive cancer indicate the need for surgical resection with lymphadenectomy. These factors include lymphatic or venous invasion, grade III cellular differentiation, and significant tumor budding (> 1). Evidence IVB [25]

When surgery is not possible due to comorbidities or high patient risk, endoscopic follow-up within 6 months of polyp removal is recommended, as well as oncologic evaluation including CT scan for possible detection of lymph node recurrence. Evidence 4B.[25]

It should not be forgotten that endoscopic resection is primarily intended for diagnosis and, secondarily, for treatment. En bloc resection should be performed as a first option so that, if invasive cancer is detected in the specimen, the pathologist can correctly assess the margin.

In early carcinoma, en bloc resection should be performed, piecemeal resection should be avoided. Resection of lesions larger than 2 cm should not be attempted, except by highly trained teams in complex endoscopy, either polypectomy or endoscopic mucosal resection (EMR). On the contrary, endoscopic submucosal dissection (ESD) allows resection of larger lesions, regardless of size or location, with very good results. Due to the high number of perforations, resection using a cap or devices for the removal of the entire colonic wall is not recommended. This last procedure is known as endoscopic transmural resection or FTRD-Ovesco.

In conclusion, whether endoscopic resection or oncologic surgical resection is performed depends on the size of the lesion and histopathological findings. Evidence IB.[25]

Treatment of colon tumors with local infiltration

This section refers to the treatment of lesions or tumors that infiltrate the muscular layer of the colon, as well as lesions with a high risk of lymphatic invasion.[27,28]

Surgical resection is the only curative treatment for locoregionally invasive colon cancer. Outcome is related to the extent of the disease and recurrence arises from clinically occult micrometastases present at the time of surgery.[29,30]

Infiltrating colonic tumors cannot be resected by colonoscopy and require surgical resection with the aim of wide resection of the involved intestinal segment and its lymphatic drainage. Evidence IA.[31]

The extent of colon resection is determined by the location of the tumor, the location of the nutrient artery of the segment to be resected, and the distribution of regional lymph nodes. Surgical resection should include a segment of the colon at least 5 cm proximal and distal to the tumor, although occasionally, due to the vascular distribution of the area to be resected, the margins on either side of the tumor should be wider. Evidence 4B.[31]

En bloc colonic resection with its mesocolon is recommended to determine whether the patient is in Stage II or Stage III, i.e. whether or not regional lymph nodes are involved. This resection should include at least 12 lymph nodes. Evidence 4B.[25]

In the case of involvement of neighbouring organs, i.e. in Stage 4B tumours, resection of the involved organ or segment should be included. Evidence IB. [31]

At the beginning of the procedure, a complete evaluation of the peritoneal cavity and female adnexa should be performed to exclude possible metastases. Evidence IC.[31]

Laparoscopic colectomy can be performed safely when there is adequate training in the technique and in the absence of contraindications. It leads to reduced morbidity, improved tolerance and the same oncological outcome. Evidence IC. [31]

Complicated tumors will be discussed in a separate chapter, but in general we will say that obstructive cancers can be treated in one, two, or three stages. Two-stage procedures include primary resection with protective colostomy followed by closure of the ostomy, or a Hartmann procedure followed by restoration of intestinal continuity, in the case of an obstruction with deterioration of general condition or intestinal perforation. The one-stage procedure is preferred if the patient's condition permits it and the experience of the team is adequate. Subtotal colectomy or segmental resection after intraoperative colonic lavage are alternatives in selected cases. Evidence III.[31,32]

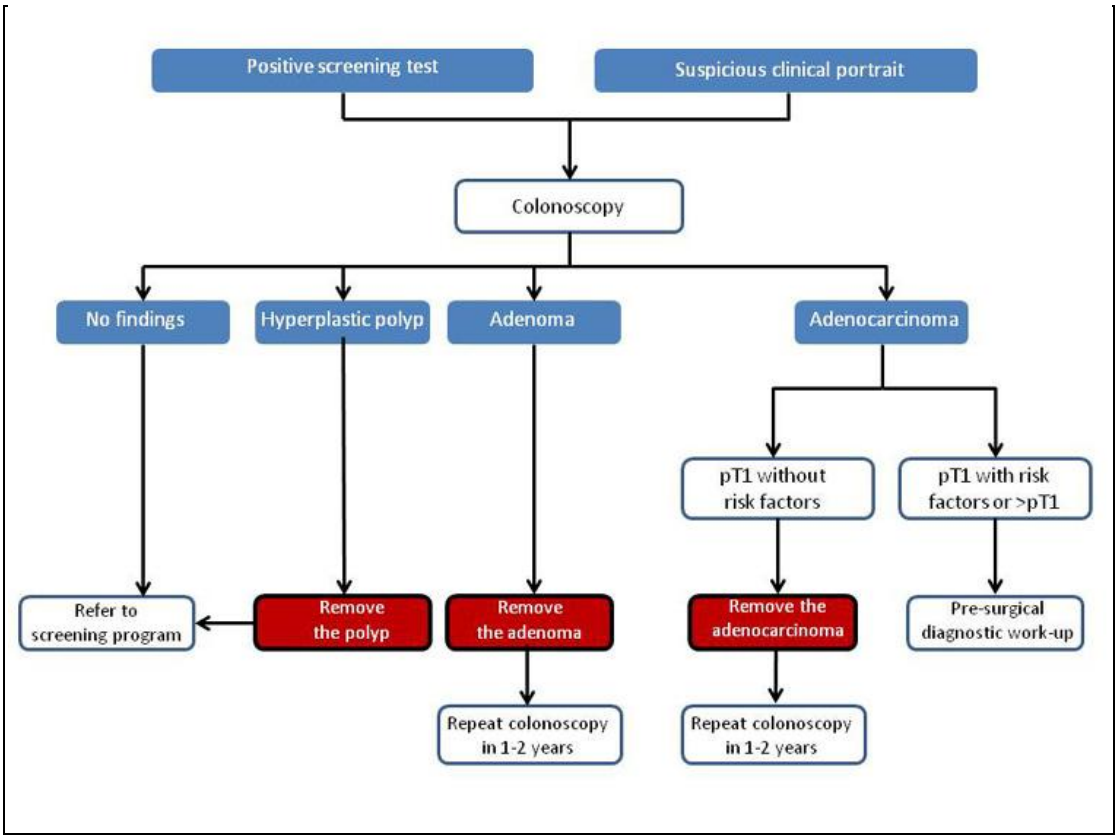


Figure 4.4. *Treatment regimen for benign polyps, and pT1 malignant polyps with and without histological risk factors.*

Final recommendations

- En bloc endoscopic resection is sufficient for polyps with noninvasive adenocarcinoma (pTis, intraepithelial, intramucosal). Evidence IVB.
- The presence of invasive cancer in a polyp requires review by the surgeon, endoscopist, and pathologist.
- The presence of high-risk factors indicates surgical resection of the colon segment plus lymphadenectomy.
- High-risk factors include: lymphatic invasion, venous invasion, grade III cell differentiation, significant tumor budding. Evidence 4B.
- Laparoscopic colectomy is safe in terms of morbidity, tolerance, and oncologic progression. Evidence IC.

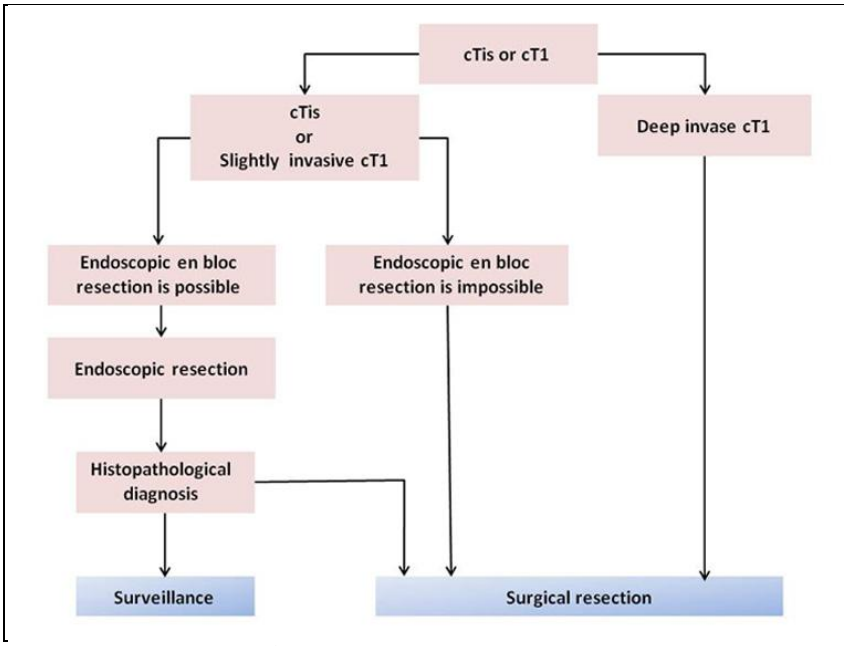


Figure 4.5. *Surgical treatment of noninvasive (cTis) and invasive (cT1) early colorectal epithelial lesions.*

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CHAPTER 5
Surgical treatment: general concepts

Time of surgery

Curative intent colectomy should be performed without delay after diagnosis. Evidence IC.[1] According to a retrospective analysis by Surveillance, Epidemiology and End Results (SEER) and the National Cancer Database, delaying surgery by 3 to 6 weeks was associated with decreased OS. However, a Canadian population-based retrospective study indicated that delaying surgery by up to 12 weeks does not affect disease free survival (DFS) or overall survival (OS).[1,2]

Since a specific interval for the timing of surgery cannot be established and evidence supports that untreated cancer progresses over time, surgery should be performed without delay.

Once surgery has been decided, surgical exploration includes visual inspection, and in open surgery, palpation to detect synchronous lesions or more advanced malignant disease, for example involvement of neighbouring organs or peritoneal metastases. If the latter are identified incidentally, a biopsy is recommended to confirm the diagnosis and ideally classify them according to the *peritoneal cancer index*.

In the event of obstruction or perforation, both colectomy and cytoreduction surgery should be deferred for a multidisciplinary discussion of the best therapeutic option.

For this reason, a thorough examination should be performed at the time of surgery and documented in the procedure report. Evidence IC.[1]

Extent and type of resection

According to a recent study, the presentation was Stage I: 25.7%, Stage II: 17.4%, Stage III: 11.7% and Stage IV: 35.6%.[1–6] The extent and type of colon resection correspond to the lymphovascular drainage of the organ. Evidence 1B.[1]

The mesocolon to be resected corresponds to the primary nutrient vessel at its origin in order to remove the central and intermediate nodes. The resection must be performed preserving the integrity of the mesocolon. This concept will be developed in more detail in the section on complete dissection of the mesocolon.

The number of lymph nodes removed has been associated with a change in survival, so their examination is important and should be performed as thoroughly as possible. Histopathological evaluation of at least 12 lymph nodes is recommended to classify tumors as N0. If fewer than 12 nodes are examined, the cancer is considered Stage II high-risk.[3,6]

The most commonly used surgical procedures are hemicolectomy and subtotal colectomy, followed by partial or segmental colectomy. In an institutional experience, the Italian Hospital of Buenos Aires reported 1549 consecutive patients operated on in 25 years: 528 right colectomies, 79 extended right colectomies, 556 left colectomies, 18 anterior resections and 74 subtotal colectomies. Resectability was 95.8% and primary anastomosis was performed in 97.4%. Postoperative morbidity was 18.6%, anastomotic dehiscence 1.4% and mortality 3.4%.[7]

Resection margins

Treatment of both the distal and proximal margins should be considered. Nodal metastases occur along the marginal artery in the epicolic and paracolic nodes, followed by the intermediate and apical or central nodes at the origin of the main artery. The oncologic outcome depends on whether colectomy ensures radical nodal resection. Historically, a 5-cm margin on either side of the lesion was considered sufficient.[8] However, today, to achieve adequate total mesocolonic excision with or without D3 lymphadenectomy, this margin must be wider and reach a minimum of 10 cm on either side. These concepts are developed in more detail in Chapter 6.

Vascular anatomy

The small intestine, the right colon, and the proximal two-thirds of the transverse colon are supplied by the superior mesenteric artery, while the inferior mesenteric artery supplies blood from the distal segment of the transverse colon to the rectum. Anatomical vascular variability is present mainly on the right side, while on the left side it tends to be more constant. The ileocolic artery is constant, but may run anterior (17 to 83%) or posterior to the superior mesenteric vein. The right colic artery may arise from the ileocolic artery or the middle colic artery and is present in up to 60% of cases. It divides into right and left branches, both of which are inconstant and may be absent, double, or have an accessory artery.

There are several anatomical and clinical studies of vascular anatomy and its variants with the aim of determining preoperatively the type of resection to be performed.

Okazaki et al.[9] from the University of Tokyo studied the arteries of the transverse mesocolon and its equivalent in 60 cadavers using software. The arteries of the splenic flexure were evaluated, finding 34 arterial variations, most of which were from the superior mesenteric artery and the middle colic artery, with its typical course below the pancreas. Another arterial course was identified that originates behind the caudal pancreas, crosses the mesocolon and moves away from the pancreas to head towards the splenic flexure. The course could not be determined by tomography. It was concluded that for the first time two types of arterial courses were shown towards the splenic flexure (below the pancreas and within the mesocolon). Complete excision of the mesocolon is probably performed more easily in the second variant.

Central vascular treatment

Central vascular ligation is key in the resection and oncological prognosis of colon cancer treatment. Its basis is the resection of all lymph nodes at the central level. According to Patrón Uriburu,10 central metastasis can occur in 11% of right colectomies and in 8.6% of left colectomies. There is a phenomenon called *skip metastasis* or discontinuous metastasis, which consists of the presence of central lymph node metastasis having skipped the intermediate lymph node stations, which occurs in approximately 2 to 4% of cases.

At this point it is important to remember that the dissection of the epicolic nodes is defined as D1, that of the intermediate nodes as D2 and the central one as D3.[11–13]

According to the available evidence, there is a direct relationship between the depth of invasion (T) and lymph node involvement (N). In T3 and T4 tumors, central lymph node metastases can be found in 8%, while they are almost nonexistent in T1 and T2 tumors. For some authors, resection of the central lymph node level has oncological results equivalent to curative resection of liver metastases.[14]

Lymph node dissection and lymphadenectomy

Theories on lymph node dissemination

The lymphatics follow the course of the arteries and the nodes are classified as epicolic (located in the wall of the colon), paracolic (along the marginal artery of Drummond), intermediate (arranged along the main vessels) and central (located at the origin of the superior and inferior mesenteric arteries).

To evaluate lymph node dissection, it is necessary to take into account the different theories that have been proposed to explain metastatic lymph node dissemination, namely:

- In 1907, Halsted assumed that the tumor spreads first to regional lymph nodes and then to different organs. This evolved into the concept of sentinel lymph node and its biopsy as a staging tool, particularly in the adjuvant setting of breast cancer.[15]
- Fisher believes that both lymph node dissemination and distant metastasis occur in early stages. However, the complexity of lymph node metastasis in colon cancer may not account for either of these cases.[16]
- Zhang in 2020 analyzed different routes of dissemination using genomic sequencing. Of 61 possible pathways of lymph node metastasis, 34% were *skip metastasis*.[17]

Types of lymph node dissection

The types of lymph node dissection according to the Japanese doctrine are:

- D1: Complete dissection of the epicolic lymph nodes along the colon and the paracolic nodes along the marginal artery, without dissection at the level of the intermediate and main arteries.
- D2: Complete dissection of D1 and of the intermediate lymph nodes along the main nutrient arteries (ileocolic, right colic, middle colic, left colic, sigmoid and inferior mesenteric artery from the origin of the left colic artery to the origin of the last sigmoid artery).
- D3: Complete dissection of D1, D2 and of the central lymph nodes. For left-sided tumors, lymph nodes are resected along the inferior mesenteric artery between the aorta and left colic artery and for right-sided tumors and those medial to the transverse colon, lymph nodes are resected along the superior mesenteric vein and lateral to the superior mesenteric artery.
- D4: Complete dissection D1 to D3, along the aorta and inferior vena cava or the superior mesenteric artery, superior mesenteric vein, central to the origin of the middle colic artery. An alternative definition of lymph node involvement includes:
- N1 (+): Metastatic lymph nodes in area D1, within 5 cm proximal and distal to the tumor margins.
- N2 (+): Metastatic lymph nodes in area D2, greater than 5 cm proximal and distal to the tumor.
- N3 (+): Metastatic lymph nodes in area D3.
- N4 (+): Metastatic lymph nodes in area D4 (consider distant metastasis).

According to the Japanese Society for CRC guidelines, mesocolic regional lymph nodes are classified as pericolic or D1 (confined to the marginal colic artery), intermediate or D2 (located along the trunks of the ileocolic, right colic, middle colic, left colic, sigmoid, and inferior mesenteric arteries), and apical or D3 (at the root of the ileocolic, right colic, middle colic, and inferior mesenteric arteries).[4]

Multiple centers are emphasizing the combination of central vascular ligation (D3 lymphadenectomy) and total mesocolon excision to achieve a better quality specimen and a better prognosis. The number of positive lymph nodes is a prognostic factor associated with stage, recurrence, and survival.

Rarely, lymph node metastases occur at sites distant from the primary tumor, with negative pericolic or intermediate nodes (*skip metastasis* described in gastric, thyroid, lung and breast cancer), which has a variable impact on survival depending on the type of cancer. Its incidence in colon cancer is variable, ranging from 2 to 9%, with some reports of up to 13.2%.[18–24]

For some authors, D3 lymphadenectomy in patients with Stage III is useful not only for lymph node staging but also to identify *skip metastases* to improve survival.[25–29]

Japanese guidelines classify lymph node involvement into three levels: L1 (epicolic and paracolic node involvement), L2 (intermediate node involvement), and L3 (central node involvement). In a study of 446 patients with stage III colon cancer, routine D3 lymphadenectomy found 6% L3, 25% L2, and 70% L1 involvement, with the number of nodes removed being 44, 40, and 42, respectively.[4]

According to ESMO and Japanese guidelines, the decision on the type of colectomy and corresponding lymphadenectomy is based on clinical findings, the presence of lymph nodes and the depth of tumor invasion, observed preoperatively.[3,4] The recommendations of the Japanese guidelines on the type of dissection indicated according to the depth of tumor invasion and lymph node involvement are detailed in Figure 5.1.

Lymph node metastases outside the standard resection territory occur in 3 to 11% and are more frequent in advanced stage tumors.

Central lymph node involvement in the absence of pericolic or intermediate lymph node involvement (*skip metastasis*) occurs in up to 4% of cases.[4,19,30]

According to a study from Taiwan, the group of tumors with *skip metastasis* had a worse prognosis in pN1 tumors.31 In the pN2 stage, a worse survival rate was not evident between both groups. Furthermore, in pN1 tumors the lymph node ratio (LNR) could be less important than the location of the positive node in the mesocolon. On the contrary, in pN2 tumors the LNR could be interpreted as a greater tumor volume in the lymph nodes and affect the lymph node distribution more strongly.

Extended lymphadenectomy with central vascular ligation (D3 resection) has demonstrated higher LNR and probable improvement in pN staging, but is also associated with increased intra- and postoperative complications. Furthermore, observational studies and meta-analyses suggest that extended lymphadenectomy decreases the incidence of colon cancer recurrence and improves recurrence-free survival.[28] In contrast, other studies have failed to determine survival benefits.[30] The ASCRS practice guidelines do not recommend routine extended lymphadenectomy, but rather selective dissection of clinically positive or suspicious nodes located outside the site of routine lymphatic drainage. Evidence 2B.[1,2] The term “complete mesocolon excision” is not synonymous with D3, but refers to the integrity of the mesocolon and its surrounding peritoneal layer after resection. That is, it refers to the type of resection and does not designate a specific level of vascular ligation or lymph node dissection.

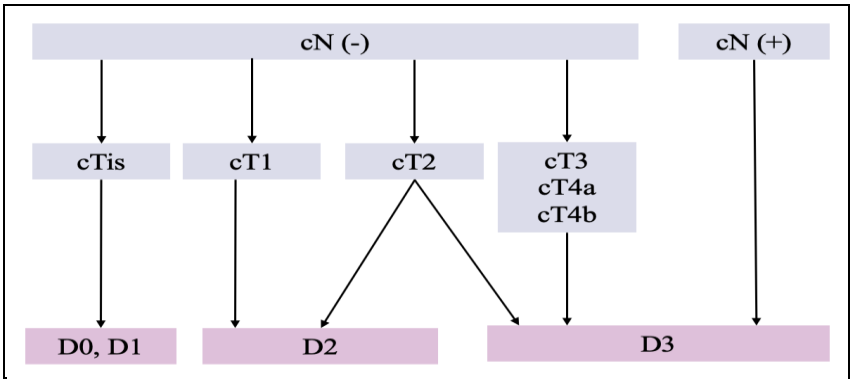

Figure 5.1. *Dissection according to preoperative T and N staging, recommended by Japanese guidelines.*[19]

Indications for the type of dissection according to the tumor stage

According to Japanese guidelines, for cTis tumors the recommended dissection is D0, since they do not present lymphatic metastases. However, if for some reason a colectomy is performed to treat a Tis, the D1 dissection is sufficient. The D2 dissection is recommended for cT1 tumors, since in these the incidence of lymphatic involvement is 10% and approximately 2% present involvement of the intermediate nodes. For cT2 tumors, despite the scarce evidence, it is recommended to perform at least a D2 dissection. However, a D3 dissection may also be indicated since approximately 1% are accompanied by positive main nodes and the exact determination of the depth of tumor invasion with the available study methods is incomplete. For tumors clinically classified as T3, T4a and T4b, colectomy should be associated with a D3 dissection.[4] The distribution of the three lymph node stations of the right and left colon is schematized in Fig. 5.2.

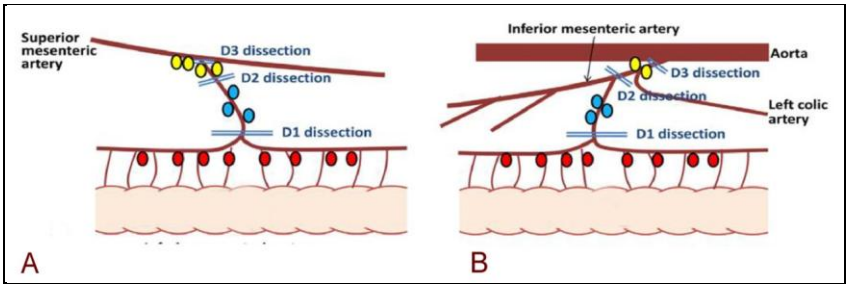

Figure 5.2. *Lymph node stations for right and left sided tumors.*

If macroscopic or suspicious lymph nodes are present as an intraoperative finding, the Japanese guidelines recommend performing a D3 dissection. If there are no visible or identifiable lymph nodes on intraoperative or preoperative studies, the lymphatic dissection to be performed should be based on the depth of the tumor. These guidelines detail the incidence of lymphatic metastases according to the depth of invasion.[4]

In D1, D2, and D3 dissections, resection of the colonic margins is determined by pericolic lymphadenectomy. This lymphadenectomy is defined by the positional relationship between the primary tumor and the feeding artery. Lymphatic metastases at a distance of 10 cm or more from the tumor edge are rare. A Japanese multicenter nationwide study investigating the distance between the primary tumor and lymphatic metastases is ongoing. Unlike what occurs in the rectum, in the colon there is no evidence on the distribution of lymphatic metastases in T4, N2 and M1 tumors, which are usually located at a significant distance from the primary tumor.

Unlike what the Japanese guidelines recommend, for other authors and guidelines there is no clear evidence on what type of lymphadenectomy to perform according to the location of the tumor and the corresponding lymphatic territory. The main controversy exists in the indication of a D2 or D3 type dissection. There is a direct relationship between the number of resected nodes, the involved nodes and survival; the greater the number of resected nodes, the greater the survival. While the Japanese guidelines recommend extended D3 type lymphadenectomies as the standard for tumors ≥ T3 without taking into account node involvement, in the West this is not a standard procedure.

Laparoscopic surgery for transverse colon cancer may be a feasible technique. In a retrospective study from a Japanese center, 252 patients who underwent laparoscopic surgery for transverse colon cancer were analyzed. The transverse colon was divided into 3 segments by performing a right colectomy, a transverse colectomy, and a left colectomy. The frequency of metastatic lymph nodes was 28.2, 19.2, and 19.2%. *Skip metastases* occurred in right- and left-sided transverse colon cancer, but not in the middle segment. The 5-year OS rate was 96.3, 92.7, and 93.7%, and the relapse-free survival rates were 92.4, 88.3, and 95.5%, respectively. In multivariate analysis, the only independent risk factor for recurrence-free survival was the absence of lymph node metastasis.[32]

The oncologic outcomes of D3 dissections have been encouraging. A 5-year OS of 90.4% was reported with open surgery and 91.4% with laparoscopic surgery. Laparoscopic D3 resection was noninferior to conventional resection in terms of OS for patients with Stage II and III colon cancer.

OS was similar and better than expected, so laparoscopic surgery might be acceptable for the suggested treatment.[33,34]

The COLD trial[35] compared D2 and D3 dissection, demonstrating that the latter is a feasible and safe technique, with similar 30-day morbidity and better surgical specimen quality. For Patrón Uriburu et al.[10] it would be sufficient to perform an adequate D2 dissection in all cases and reserve a D3 dissection for selected cases.

In a conference given at the Argentine Academy of Surgery, Vaccaro[36] concludes in his final comments:

- An adequate D2 dissection is associated with a low local recurrence and it is advisable to audit one's own results.
- D3 dissection is safe when performed by experts, with no advantages to date in Stages I and II.
- The overall advantage is controversial, with contradictory evidence in non-systematized D2 dissections.
- Not all Stage III would benefit, considering tumor biology, aggressiveness and response to chemotherapy.
- Systematic use in groups with good results implies a high number of patients to treat without clear evidence.
- Selective use by experts could be justified in young patients with advanced tumors.

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CHAPTER 6
Surgical treatment: complete mesocolic lymphatic excision

Complete mesocolic excision is a precise embryologic dissection that includes the visceral and parietal peritoneal layers and preserves the mesocolon with its peritoneal envelope and colonic fascia in a manner similar to total mesorectal resection (TME).[1] It is a complete oncological resection, which includes the colon and the peritoneal embryological envelope, with the perineural and lymphovascular structures of the mesenchyme. According to Patrón Uriburu,[2] two types of visceral fascia must be distinguished: the colonic fascia, which is the fusion of Toldt's fascia and the colon, and the mesocolic fascia, the fusion of Toldt's fascia and the mesocolon. There is also a parietal fascia known as the retroperitoneal fascia or Toldt's fascia that covers the retroperitoneum. The fusion plane of the visceral and parietal fascia is the dissection site. The concept includes an anatomical, embryological and oncological dissection, with resection of both the lymphovascular-neural structures of the mesocolon and the retroperitoneum. Since there is no interconnection between the two, the preservation of the fascia is essential to prevent the dissemination of tumor cells. This situation only occurs in tumors with invasion ≥ T3. Like the mesorectum, the mesocolon is currently considered an associated but distinct organ from the colon. There are some differences between the right and left mesocolon, such as the existing peritoneal windows on the right side (e.g. duodenal window) and the greater thickness of fat on the left side. The concept of partial or total, right or left mesocolectomy is supported by some authors.[3–5]

The literature reports a slightly better prognosis in right-sided stage II tumors, given the high prevalence of microsatellite instability-high (MSI-H) in them, while stage III tumors have a worse prognosis. Likewise, some studies have reported lower DFS in right-sided tumors that received chemotherapy and in metastatic tumors, compared to left-sided tumors. In the 1990s, rectal cancer had a poor prognosis due to a high rate of local recurrence. In 1988, Heald et al.[1] introduced the concept of total mesorectal excision (TME) based on a dissection that follows the anatomical and embryological planes. TME provides a surgical specimen with intact coverage not only of the tumor but also of the mesorectal fat with its lymphatics and nodes. It has also been shown that results have improved with standardization, so that rectal cancer surgery has experienced a significant reduction in recurrence and an improvement in OS.

In 2009, Hohenberger et al.[6] reported improved outcomes in patients with right-sided tumors undergoing complete mesocolon excision (CME) using the same principles as TME. Thus, a new concept for right colectomy was introduced based on 3 main aspects: 1) dissection of the embryological planes to completely remove the envelope containing the mesocolon with the tumor-related lymph nodes, 2) central vascular ligation to remove the major tumor-related lymph nodes in a central direction, and 3) resection of a sufficient length of colon to remove pericolic lymph nodes. Figure 6.1 shows the different groups of lymph nodes that may be affected.

The goals of CME are to reduce local recurrence and improve survival. The rationale is that lymph nodes follow the distribution of arteries and negative lymph node count correlates with survival. Furthermore, the ratio of the number of metastatic nodes to the total lymph node count, known as lymph node ratio (LNR), has been shown to be an even better prognostic factor than the rate of affected lymph nodes (pN stage) alone.[7]

Some studies have questioned the minimum number of 12 lymph nodes removed to define an oncologically successful surgery, particularly in the presence of an adequate resection with a good lymph node count, so it is difficult to define a limit number of lymph nodes to be resected based on the quality of the surgery.[8]

Some studies have failed to demonstrate that performing high ligations without removing the entire mesocolon ensures a greater number of lymph nodes and improves survival. Others have argued that metastatic lymph nodes outside the resection territory would behave as distant metastases and that the extent of resection would have no influence on survival and would be associated with a poor oncological outcome.[8–10]

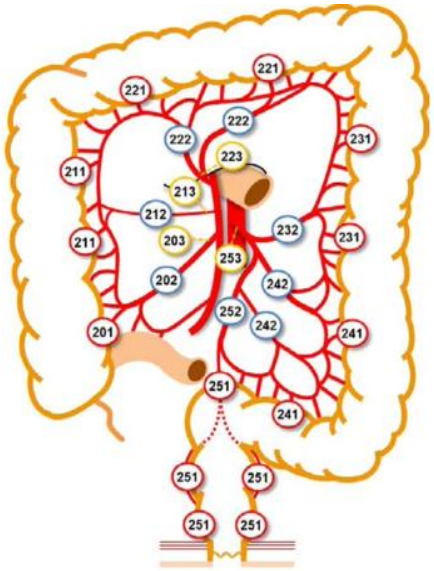

Figure 6.1. *Lymph node groups according to the Japanese Colon Cancer Society.*

Multiple authors advocate establishing CME as the standard of care for right-sided colon tumors, based on existing evidence of a potentially better oncologic outcome, with the same morbidity and mortality as traditional colectomy. This is due to better lymph node dissection, which could include remote lymph nodes and those located in major arteries, such as the superior mesenteric artery.[11,12]

Nicholas West, a digestive pathologist and Hohenberger defined the morphology or morphometry of the specimen consisting of 4 components:[7,13]

1. Distance between the tumor and the highest vascular ligation.
2. Distance between the colon wall and the highest vascular ligation.
3. Length of the removed intestine.
4. Surface of the mesocolon.

This was the conclusion of a retrospective study that demonstrated a 27% advantage in 5-year survival for patients with stage III colon cancer resected by mesocolon plane dissection.[13]

Many studies have shown that colon cancer survival is related to the number of lymph nodes removed. Chen et al.[14] reported that resection of 15 or more nodes increased survival by 11 months in stage I patients, 54 months in stage II patients, and 21 months in stage III patients, so they concluded that it is necessary to remove at least 15 nodes in right-sided colon tumors. Chen said, *"I would recommend*

surgeons to remember that the number of nodes makes a difference"

Prandi et al.[15] demonstrated a direct relationship between the number of lymph nodes removed and survival, which was even higher in stage II (pN0). Swanson et al.16 demonstrated that the prognosis of T3N0 tumors is dependent on the number of nodes examined. Le Voyer et al.[17] demonstrated that not only the number of nodes is important, but even the number of negative nodes is related to the prognosis.

Kataoka et al.[18] argue that right-sided colon cancer has higher *skip metastasis* rates than left-sided colon cancer, confirming the previous finding by Nagasaki et al.[19] of greater central lymph node involvement in right-sided tumors. In their study of 4034 patients with stage III colon cancer (1618 right and 2416 left), they concluded that there are significant differences in the pattern of lymph node invasion and prognosis between both sides of the colon, suggesting that laterality might define the surgical approach. Patients with right-sided colon cancer compared with those with left-sided colon cancer had greater L3 lymph node involvement (8.5 vs. 3.7%) and greater discontinuous lymph node spread between levels (13.7 vs. 9%). In multivariate analysis, L3 lymph node invasion was associated with worse OS in left-sided colon cancer but not in right-sided colon cancer.

Nagasaki et al.[19] identified for D1, D2 and D3 an incidence of lymph node involvement of 67, 27.4 and 5.6% and a 5-year DFS of 82.8, 65.4 and 52%, respectively, with a highly significant difference. Multivariate analysis demonstrated that D2 lymph node involvement was an independent prognostic factor for recurrence-free survival. The 5-year recurrence-free survival between pN1 patients with D1 vs. D2+D3 was significantly different (84.4 vs. 71.5%) and a similar trend was presented by pN2 patients (72 vs. 53%), concluding that the high survival in stage III, even in patients with D2 and D3, would justify standard central vascular ligation for advanced colon cancer.

A study conducted at a low-volume center in Italy has shown that CME is feasible and safe and results in higher lymph node counts and longer specimen length, without increasing surgical time or morbidity.[20]

Between 2006 and 2015, 461 cases of stage III pN1 colon cancer were retrospectively reviewed at a center in Taiwan, where patients with lymph node metastasis accounted for 13.2%. Patients with discontinuous lymph node metastasis tended to have a higher proportion of right colon cancer, a lower number of positive lymph nodes, and a lower LNR, with a higher average body mass index. Liver recurrences were more prevalent in the discontinuous metastasis group (p = 0.028). The presence of discontinuous metastasis was a negative prognostic factor for 5-year recurrence-free survival (51.4 vs. 68.7%; p = 0.002) and 5-year OS (66.4 vs. 80.4%; p = 0.024). Subgroup analysis revealed the significance of recurrence-free survival (p = 0.001) and OS (p = 0.011) in cases with discontinuous metastases with pN1 disease. They conclude that discontinuous lymph node metastases are an independent negative prognostic factor in cases of stage III colon cancer with pN1 disease.[21]

The concept of surgical dissection by embryologic and fascial planes allows the resection of an intact mesocolon containing lymph nodes, a key point of CME. This approach would allow not only the recovery of lymph nodes but also the reduction of the dissemination of neoplastic cells.6 In addition, a better OS and prognosis of patients with intact mesocolon and stage III have been demonstrated.[7]

Hohenberger et al.[6] studied 1329 patients with colon cancer and compared two groups, one operated on between 1978 and 1984 without CME vs. another operated on between 1995 and 2002 with CME. Local recurrence was 6.5 vs. 3.6% and DFS was 82 vs. 89%. The Danish registry shows a high complication rate after CME. Berthelesen et al.[22] reported a significantly higher rate of superior mesenteric vein injury comparing CME with conventional surgery (1.7 vs. 0.2%), although the 90-day mortality was 6.2 vs. 4.9%, respectively. Intraoperative injuries, including superior mesenteric and splenic vein injury, were more common in the CME group (9.1 vs. 3.6%), as were sepsis and respiratory failure. This correlates with data from an Israeli study of 304 colectomies with a 10-year rate of superior mesenteric vein injury of 1.6%.[23]

Pelz et al.[24] reported a high rate of reinterventions (19%), with 5.5% postoperative complications, 1% anastomotic dehiscence, and 0.5% mortality.

In a multicenter randomized controlled trial (COLD trial), 100 patients (43 D2 and 56 D3) were studied. There was no mortality and morbidity at 30 days was 47 and 48%, respectively. The average number of lymph nodes removed was 26.6 and 27.8. 5% presented metastasis in D3 and it was never the only affected level. Positive N was more frequent in D3 (46 vs. 26%). It is concluded that D3 dissection is feasible and provides better lymph node staging.[11]

In another multicenter study of 17 hospitals in China (RELARC), 995 patients operated on between 2016 and 2019 (495 with CME and 500 with D2 dissection) were analyzed. There was no mortality and postoperative complications were 20% and 22%, respectively (p = NS), with more severe complications (Dindo III-IV) in the CME group (1 vs. 3%). Intraoperative complications were also more frequent in the CME group (3 vs. 1%). Central lymph node metastases were detected in 3% of D3 dissections, with no isolated central lymph node metastases found. Although CME may increase the risk of intraoperative vascular injury, it appears to be generally safe and feasible among experienced surgeons.[25] The low number of positive central nodes in D3 and the high rate of incomplete mesocolon might provide uncertain clues as to whether D3+CME dissection is actually superior given that the Chinese study found a better lymph node harvest in D2 dissections. Table 6.1 shows a comparison of the data found in the COLD and RELARC trials.

In 2022, a systematic review evaluated the definitions and steps of D3 lymphadenectomy and CME for right radical colectomy, concluding that the only universally accepted step is high arterial ligation, while there is great heterogeneity in the other steps and definitions.[26]

Table 6.1. Comparative analysis between the results of the COLD and RELARC trials.

Trial	**COLD TRIAL**		**RELARC TRIAL**	
LD	**D2**	**D3**	**D2**	**D3**
N	43	56	500	495
BMI	27	27	23	23
N	27	28	23	26
D3+	0	7%	0	3%

LD: lymphadenectomy. BMI: body mass index.

A 2021 meta-analysis of 27 studies with 19,989 patients found a higher rate of postoperative adverse events in the CME group, with no differences in anastomotic leaks or perioperative complications. CME had higher lymph node harvesting, longer length of removed colon and mesocolon, and positive effects on overall survival and 3-year disease-free survival, with decreased local and distant recurrence. It concluded that, despite limited evidence, CME improves oncologic outcome, albeit with a higher rate of adverse events.[27] In another meta-analysis, 7 articles out of 714 articles with a total of 1368 patients were included, compar-

ing D2 and D3 lymphadenectomies. D3 was found to improve outcomes in terms of blood loss, lymph node salvage, and 5-year overall survival. There were no differences in operative time, anastomotic dehiscence, wound infection, general morbidity, hospital stay, mortality, duration of resected colon, and 3-year overall disease-free survival. This review suggests that D3 lymphadenectomy is superior to D2, although it recommends careful consideration of this conclusion given the limited evidence available and the need for further randomized controlled trials.[28] As mentioned above, the rate of central lymph node metastasis varies from 0 to 18%, which would support the determination of CME+CVL as the gold standard. Studies have shown that when there is N3 involvement, N1 and N2 are also positive. Furthermore, there is variation in the rate of central lymph node metastasis between different segments of the right colon, being found in 0% of the cecum tumors, 4% of the ascending colon and 8% of the right transverse colon.[22]

The international prospective study of 4000 patients at 36 institutions, *Cohort for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer or T-Rex*, is ongoing and will provide fundamental information on the distribution of the pattern of lymphatic metastases.[29]

In a recent Italian multicenter randomized controlled trial, including 258 patients from 9 centers, the number of lymph nodes retrieved was significantly higher after CME (25 vs. 20%). There were no differences in intra- or postoperative complications, mortality, and duration of surgery, with a shorter hospital stay for the CME group. Survival rates are pending. To date, CME in right-sided colon cancer operated on at referral centers has been shown to be safe and feasible and does not increase perioperative complications. It also documented that the quality of surgery and lymph node recovery are higher after CME.[30]

According to SEER, in 83,000 patients the 5-year DFS for all stages was greater than 80%, except for Stage IV (48%).[31] In a study from the National Cancer Database, 379,785 patients had an OS at 3 and 5 years of 61% and 51%, respectively.[32] Yu et al.[33] documented a 5-year DFS of 68% with standard colectomy (92.8% in EI, 85% in EII, 64.9% in EIII, and 11.2% in EIV). The 3- and 5-year survival rates reported by the CME studies were 89.6 and 82.8%, higher than those reported for conventional right colectomies.

There are several studies, some retrospective, showing that prognosis is related to the pattern of lymph node metastasis and that metastases at level 223 (right colic root) are rare. In one study, they occurred in only 1.8% of patients and all those with metastases at level 223 had regional metastases in other lymph node groups.

Furthermore, metastases at this level are the only independent risk factor related to DFS. Metastases at level D3 occur at an advanced stage of the disease in patients with cecal cancer, so CME would be too extensive in most cases for a proximal right colon cancer.[34]

Park et al.[35] reported 6.1% of lymph node metastasis along the right branch of the middle colic artery in cecal cancer..

A retrospective study of 2084 cancers of the cecum and ascending colon demonstrated no benefit from extended mesocolic resection, indicating that there is no need to include the middle colic vessels in their resection.[36]

A systematic review and meta-analysis of 17 studies indicated that the existing evidence did not demonstrate oncological superiority of standard colectomy compared to CME in terms of survival. The described technique is not inferior in safety and achieves greater lymph node dissection. In addition, it is associated with better OS and DFS at 3 and 5 years.[37] Mazzarella et al.[38] performed a systematic review and meta-analysis of 30 studies, evaluating 5931 procedures with this technique and concluded that it does not increase the risk of postoperative complications and significantly improves long-term oncological outcome. It suggests that prospective, multicenter, randomized studies should be awaited before considering this procedure as the standard of care.

Therefore, it is not yet conclusive to consider CME with high vascular ligation to be adequate in oncological terms for right-sided colon cancer. In fact, it could be adequate for tumors of the ascending colon or hepatic flexure, while considering it as a standard for those of the cecum could be excessive.

Bertani, from the European Institute of Oncology concludes in his editorial that despite the wonderful videos of the technique available on the web, adoption of CME should be limited to high-volume centers and in licensed programs until it demonstrates its superiority in long-term oncologic outcomes.[39]

Evidence from the extensive literature that CME may improve survival and oncologic prognosis appears promising. However, to date the quality of the evidence is limited and does not support CME as a standard tactic to replace conventional colectomy.

Although the benefits remain tempting, better designed studies are needed to justify the learning curve, risks and effort required to perform CME, especially when its benefit may be limited to a carefully selected group of patients.

Training

When colon resections performed by general surgeons and trained colorectal surgeons are compared, the latter are found to be associated with significantly better postoperative outcomes, with low perioperative morbidity and mortality rates.[40,41]

This fact is not exclusive for the performance of CME and D3 dissection.[42,43] Skill assessments have shown that competence in laparoscopic D3+CME can be achieved after 20 to 30 cases, even in previously trained surgeons. This consideration is critical given that the majority of colorectal procedures are performed by general surgeons and for multiple indications depending on the context.

Surgical protocol or surgeon's report

The surgical procedure should be well documented and include a description of the intraoperative findings: presence of synchronous metastases or macroscopic involvement of mesocolic or mesenteric lymph nodes, tumor location, and involvement of adjacent organs. The type of incision, presence or absence of adhesions, extent of colon and small bowel resection, level of vascular ligation, anastomotic technique, en bloc resection of neighboring organs, and intraoperative assessment of resection margins should also be described. The use of standardized protocols improves documentation. Those currently developed by the American College of Surgeons Commission on Cancer are recommended.

Conclusions and new concepts

In summary, the surgical technique of a colectomy is currently based on two basic concepts:
- A correct anatomical dissection: equivalent to the embryological dissection proposed by Hohenberger, West et al. (complete removal of the mesocolon).
- An adequate oncological dissection: dissection and resection of D2 or D3 lymph nodes, depending on the depth of the tumor and its stage.

Recently, a more integrative concept has been proposed that would unify these criteria: Tumor-Specific Mesocolic Excision (TSME) or Complete Mesocolic Lymph Node Dissection (CMLND). This nomenclature includes a complete individualized removal of the mesocolic lymph nodes, depending on the location of the tumor and the vascular anatomy, which ensures the radicality of the resection, the corresponding lymphadenectomy and the adequate margins.[44]

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CHAPTER 7
Surgical treatment: minimally invasive surgery

More than 3 decades have passed since Jacobs and Plasencia[1] first reported on laparoscopic colectomy for colon cancer.

The history of minimally invasive surgery in colon cancer has been negatively impacted by numerous reports of isolated cases of tumor implants at the trocar site or in the incision for the extraction of the surgical specimen. This situation has caused many groups not to adopt the technique and has forced a detailed analysis of this approach.[2]

Minimally invasive surgical procedures include multiport, single-port, hand-assisted laparoscopic surgery, and robotic surgery. This approach can achieve the same goals as open surgery.

Indications for laparoscopic surgery are determined by the experience of the surgeon and the care center, the characteristics of the tumor (location, degree of disease progression, and its response to previous treatment), and patient factors (obesity, history of previous surgeries).

There is evidence that the magnitude of the resected specimen is similar, both in the extent of the margins and in the number of nodes removed.[3]

A study by Bokey et al.,[4] demonstrated in 61 cases that laparoscopic right hemicolectomy for cancer does not differ from conventional surgery in mean proximal (10.1 vs 11.9 cm) and distal (10 vs 13.4 cm) resection margins or in the number of lymph nodes removed. Multiple multi-institutional randomized trials from centers and surgeons trained in the United States and around the world have demonstrated an oncologic outcome equivalent to open surgery, with a decrease in hospital stay and better short-term results.[5,6]

The proven advantages of laparoscopic surgery over conventional surgery are reduced postoperative pain, hospital stay, and postoperative ileus. While Japanese guidelines recommend laparoscopic surgery as an acceptable treatment for colon cancer, NCCN and ESMO recommend it in limited cases without advanced local disease, bowel obstruction, or tumor perforation.

The rate of parietal implants reported in various series is highly variable and ranges from 0 to 21%. The period of appearance of metastases ranges from 7 days to 24 months.[2] Cutaneous implants are also observed in laparoscopic surgery of other affected organs (pancreas, ovary, gallbladder) and the common factor is the surgical technique. Observational studies and meta-analyses on single-port vs. multiport technique have demonstrated equivalent surgical and oncologic outcomes.[7,8] There is no difference in operative time, number of lymph nodes removed, length of resection, and postoperative complications.[9]

Hand-assisted surgery for the treatment of right colon cancer has been evaluated in randomized controlled trials and its comparison with classical laparoscopic surgery has shown similar short-term results. Compared with open surgery, it was associated with less pain and better recovery, with no long-term oncological differences.[10,11]

Comparison of robotic surgery with laparoscopic surgery for the treatment of right colon cancer indicates no differences in postoperative morbidity and short-term oncological progression, although robotics requires longer operating times and higher costs.[12]

In an early retrospective study, Salomon[13] compared 92 patients operated on for CRC, 46 by laparoscopy and 46 by conventional surgery. The conversion rate was 8.7%. The hospital stay for laparoscopy was shorter and there were no differences in the number of lymph nodes removed, recurrence and overall survival. No implants were reported. In a later study, they compared 170 patients, 49% with cancer. They found no metastases at the trocar sites and survival was similar in both groups.

Rossi et al.[14] analyzed the results of their initial experience in laparoscopic colorectal surgery. Of their first 100 laparoscopic surgeries, 39% were for cancer. Conversion was 17%, operating time 240 minutes, hospital stay 3 days, morbidity 14%, and mortality 1%. They have established this approach as their preferred approach ever since.

Rotholz,[15] together with the group from the Hospital Alemán of Buenos Aires, among their multiple publications on laparoscopic colorectal surgery, reported a feasibility study on sentinel node research, the performance of which is neither standard nor recommended. They identified 91% of the nodes, with a sensitivity and specificity of 100%.

Therefore, it is stated that when there is training and resources available, it is preferable to perform colectomy for colon cancer using a selective minimally invasive approach. Evidence IA.[3]

Operating time

Although increased operating time in colorectal surgery is associated with worse surgical outcomes, laparoscopic and robotic operations have improved outcomes despite longer operating times. However, "prolonged" operating time has not been consistently defined.

A very recent retrospective cohort study of 42 hospitals included 23,098 adult patients who underwent six elective colorectal surgical procedures (right colectomy, left/sigmoid colectomy, total colectomy, low anterior resection, ileal pouch-anal anastomosis, and abdominoperineal resection) performed by open, laparoscopic, or robotic approaches between 2011 and 2019. Operative time was 7 vs. 5 days in the open approach, 5 vs. 4 days in the laparoscopic approaches, and 4 vs. 3 days in the robotic approach. Complications occurred in 42 vs. 28% in the open approach, 24 vs. 17% in the laparoscopic approach, and 27 vs. 13% in the robotic approach, and hospital discharge was similar in the 3 groups. It was concluded that prolonged operating time is associated with a longer hospital stay and a higher probability of complications, although this negative effect is reduced with minimally invasive approaches.[16]

The advantages of the multiport laparoscopic approach apply to the surgical treatment of all segments of the colon for cancer.

The conversion rate from minimally invasive to open surgery has decreased over time, from 12% to 10% in the right colon and from 11.9% to 9.9% in the left colon. The number of lymph nodes removed has also increased and the incidence of involved surgical margins has decreased.[3,13]

Laparoscopy in the emergency setting

In a nationwide observational study, 158 patients undergoing laparoscopic resection were compared with 474 patients undergoing open resection in an emergency setting between 2009 and 2016. At 90 days, laparoscopy had significantly fewer complications (26.6 vs 38.4%, OR 0.59, 95% CI 0.39–0.87) and similar mortality. At 3 years, laparoscopy resulted in better OS (81 vs 69.4%, HR 0.54, 95% CI 0.37–0.79) and DFS (68.3 vs 52.3%, HR 0.64, 95% CI 0.47–0.87). Multivariate regression analyses of the 2002 unmatched patients confirmed an independent association of

laparoscopy with fewer 90-day complications and improved 3-year survival. It was concluded that intentional emergency laparoscopic resection might improve short- and long-term outcomes in patients with left-sided obstructive colon cancer compared with emergency open resection, which requires confirmation in future studies.[6]

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CHAPTER 8
Surgical treatment: robotic surgery

With the collaboration of Romina Bianchi, MD, MAAC, MSACP, FACS

The standard treatment for colon cancer is surgical resection. The advantages of the laparoscopic approach have been demonstrated in numerous publications when comparing short-term results. The benefits over open surgery are clear, taking into account the early recovery of bowel motility and the short hospital stay.[1,2] However, there are limitations associated with this approach, such as the high incidence of conversion to open surgery and the lack of evidence of superiority or non-inferiority observed in long-term oncological outcomes.[3–6]

Although the long-term superiority of the laparoscopic approach has not been demonstrated, its indication for patients with CRC has expanded worldwide over the past two decades. However, technical difficulties associated with this procedure have recently begun to be reported, mainly for the treatment of right-sided CRC.[7–9]

According to the 2020 annual report of the Japanese National Clinical Database, the rate of right hemicolectomy is only 54.2%, which is low compared with other procedures for CRC. The report also found that the 90-day postoperative mortality of right hemicolectomy is 2.2%, approximately 4 times higher than that of low anterior resection.[10]

With the advent and development of robotic-assisted surgery (RAS), it is hoped to overcome the disadvantages of conventional laparoscopic surgery, since with its three components (console, robotic cart and viewing tower), it allows the use of instruments with a greater range, rotation capacity (*endowrist*), multiple movements through the robotic arms and greater work stability without tremors due to stress or fatigue of the surgeon (Figs. 8.1 and 8.2). It also provides the possibility of performing delicate movements with greater skill, since the image is reproduced binocularly on the console by two 5 mm high-definition (3D) endocameras that also provide a stable view. All these factors make robotic surgery a more precise approach in trained hands that allows for obtaining a resection of oncological quality. This approach has gained popularity; although it was initially used for pathology confined to difficult-to-access spaces such as the pelvis, its results have led to its indication being extended to the rest of the pathology, especially CRC.[11–14]

Results using the da Vinci Xi system

The da Vinci Xi (dVXi) Surgical System is the fourth generation of the robotic platform from Intuitive Surgical, Inc. (Sunnyvale, CA, USA) and therefore the most developed and experienced, which attracted the attention of surgeons as soon as it was introduced to the market. This new system features increased versatility, including integrated table movement, more sophisticated arms, and complex imaging units that enable a wide range of colonic procedures, from complex multi-quadrant colectomies to intracorporeal anastomoses in a narrow space.[15]

Robots currently in development and new platforms

For a long time, robotics applied to colon surgery was synonymous with the da Vinci system. Currently, there are new robotic platforms that will grow in the near future, as several manufacturers are in different stages of either active development, launch, or awaiting regulatory approval.

MicroHand S, a surgical robot from China, has entered several clinical trials and some have already reported good performance and application prospects. Yi et al.[16] reported 10 surgical procedures with the aid of MicroHand S without intraoperative complications or technical problems. Luo et al.[17] retrospectively analyzed 45 patients with sigmoid colon cancer who underwent robotic surgery with MicroHand S or da Vinci. The da Vinci system did not demonstrate obvious clinical advantages compared with MicroHand S. In contrast, MicroHand S was associated with lower cost and shorter postoperative hospital stay.

The novel Senhance robotic system (TransEnterix Surgical Inc., Morrisville, North Carolina, USA) has been used in Europe and was approved for limited treatment in the USA. Samalavicius et al.[18] performed a prospective survey of the first 100 surgeries with this robotic system in Lithuania, demonstrating that its use is feasible and safe in general surgery. Hugo RAS from Medtronic Inc. (Dublin, Ireland) and Versius from CMR Surgical Ltd. (Cambridge, UK), the latter recently incorporated in our country, have demonstrated promising results in the clinical field. The emergence of new platforms increases competition and generates greater access to robotic surgery by reducing the costs of the different systems and simultaneously increasing their quality.[15]

Evolution of robotic surgery

Between 2012 and 2020, the use of robotic technology for colectomies has increased, with approximately one in four cases being performed this way. The US National Cancer Database has shown that robotic surgery for colon cancer is increasing rapidly, particularly in younger, healthier patients.[14,19] In Japan, RAS has had coverage since 2018, leading to a rapid increase in the number of robotic rectal surgeries.[20]

Only in March 2022, following the first prospective multicenter study examining the short-term outcomes of robotic-assisted colectomies (RAC) for colon cancer in Japan, did this approach begin to be covered in that country. In this study, which evaluated patients with resectable stage II-III colon cancer, the conversion rate to laparotomy was zero, indicating noninferiority and demonstrating the safety and feasibility of the approach.[21]

JCOG0404,[6] is a multicenter study that demonstrated non-inferiority of the laparoscopic approach in patients with stage II/III colon cancer compared to open surgery. This study determined that the conventional laparoscopic approach can be performed safely without increasing postoperative complications, although with longer operating times. Furthermore, it is associated with better recovery of bowel function, lower analgesic requirements, and shorter hospital stay. However, non-inferiority of the laparoscopic approach could not be demonstrated in long-term outcomes, with a survival rate of 90.4% in the open group comparable to 91.8% in the laparoscopic group. Despite the results of most studies, the favorable results made laparoscopic surgery an acceptable alternative.

When RAS was compared to this historical baseline, the data showed a conversion rate of zero, blood loss of 0 mL, complication rate of 4%, median operative time of 211 min, bowel transit recovery time of 3 days, and hospital stay of 6 days, all similar to previous studies.[21]

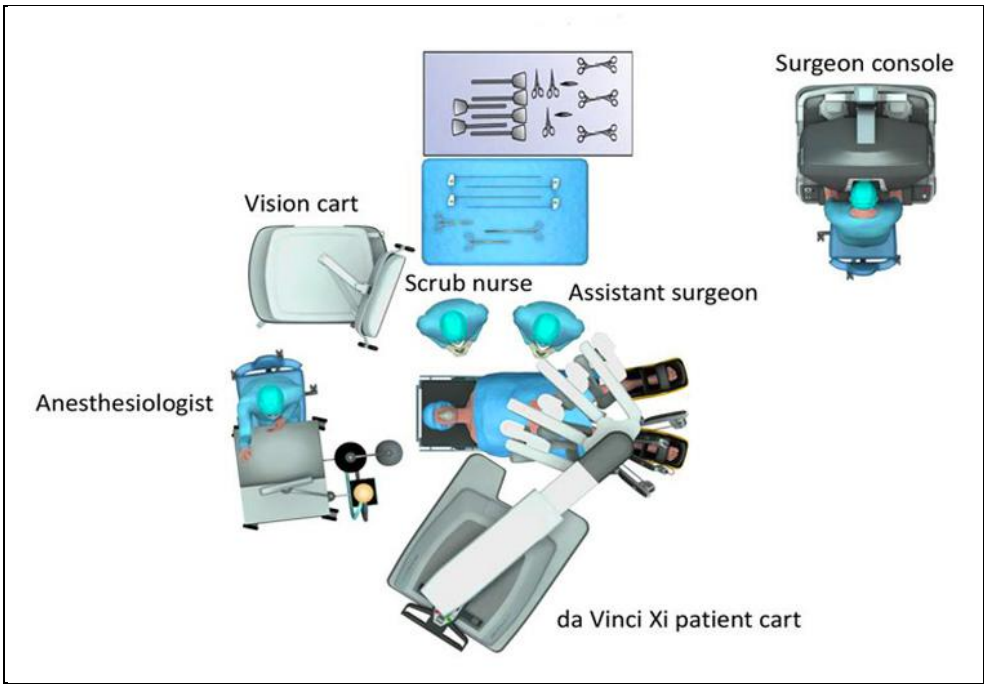

Figure 8.1. *Components and organization of the operating room for robotic colectomy.*

Figure 8.2. *Preoperative assembly. Operating table in Trendeleburg/Fowler >10º as required. Rotation >10º. Height of the operating table as low as possible. Implantation of the robotic system. Implantation of the robotic arms. Location of the laparoscope cart. Adjustment of the multiport and variation of the arms.*

Although long-term results are still expected, as patient registration was completed in 2022, the number of centers that started to introduce this approach is gradually increasing in Japan since it is covered by insurance. Although several studies have shown a lower conversion rate of RAC compared to laparoscopic colectomy (LC),[22] since robotics has just been introduced in Japan and is still in the learning curve stage, the study was designed to verify the non-inferiority of the safety of the new technology compared to existing ones.

Although most of the published works are retrospective, there are certain prospective results that jointly demonstrate less blood loss, lower intraoperative transfusion rate, lower conversion rate and fewer complications such as ileus and anastomotic leak, indicating better short-term results with the robotic approach.[23,24]

To date, there are few studies with significant evidence or that have evaluated oncological results. Park et al. found no short-[23] or long-term[25] differences between RAC and LS, although the sample analyzed was small. A more recent study that includes prospective data is that of Schootman et al.,[26] who used the American College of Surgeons database between 2013-2015 to compare 2233 cases of RAC vs. 10844 cases of LS, with adjustment for selection bias based on a propensity score. The results showed a lower conversion rate (5.7 vs. 18.6%; $p < 0.05$) and shorter hospital stay (5.1 vs. 5.3 days; $p < 0.05$) in the robotic group. Kulaylat et al.[27] used the same database and the same methods to compare 3864 cases of RAC vs. 40,063 cases of LS, and reported a significantly lower conversion rate in RAC (6 vs. 11.5%; $p < 0.001$).

Some meta-analyses suggest that robotic right hemicolectomy contributes to reduce the risk of conversion and has an earlier postoperative recovery.[22] Ma et al.[28] reported a longer hospital stay in the laparoscopic group and lower complication rate, less blood loss, shorter time to recovery of intestinal transit and lower conversion rate in the robotic group (OR 0.34; $p = 0.008$). Solaini et al.2[2] demonstrated a higher risk of conversion (RR 1.7; $p = 0.020$) and a longer time until recovery of bowel transit in LC.

Just as favorable long-term results of LC vs. open surgery have not yet been demonstrated, OS and DFS data provided to date are comparable between LC and RAC.

The true goal of surgery for malignant tumors is overall survival. However, a long period of observation is required before obtaining results. The conversion rate, which can be assessed in a short period, has served as a surrogate endpoint in certain studies and has been reported to be associated with postoperative complications, mortality, increased blood transfusions, and recurrence due to residual tumor.[29] Although several studies have shown a lower conversion rate in RAC compared with LC, in certain series, such as the Japanese one that is still in the learning curve, conversion rates were similar with both approaches.[9]

On the other hand, cost has not been analyzed in most studies. The disadvantages of robotic surgery are associated with longer operating time and costs, but these can be overcome by shortening operating time and decreasing the incidence of complications through improved surgeon skills.[26,27]

The advantages of the robotic approach include improved postoperative recovery and therefore shorter hospital stay, factors that should be taken into account when making a cost/benefit assessment. To determine the real disadvantages of the robotic approach, along with the longer operating time, variables such as the learning curve (inversely proportional to operating time) and long-term results should also be included. Comparative data between RAC and LC are shown in Table 8.1.

Table 8.1. Comparison of robot-assisted right (CDAR) and left (CIAR) colectomy with laparoscopic Colectomy (LC).

Comparison with CL	CDAR	CIAR
Advantages	- Lower conversion rate - Lower complication rate, including anastomotic leak - Greater number of lymph nodes removed	- Lower conversion rate - Better mobilization ofthe splenic flexure
Disadvantages	Higher cost	Higher cost
No differences	Long-term results	Complication rate

Optimizing robotic surgery

- Suprapubic surgical approach

Like any other approach, robotic surgery has been exploring trocar placement, depending not only on the available platform, but also on the location of the tumor. An optimal surgical approach can increase the fluidity of the operation and reduce the collision of the internal and external robotic arms, which directly impacts short- and long-term results.

In the suprapubic approach, especially applied in robotic right hemicolectomy (RRHC), colonic resection is performed with horizontal linear placement of ports in the suprapubic area (Fig. 8.3).

Hamilton et al.32 reviewed the techniques and perioperative outcomes using the dVXi and da Vinci Si (dVSi) systems, with either suprapubic port (SPP) or traditional placement in 138 patients undergoing RRHC. They reported that the SPP technique had more advantages, with less console time and shorter hospital stay. Yeo et al.[33] developed a SPP strategy for robotic colectomy with CME and central vascular ligation using the dVXi robotic system in cadaveric models. Lee et al.[34] from Korea, and Schulte et al.[35] from Germany, separately described RRHC using the suprapubic access strategy with relatively satisfactory perioperative outcomes. Long-term results and further application are awaited to broadly determine its benefit.[15]

- Application of single-port (SP) robotic surgery

The intention of surgeons to reduce the number of ports in robotic colonic resection is due to its cosmetic effect and early recovery. SP has begun to be applied through a single incision. Juo et al.[36] completed one case of SP total colectomy and reported that it was a feasible procedure associated with a shorter operation time. Marks et al.[37] reported 2 cases and Bae et al.[38] from Korea, 23 cases of SP left colec-

tomy, indicating that it is a feasible and safe method. Spinoglio et al.[39] successfully performed 3 right colectomies with intracorporeal anastomosis (ICA) using the da Vinci SP platform. A systematic review of current studies revealed that SP surgery for colon diseases is feasible and safe, with acceptable perioperative outcomes (complications 0-36.4% and hospital stay 2-9 days) and comparable with those of multiport robotic surgery.[40]

- Use of ICA

ICA is a relatively new surgical method that has modified the way the surgical specimen is removed through the abdominal surgical incision (Fig. 8.4). This anastomosis decreases the traction of the bowel to be anastomosed, which may reduce postoperative complications. A systematic review and meta-analysis from Italy found a higher rate of ICA in RRHC.[22] Ngu et al.[41]reported shorter operative time and higher number of lymph nodes removed with statistically significant values, and similar rates of postoperative recovery and complications in RRHC with ICA. Some studies have verified the safety. Other studies have reported not only the feasibility and safety of robotic ICA, but its association with a shorter incision length to remove the specimen, earlier bowel recovery, fewer complications (including anastomotic leak, surgical site infection and incisional hernia) and lower conversion rate, but longer operative time, compared with extracorporeal anastomosis (ECA). Long-term results comparing ICA vs. ECA in robotic colonic resections are pending.[15]

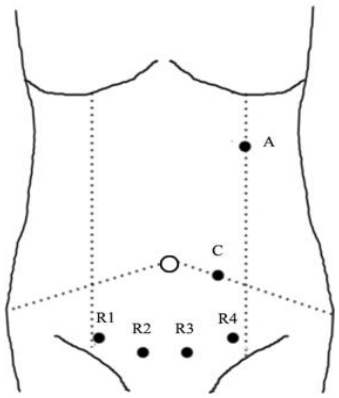

Figure 8.3. *Suprapubic robotic approach.*

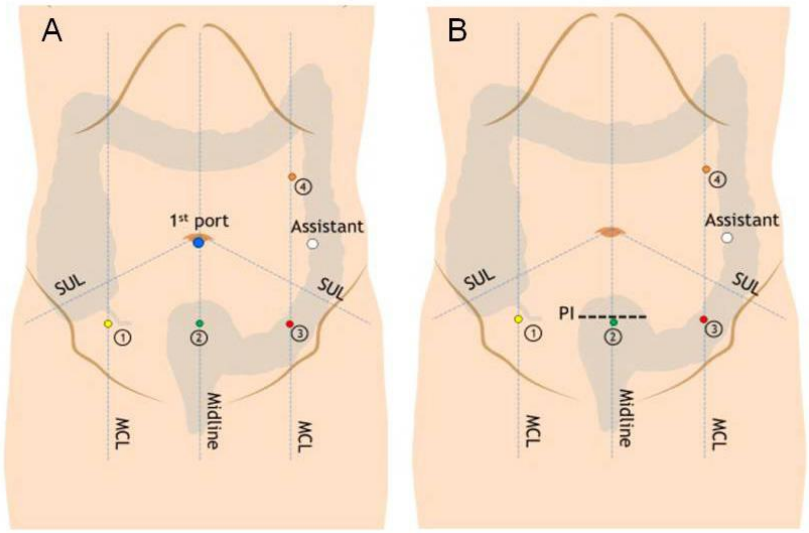

Figure 8.4. *Placement of robotic ports for right colectomy with extracorporeal* ***(A)*** *and intracorporeal* ***(B)*** *anastomosis. MCL: Midclavicular line. UCL: Umbilicospinous line. PI: Pfannenstiel incision.*

- Use of tracers

In recent years, the use of tracers has changed, especially in colorectal surgery, for which indocyanine green (ICG) is the most commonly used tracer. Currently, ICG is used to assess anastomotic vascularity, as it delineates the blood supply and avoids anastomosis of nonperfused segments. Several studies demonstrate its utility and benefits in LC.[42–44] Furthermore, it is used as a lymph node marker in lateral lymphadenectomies and may improve performance in D3 lymphadenectomy.[44] Robotic platforms feature *Firefly*

technology integrated into the dVXi, allowing efficient ICG identification for assessing colon perfusion and lymph node dissection. This suggests that in future publications, tracers will begin to appear alongside the robotic approach.[15]

Future of robotic surgery in colon cancer

Robotic platforms are expected to reduce intraoperative adverse events and provide a higher level of safety by generating ergonomic improvements in the robot and promoting greater surgical performance, which will continue to impact short-term outcomes. Meanwhile, long-term oncological results are expected to demonstrate the cost-benefit and non-inferiority of the robotic approach for colon cancer compared to LC.

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CHAPTER 9
Surgical treatment: fluorescence-guided colorectal surgery

With the collaboration of Alejandro Moreira Grecco, MD, PhD, MAAC, MSACP

Fluorescence, particularly with indocyanine green (ICG), has emerged as a tool that improves the safety and precision of colorectal surgical procedures. It allows for intraoperative identification of anatomical structures and assessment of tissue perfusion in real time, guiding resections and anastomoses, with a potential reduction in postoperative complications.

In fluorescence-guided surgery, a fluorophore (e.g. ICG) is used and evaluated with a specific optical system with an infrared light source and a camera specially adapted to capture the fluorescent signal. The signal is processed by different computer programs that create an image that is evaluated in real time by the surgeon.

Particularly in colorectal surgery, fluorescence is used for the assessment of intestinal perfusion, the localization of lesions with lymphatic mapping, and the identification of the ureters.

Assessment of intestinal perfusión

Fluorescent angiography (FA) is an additional procedure performed during colorectal surgery to achieve real-time assessment of perfusion and blood flow in a bowel segment. It is applicable during conventional, laparoscopic, or robotic surgery.[1–3]

Anastomotic dehiscence is one of the most serious and feared complications of colorectal surgery.[4] To create a safe anastomosis, it is recommended that it be well perfused, not rotated, and without tension.[5] The use of fluorescence allows the perfusion of the bowel ends to be assessed to create anastomoses with optimal perfusion and greater chances of adequate healing, without fistulization.

In 4% to 27% of cases, FA results in a change of the chosen site for the anastomosis.[6-9] In a multicenter study in the USA that included 139 patients, a change in the plan occurred in 11 (7.9%), which did not significantly modify the operative time (with ICG: 214.9 ± 67.5 min vs. without ICG 228.9 ± 66.1 min).[10]

A national case series reported a change in management in 11% of patients, with revision of the anastomosis site in 8.7%, taking a short extra operative time.[11]

An average of 2 cm of proximal colon resection has been reported after FA.[6] This change in intraoperative management is reflected in the lower incidence of fistulas in series using FA.[12] Degget et al.[13] performed a systematic review in which series using FA showed an anastomotic leak rate of 3.8%, compared with 7.6% in series not using FA. The use of FA decreases the risk of fistulas but does not eliminate it, because other factors intervene in their development.

The advantage of using angiography is even more evident in the case of rectal surgeries, in which the colon descended after mobilization of the splenic flexure is most often irrigated only through the vascular arcade connected to the middle colic artery.

In the meta-analysis by Blanco Colino et al.,14 when all colorectal surgeries were analyzed, the use of AF was associated with an OR of 0.5 for the development of anastomotic dehiscence. However, when only rectal surgeries were evaluated, the OR was 0.19, equivalent to an 81% reduction in the risk of colorectal anastomotic dehiscence.

Despite presenting a trend, not all studies found a statistically significant difference for fistula prevention. In this regard, De Nardi et al.[15] reported a rate of 5% in the group with fluorescence compared to 9% in the group without fluorescence, without reaching statistical significance. However, other groups found a difference. The EssentiAL study, in 850 randomized patients, reported an anastomotic dehiscence rate of 7.6% when FA was used vs. 11.8% when it was not used. (RR 0.645; $p = 0.041$).[16] When fistulas requiring some intervention for resolution were analyzed, the difference was even more significant (4.7 vs. 8.2%; $p = 0.044$).[17]

Quantification of the intensity of the fluorescent signal, as well as the speed at which perfusion occurs, allows for an objective measurement of intestinal perfusion, identifying risk groups for performing an anastomosis.[18]

Lesion marking and fluorescent lymphography

Another application of fluorescence in colorectal surgery is lesion marking and fluorescent lymphography. Injection of ICG into the submucosa or subserosa of the colon migrates and produces a real-time lymphography with the possibility of visualizing lymphatic vessels and nodes. In this way, the sentinel node and the lymphatic drainage territory of the intestinal segment under study can be identified.[19,20]

Endoscopic marking prior to or during surgery allows the location of the lesion in a similar way to what happens with a tattoo with Indian ink, but with better visualization.21 The migration of the contrast occurs in an average time of 4-9 minutes and does not progress after 25 minutes of its application.[22,23]

Identification of the sentinel node is possible in 80 to 98% of cases.[22] Aberrant drainage is detected in 25% of patients, especially in lesions located near colon flexures. Detection of aberrant drainage allows the area of previously unsuspected drainage to be included in lymph node dissection and can therefore modify the choice of the central vessel to be ligated.[24,25] Fluorescent lymphography has a sensitivity of 78% and a specificity of 84% for determining the territory of lymphatic drainage.[26]

During rectal surgery, fluorescent lymphography guides the fascial plane of the TME, improves mesorectal and lateral lymph node dissection, and reduces residual mesorectal tissue.[27]

Some factors may affect the results of fluorescent lymphography, such as the presence of a large T3-4 tumor, the use of an inadequate concentration of ICG, the presence of a thick mesocolon, and the use of rigid needles.[10]

Identification of the ureters

An additional application of fluorescence in colorectal surgery includes the identification of the ureters, for which different compounds with urinary excretion have been described.[28] ICG circulates in the bloodstream bound to albumin, so it is not filtered by the kidneys and is not excreted in the urine. However, low-weight compounds with affinity for ICG are being developed to achieve urinary excretion.[29] Currently, visualization of the ureters with ICG requires injection of the dye into the ureter by cystoscopy. This maneuver has resulted in a decrease in operating time in colorectal surgeries by minimizing the time spent searching for the ureter.[30]

In summary, fluorescence-guided surgery offers the possibility of visualizing structures and phenomena that were previously unidentifiable and improves the surgeon's ability to make intraoperative decisions. Although fluorescence does not completely eliminate the risks of colorectal

surgery, its systematic use is associated with a significant improvement in outcomes, in particular a reduction in the incidence of anastomotic dehiscence.

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CHAPTER 10
Surgical treatment: types of resection according to the location of the primary tumor

Right and left colon cancer

Right-sided colon tumors are more common in older women (sporadic), in patients with insulin resistance, and in patients with a family history of cancer and at a younger age. Right-sided colon tumors are more associated with serrated adenomas, sessile and flat polyps, mucinous adenocarcinomas, and more advanced tumors.[1–4] From a molecular point of view, they present a greater deficiency of DNA repair proteins (dMMR) and greater hypermethylation, especially in women. In addition, they are associated with greater resistance to epidermal growth factor receptor (EGFR) inhibitors, greater sensitivity to vascular endothelial growth factor (VEGF) inhibitors, and a higher rate of mutated BRAF and RAS.[5–7]

Left-sided colon tumors are generally sporadic and are related to dietary habits such as lack of fiber intake, alcohol consumption, and smoking. They are more frequent and are more associated with pedunculated polyps, tubulovillous adenomas, and typical adenocarcinomas. From a molecular point of view, they present mutations in the APC gene, lack of p53, and greater sensitivity to EGFR inhibitors. However, OS is similar in both groups.[8]

A SEER-based study reported that right-sided colon tumors in EI and EII had better OS and DFS than left-sided colon tumors at the same stages, although no differences were found in EIII.[9] Although evidence may be conflicting on this issue, in general right-sided colon tumors in EI and EII have a better prognosis than left-sided ones, whereas in EIII and EIV they are associated with a worse prognosis.[3,4,7,8]

The difference in survival and risk of death in patients treated with adjuvant therapy (more frequent in right-sided tumors) between 1992 and 2005 was analyzed, studying 23,578 patients in EII and 17,148 patients in EIII (Table 10.1). Chemotherapy for tumors in EII was received by 18% of patients with right-sided tumors and 22% with left-sided tumors. The 5-year survival benefit was only observed in EIII, regardless of tumor location (HR RC 0.64 vs. HR LC 0.61). This study considers that adjuvant therapy in EII should be reserved for older patients.[10,11]

Table 10.1. Difference in 5-year survival rate, according to tumor side for stages II and III.

Period of time	Right colon	Left colon	*P* value
1980-1989	Equal	Equal	NS
1990-1999	56%	59%	< 0.01
> 2000	67%	71%	< 0.01

The difference in 5-year survival varies between the right and left side, probably due to variation in tumor biology (MSI and KRAS and BRAF mutations), although some authors postulate differences between the type and quality of surgery, related to the greater complexity of surgery on the right side and the better performance of an extended surgery on the left side. Several studies addressed the important relationship between modifications in surgical technique (e.g. introduction of TME) and the substantial improvement in oncological evolution and clinical results.[12]

Extended mesocolon resections with lymph node dissection, aim to improve oncologic outcome. An evaluation of 2052 articles found that the risk of developing central lymph node metastatic involvement in right-sided tumors ranges from 1 to 22%. In sigmoid tumors, the risk is less than 12% and is associated with advanced T stages.[13]

The group from the Hospital Italiano of Buenos Aires compared 292 patients with right colon tumors and 255 with left colon tumors, operated on by laparoscopy between 2004 and 2014. Patients with right tumors were older (71 vs. 65 years), with more ASA 3 and 4 (36 vs. 26%), and had a higher percentage of women without intraoperative complications (4.1 vs. 5.9%), higher conversion rate (6 vs. 3.9%) and more postoperative complications related to surgery (61 vs. 48%). Right colectomy had a shorter operative time (162 vs. 185 min) (Table 10.2), but higher overall morbidity (20.5 vs. 13.3%) and postoperative ileus (10.6 vs. 2.4%), and longer hospital stay (4.7 vs. 3.9 days), with no differences in reoperations, readmissions, and mortality. On multivariate analysis, right colectomy was associated with shorter operative time, higher ileus, and longer hospital stay.[14]

Table 10.2. Differences in operativetime between right colectomy (RC) and left colectomy (LC).

Operative time	RC	LC	*P value*
All cases	162	185	0.001
With splenic flexure mobilization	161	166	0.38
Without splenic flexure mobilization	166	201	0.001

Tumors of the right and left colon are two distinct entities and treatment must be adapted to each case, depending on the molecular phenotype, age, location and stage.

Type of resection

Right colon

Right colectomy is the standard surgical treatment for any tumor located in the cecum, ascending colon, hepatic flexure, and proximal transverse colon. Section of the ileocolic pedicle and the right branch of the middle colic artery at its origin is recommended, along with treatment of the mesocolon and lymphadenectomy.

Resection of the mesocolon with specific technique and the type of lymphadenectomy according to location will be discussed separately.

Left colon

For the treatment of tumors located in the descending colon, sigmoid colon and rectosigmoid junction, left colectomy is the standard. For this purpose, section of the superior rectal artery and the left colic artery at their origin is recommended, together with section of the inferior mesenteric vein at the lower border of the pancreas, together with lymphadenectomy corresponding to this territory.

Transverse colon

In the transverse colon, resection should be individualized based on careful inspection of the tumor location and its feeding vessel, as well as considering the functional results of surgery at this site. There is controversy over whether segmental resection, extended right colectomy, or extended left colectomy should be performed in tumors located on the left side of the transverse colon, although the latter option is less discussed. This topic will be discussed in a separate section.

A 2019 meta-analysis of patients with transverse colon cancer indicated that the short- and long-term outcomes of segmental colectomy or extended right or left colectomy are similar.[15]

In 2020, an Italian national study found that segmental resection had fewer postoperative complications, including less anastomotic dehiscence (2 vs 4%) and better 3-year DFS (86 vs 78%), both differences with statistical significance.[16]

In 2021, a National Cancer Database study on transverse colon cancer EI, EII and EIII found a similar 5-year survival between segmental and extended colectomy (40.7 vs. 41.3%), although after multivariate analysis, extended colectomy was associated with lower survival (HR 1.07; 95% CI 1.04-1.10; $p < 0.001$).[17]

Splenic flexure

Tumors of the splenic flexure usually involve the lymphatic vessels of the pedicle of the left colic artery. However, positive lymph nodes have been identified along the middle colic, right colic, and occasionally ileocolic arteries in up to 9% of cases.[18] Evidence based on retrospective studies and meta-analyses suggests that segmental resection is a reasonable alternative to extended colectomy.[19]

In the Delphi Consensus for the investigation and management of splenic flexure cancer, 18 experts from 12 countries voted on different aspects, based on the background that treatment remains controversial. There was moderate consensus (55%) regarding the definition, which includes the 10 cm segment on either side from where the transverse colon becomes the proximal descending colon, and on the recommendation of CT for localization (72%). Segmental colectomy was the preferred elective treatment (72%), with moderate consensus regarding CME with central vascular ligation (74%). Strong consensus was only achieved on the use of minimally invasive surgery for the surgical approach (88%).[18]

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CHAPTER 11
Surgical treatment: surgical technique

For the purposes of this report, we will not cover all the techniques in detail, but will briefly describe the two main types of colectomies (right and left), taking into account that they can be performed by conventional open approach, by uniportal, multiportal, or hand-assisted laparoscopic approach, and by robotic approach.

Preoperative evaluation

Standard evaluation of a colectomy includes general clinical and cardiovascular evaluation (arrhythmias or asymptomatic cardiovascular pathology), anesthetic evaluation according to the ASA classification, humoral evaluation (general, hemostasis, renal function, proteinogram, tumor markers, Rh factor and group) and specific evaluation of the pathology (colonoscopy, CT, MRI, PET-scan). Likewise, the risk of thrombosis must be assessed pre-, intra- and postoperatively, according to the characteristics of the patient, the pathology and the surgical procedure to be performed.

Bowel preparation

This is an aspect that has undergone great changes in the last decade, from total preparation to no preparation at all. Current ERAS (enhanced recovery after surgery) protocols suggest not preparing the bowel in elective left colectomy, except when an extraperitoneal colorectal anastomosis is required.

Preparation will also depend on the pathology to be treated. In the case of early or small polyps and tumors, bowel preparation is suggested given the possibility of requiring an intraoperative colonoscopy due to the difficulty of locating the lesion if it was not tattooed. Whenever possible, it is important to tattoo the site within a period of no more than 30 days after resection.

In advanced non-obstructive tumors, surgery can be performed with a single preoperative enema, without laxative. However, in an obstructive tumor and depending on the clinical condition of the patient, endoscopic placement of a colonic stent should be considered to resolve the acute event and schedule subsequent surgery. If a colonic stent is not available, the patient should be operated on without any bowel preparation. If bowel preparation can be used, polyethylene glycol-based preparations are suggested.

Tip – Following the ERAS protocol, there is a tendency to perform a less aggressive bowel preparation and not to suspend the diet or prescribe only a liquid diet, except in rectal surgery.

Antibiotic prophylaxis

It is necessary to systematically assess the possible allergy to antibiotics and analgesics or non-steroidal anti-inflammatory drugs during the anamnesis. Currently, the prophylaxis suggested by any ERAS protocol includes the combination of antibiotics for Gram-negative and anaerobic germs, administered orally the day before and on the day of surgery. This prophylaxis is reinforced during anesthetic induction with the same regimen and should not exceed one postoperative dose.

Antithrombotic and antitetanus prophylaxis

Tetanus prophylaxis is no different than for any elective surgery. In laparoscopic left colectomy, the use of stockings for the entire lower limb and intermittent pneumatic compression boots with a pump is suggested during surgery and in the postoperative period while the patient is at rest to prevent deep vein thrombosis. The use of pharmacological thromboprophylaxis follows the protocol of each institution and international standards according to the risk of each patient.

Anesthesia

General anesthesia with endotracheal intubation, with or without regional spinal block and with or without transversus abdominis muscle block, is the standard option. Postoperative analgesia may be intravenous, by transversus abdominis muscle block, or by placement of a spinal catheter that will serve for the first 24 hours.

Patient position

The modified Lloyd-Davies position is used with the legs semiflexed, with the perineum free to allow access for endoanal circular suturing, intraoperative colonoscopy, or rectoscopy for hydropneumatic testing. Recently, this access has been included for endoscopic control of the colorectal anastomosis. For right colectomy, although this position can be used, the usual position is supine.

Bladder catheterization is indicated in prolonged surgeries, to protect the bladder during the placement of trocars in the hypogastrium or to empty it and avoid its interposition in a minor pelvic approach. The patient is fixed to the operating table with a non-slip surface and shoulder and pelvic fixation elements, with bilateral protection. In our experience, we suggest positioning both upper limbs at 60-90º to facilitate access.

It is important to protect the decubitus and fixation areas of the upper and lower limbs in order to avoid passive nerve compression and postoperative functional neurological syndromes that may become permanent or require muscle-aponeurotic decompression due to compartment syndrome.

The position is dynamic and depends fundamentally on the anatomical location of the organ and the time of surgery. The usual position is a forced variable Trendelenburg position and rotation to the right side. This position facilitates the visualization of the area to be treated and the displacement of the viscera that interfere with the approach to the pathology.

Surgical team

In conventional right colectomy, the surgeon is located on the right side of the patient and the two assistants on the left side. The opposite occurs in laparoscopic right colectomy, where the surgeon is located on the left side, or between the legs of the patient, and the assistant with the camera is located on the left side next to the surgeon. Usually only one assistant is needed; if another is needed, the position will depend on the location of the accessory trocar.

In conventional left colectomy, it is usual for the surgeon to be located on the left side and the assistants on the opposite side. For laparoscopic left colectomy, the surgeon is located on the right side of the patient, with the first assistant (camera) on the same side, to the left of the surgeon. The second assistant is located on the left side of the patient, provided that a fourth ipsilateral trocar is placed. The scrub nurse is located to the right of the surgeon. In the absence of articulated arms, the laparoscopy tower is located towards the patient's left lower limb diagonally to the surgeon and the energy platforms behind the surgeon, if wireless technology is not available.

Necessary surgical instruments

In the conventional approach, the instruments are those usually used for major abdominal surgery. In the laparoscopic approach, a 30º optic is used. The instruments consist of atraumatic intestinal grasping forceps, forceps for dissecting vascular elements, metal or polymeric clips, and energy devices for dissection and treatment of the mesentery and vessels (vascular sealant, harmonic scalpel, or monopolar dissector). In addition, at least two universal staplers must be available in case of malfunction or jamming of the device. The available cartridges, articulated or not, must be of variable thickness and length depending on the case and the height of the section of the rectum. The more distal the rectum is divided, the more necessary the articulated cartridges are. The circular suture for colorectal anastomoses is a constant element. Bougies must always be available to dilate the rectum prior to the introduction of the stapling device and the rectoscope to perform the hydropneumatic test. Recently, the use of a colonoscope has been recommended to monitor the anastomosis under direct vision and treat any occult bleeding.

Tip – Bring all necessary instruments with you. Having spare staplers and alternative cartridges will ensure the success of the surgery.

Laparoscopic surgery in steps

The common step for both right and left colectomies is the creation of pneumoperitoneum and initial exploratory laparoscopy.

- Creation of pneumoperitoneum:
The placement of the Veress needle or umbilical trocar must be performed with the appropriate technique to avoid visceral or vascular injuries, especially in patients with abdominal distension or previous surgeries. If possible, it is always advisable to perform transillumination of the wall to avoid injuries to the inferior epigastric vessels during the placement of the lateral trocars.

Tip – Perform pneumoperitoneum according to the instruments and experience of the surgical team.

- Exploratory laparoscopy:
Once the first trocar has been placed, we suggest performing an exploratory laparoscopy and evaluating the placement sites of the other trocars based on the anatomy of the peritoneal cavity, the abdominal wall (previous scars) and the pathology to be treated. In this step, signs of secondary involvement (peritoneal carcinomatosis, free fluid, liver or other organ metastases) should also be sought. Tumors should be located by their size or fixation to neighboring organs, and tattoos and adhesions to the wall and omentum should be identified.

Tip – Always initial exploratory laparoscopy.

RIGHT COLECTOMY

- Trocars. Arrangement and variations:
The first 10-12-mm trocar is used for the initial placement of the camera that will guide the placement of the remaining portals under direct vision. This trocar can be placed after performing the pneumoperitoneum with a Veress needle, or using an open technique. After placing the first trocar, it is suggested to explore the abdominal cavity and evaluate the type of colon (dolicho, mega or short colon), its corresponding meso and the greater omentum, looking for adhesions (postoperative or secondary to the underlying pathology) that could interfere with the placement of the other trocars and proceed to their release.
Right colectomy is probably the one with the greatest individual variation in trocar placement, depending on the surgical team. We will describe the one most commonly used by our team. The first umbilical trocar assists in the placement of the second trocar (5- or 10-mm depending on the available instruments) in the right iliac fossa, for the left hand and the third trocar (5- or 10-mm) in the hypogastrium, left iliac fossa or epigastrium, for the right hand. The umbilical trocar and the third trocar can be used alternately for the camera or the surgeon's right hand. A fourth 5-mm trocar for the assistant can be placed on demand for the dolichocolon or greater omentum.

- Approach to the inferior vascular pedicle, medial vs. lateral:
Right colectomy can be started by performing a right coloparietal dissection from caudal to cranial to free the colon from the prerenal fascia and then descending the hepatic flexure. The main vascular pedicles (ileocolic, right colic, and right branch of the middle colic arteries) are then treated by monopolar dissection and vascular occlusion with a harmonic scalpel, vascular sealant, or polymer clips. Another way to approach the right colon is to first perform a medial approach to treat the proximal ileocecal arterial pedicle or over the vein, depending on the level of dissection D2 or D3. The dissection is then continued cranially until the right and medial pedicles are found, finding and releasing the preduodenal Fredet fascia from its adherence to the colon, until reaching the hepatic flexure. According to the latest published works on CME with or without D3 and high vascular ligation, the lymphadenectomy to be considered D3 must be performed along the origin of the right colic veins (ileocecal, right colic and middle colic) at their origin in the superior mesenteric vein (SMV), on the right lateral border or on its anterior surface, identifying the homonymous arteries and ligating them at their origin. It is not necessary to ligate the Henle trunk, but it is necessary to ligate the right colic veins at their origin in said trunk up to the root of the mesocolon. Monopolar vascular dissection together with the placement of polymeric clips is optimal at this time. According to the Japanese doctrine the level of lymph node dissection can be classified by the relationship with the SMV. This classification is attached in the corresponding section.

- Identification of the right ureter and duodenum:
Although the release of the right colon does not imply a probable injury to the right ureter because vascular ligatures should not be performed at that level as in the left colon, it is necessary to remember the intimate relationship of the ureter with the posterior aspect of the colon. However, if the interureteral fascia is not injured, the injury to the retroperitoneum probably does not imply injury to the ureter. Another situation in this colectomy, particularly in the medial approach, is the intimate contact of the right mesocolon with the duodenum. The preservation of the duodenal peritoneal window, identified as the mesothelial tissue between the ileocolic pedicle and the middle colic pedicle, is essential to perform a complete and adequate dissection of the mesocolon, together with the lymph node dissection.

- Lymph node count:
Central vascular ligation is key in the oncological resection of right and left colon tumors and is based on the removal of the involved central lymph nodes, which occurs in up to 11% in right colectomy and in 8.6% in left colectomy.[1] There is also the possibility of discontinuous lymph node metastases (*skip metastases*) in 2 to 18% of cases. Furthermore, there is a direct relationship between T and N, since T3 and T4 tumors are associated with central lymph node metastases in up to 8%, while the *skip metastasis* rate is almost zero in T1 and T2 tumors.[2] Resection of this lymph node level would bring an additional oncological benefit equivalent to resection of liver metastases, due to a decrease in local lymph node recurrence. The importance of lymphadenectomy involves knowing the territory corresponding

to each tumor level, since there is a direct correlation between the number of lymph nodes removed and survival. Therefore, until the results of new randomized studies are published, the recommendation would be to perform a wide and adequate D2 dissection, with central vascular ligation and complete dissection of the mesocolon in all cases. D3 dissection would be reserved for groups trained in a research context. Table 11.1 specifies the type of surgery, vascular ligation and lymphadenectomy indicated according to the tumor location.

Table 11.1. Type of surgery, ligation, and lymphadenectomy according to tumor location.

Site of the tumor	Type of surgery	Vascular ligation	Lymphadenectomy*
Cecum	Right colectomy	Ileocolic Right colic: under discussion	Regular 201-202 Trained 203-213
Ascending colon	Right colectomy	Ileocólica + cólica derecha + rama derecha cólica media	201-202, 211-212, 201-222 Central: 203-213-223

*Numbering according to Japanese literature.

- Anastomosis:
Following colectomy and vascular treatment, the terminal ileum and transverse colon are divided with a linear cutting stapler, whether articulated or not. A sutured or stapled anastomosis is then performed, usually in a side-to-side and anisoperistaltic manner. The anastomosis may be reinforced with sutures to ensure its tightness.

- Extraction of the surgical specimen:
The specimen is usually removed through a Pfannenstiel incision. Alternatively, it may be removed through the extended umbilical incision (at the cost of a higher rate of incisional hernia), through a right subcostal incision, or through the vagina. Wound closure, drain placement, and postoperative care are similar to those for laparoscopic left colectomy.

LEFT COLECTOMY

Left colectomy is the most common surgical procedure in colorectal pathology, so it is essential to have adequate training, both in laparoscopy and in colorectal pathology, to perform a safe surgery.

In the early days of laparoscopic colorectal surgery, it was considered that left colectomy should be the first surgery to be performed after formal training in simulators. However, it is a procedure that has a potential risk of injuring organs or structures that can cause immediate major complications, or anatomical or functional sequelae.

This procedure is feasible to be regulated and has perfectly established steps. It is noted that laparoscopic colectomy does not only involve the technical procedure of removing a segment of the colon, but the treatment begins several days before with aspects related to diet, bowel preparation and general preparation of the patient, since all of this improves surgical results

- Trocars. Arrangement and variations:
The establishment of pneumoperitoneum and initial exploration of the abdominal cavity are identical to those performed in right colectomy. For left colectomy, it is usual to place 4 trocars, two of 10-12 mm in the umbilical region (camera and grasper for left hand) and the right upper quadrant (camera) and one of 10-12-mm or 12-15-mm (right hand and placement of the linear articulated cutting stapler). In the presence of large and lipomatous mesentery, exuberant epiploic appendices, dolichocolon or redundant omentum, the placement of a 5-mm trocar in the left flank for an assistant's traction forceps is suggested, although it is possible to complete the surgery without this trocar, as has occurred in our experience with selected cases performed with only 3 trocars and without an assistant. In case of technical difficulty, it is possible to add a fifth 5-mm trocar, either in the hypogastrium (to eventually migrate to a larger trocar to perform the bowel section), or in the epigastrium (to mobilize the splenic flexure). It is possible to perform the operation with disposable or metal trocars (consider capacitance in the metal ones). The pneumoperitoneum is usually with medium-high flow (20 to 30 liters of CO2) with a pressure of 10 to 12 mm Hg.
Other surgical schools use a 10-mm umbilical trocar for the camera, a 5-mm trocar in the left upper quadrant for the surgeon's left hand and a 10-12-mm trocar in the right lower quadrant for the right hand, adding a fourth 5-mm trocar in the left flank or left upper quadrant.

Tip – The placement of 5-mm trocars does not alter the postoperative course, so it is suggested that the surgery be performed in the most comfortable way possible.

- Approach to the inferior vascular pedicle, medial vs. lateral
One of the main steps of this surgery is the approach to the inferior mesenteric vascular pedicle, which can be either lateral or medial. The lateral approach, recently prioritized, is similar to the historical lateral approach performed in a conventional colectomy, with the left coloparietal detachment expanding all the elements of the retroperitoneum and separating the mesocolon from the left Toldt fascia to the prerenal Gerota fascia and splenic flexure. On the other hand, the medial approach, which was primarily described in laparoscopy of the left colon, is performed by creating a triangular window formed by the mesenteric artery on the left, the mesorectum above and the retroperitoneum below. At the base, the left ureter is identified and progress is made laterally to complete the dissection of the mesocolon. The choice of each approach depends on the surgeon, although they can be combined in a complex case.

Tip – Both medial and lateral approaches are useful. They should be adapted to the case. Do not hesitate to alternate the approach if the one initially chosen is difficult.

- Identification of the left ureter
The left ureter is one of the most important elements of the retroperitoneum in left colon surgery. It must be identified before ligating the inferior mesenteric vascular bundle in oncological cases and also before performing more distal ligatures (left colic, etc.). In complex cases, tutoring of the ureter with a conventional catheter or with transillumination should be considered. Although the ureter can be injured along its entire length, identification is essential in 3 places: 1) when it runs lateral to the inferior mesenteric artery in a triangle formed by the aorta downwards, the inferior mesenteric to the left and the mesocolon or mesorectum to the right, 2) when it makes contact with the iliac artery on its entry into the lesser pelvis and 3) when it leaves the pelvis and runs on its lateral wall to find the bladder, particularly in TME surgery.

Tip 1 – If the iliac vessels are identified, the dissection is in a deeper plane than intended and the ureter may be injured.

Tip 2 – Do not forget that the ureter can be injured in 3 places and not only during artery dissection.

- High or low vascular ligation
Ligation of the inferior mesenteric artery is performed after identification of the left ureter. Placement of polymer or

metal clips and sectioning with a sealant-type energy platform or harmonic scalpel is suggested. In a complete left colectomy, the artery should be sectioned close to its origin in the aorta, traditionally 1 cm above it to avoid injury to the autonomic nerves that will form the hypogastric plexuses. However, in ideal situations this nerve can be identified and isolated, allowing arterial section as close to its origin as possible. In a sigmoid resection, it is possible to ligate the sigmoid artery trunk and spare the left colic artery.

Tip – Do not ligate the mesenteric artery less than 10-mm from its origin in the aorta because vascular control will be very difficult.

- Ligation of the mesenteric vein

Once the patient is in the Trendelenburg position and rotated to the right, the entire small intestine is deployed upward and to the right, taking care not to injure it. This should be done without pressure and with maneuvers directed toward the mesentery. The inferior mesenteric vein (IMV) is located at the lower border of the transverse mesocolon, below the angle of Treitz. This is initially ligated and divided, especially in complete left colectomies (it may be omitted in sigmoidectomies). By dissecting to the right of the vein, it is possible to begin mobilization of the splenic flexure by a medial approach (see below).

Tip 1 – For sealing and sectioning any vascular element, particularly a vein, always reduce traction to allow for proper sealing. It is also suggested to place distal and proximal clips to ensure hemostasis, although this is debatable.

Tip 2 – To avoid sealing failure, use sealing forceps of the appropriate size for the size of the vessel being treated.

Tip 3 – Sometimes the vein runs alongside the ascending branch of the left colic artery, a configuration known as the vascular arch of Treitz.

- Mobilization of the splenic flexure - how and when?

It can be performed systematically or selectively depending on the service. If it is performed systematically, it is suggested to do so at first, after sectioning the IMV. After this section, one option is to complete the mobilization of the splenic flexure by a medial approach.

When the splenic flexure is mobilized, the colectomy is considered as a left upper colectomy, similar in all steps to the left lower colectomy or sigmoid colectomy. Left upper colectomy, which involves segmental resection with colocolic anastomosis, is performed for tumors of the splenic flexure or proximal descending colon.

There are three types of mobilization of the splenic flexure by laparoscopic means, which can even be reproduced by conventional means. They are named according to the anatomical route used to access the epiplonic cavity: 1) anterior approach, between the transverse colon and the greater omentum, through the embryological layer, 2) lateral approach, through the lateral edge of the greater omentum and the splenocolic ligament and 3) medial approach, between the transverse colon and the pancreas, approaching the retroperitoneum. These approaches can be combined, taking parts of each one. Other authors consider two types of approach: the anterior approach itself, with division of the gastrocolic ligament and the anterior transepiploic approach, with division of the greater omentum. There are two accessory medial approaches, one inframesocolic, which accesses the lesser sac through the lower edge of the pancreas without opening the transverse mesocolon, and another transmesocolonic, in which the transverse mesocolon is directly sectioned to the left of the middle colic vessels. Angular mobilization consists of sectioning the splenocolic, phrenocolic, gastrocolic and finally pancreatocolic ligaments. The IMV is ligated at its origin at the lower border of the pancreas, a maneuver that involves a mobilization of 10 to 12 cm.

- **Lateral approach:** the descending colon is mobilized on its lateral side, separating it from Gerota's fascia up to the splenic flexure, a lateral release of its adhesions to the spleen is performed, and then the lesser sac is accessed near the tail of the pancreas. The greater omentum is separated from the transverse colon. This approach presents a higher risk of bleeding and increases operating time, so it should not be the first option.
- **Medial approach:** the IMV is accessed by separating the descending colon from Gerota's fascia towards the cranial side. Near the anterior border of the pancreas, the lesser sac is accessed and the medial mobilization is completed. The vein at the inferior border of the pancreas is divided and the greater omentum is separated from the transverse colon towards the lateral side. This approach is associated with greater difficulty in obese patients and those with a history of pancreatitis. Ten percent of patients have an accessory artery (Moskowitz artery) that joins the middle colic artery with the left colic artery, which makes dissection difficult and increases the risk of bleeding.
- **Anterior approach:** the lesser sac is entered between the greater omentum cranially and the transverse colon caudally, continuing the dissection towards the left lateral border until the splenic flexure and the descending colon are mobilized.

Tip 1 – For the descent of the splenic flexure, after ligation of the IMV, it is recommended to continue along this plane towards the cranial plane, preserving the lower edge of the pancreas, with the colon above and the retroperitoneum below the dissection plane. Then, along the lower edge of the coloepiploic plane, approach the lesser sac towards the left up to the lateral wall, and from there, complete the mobilization. In this way, it will generally not even be necessary to visualize or dissect the spleen.

Tip 2 – Both the medial and lateral routes can be complex approaches in obese patients or those with difficulty identifying embryological planes.

- Division of the mesorectum and distal rectum

After identifying the elements of the retroperitoneum and performing the vascular division, the mesorectum is dissected. In left colectomies, it is limited to a partial dissection, generally with the rectum divided at the rectosigmoid junction, at the level of the sacral promontory or below it. For the division of the mesorectum, it is suggested to use an energy platform (vascular sealant, harmonic scalpel) to avoid bleeding. It is important to release the rectum circumferentially to avoid its fixation and possible difficulties or complications at the time of the circular stapled anastomosis. The rectal transection is performed with a straight or articulated linear cutting stapler depending on the height. In general, 1 to 2 stapler fires are necessary. The use of a curved cutting stapler is not usually indispensable, it is generally reserved for low rectal resections.

Tip – Free the rectum with adequate circumferential dissection. This prevents tractions that may cause tears or bleeding during placement of the circular stapler.

- Extraction of the surgical specimen

The extraction of the specimen can be done through an oblique incision on the left side, a median incision (extension of the umbilical port) or the Pfannenstiel incision. Each has its advantages and disadvantages and are indicated by the surgeon on an individual basis. If possible, a hermetic wound protector is placed to be able to reconstruct the pneumoperitoneum.

After extracting the specimen, the anvil of the circular stapled is placed, the colon is reintroduced and the pneumoperitoneum is restored, closing the wound or the

wound protector. In the case of performing an intracorporeal anastomosis, it is suggested to remove the specimen with a bag through the suggested incisions or natural orifices.

- Anastomosis, rectal lavage and air leak test
Colorectal anastomosis for left colectomy is performed end-to-end with a circular stapler. After the anastomosis and before performing the leak test, it is advisable to place a proximal clamp to perform a washout with cytotoxic iodine solution or a profuse transanastomotic saline washout. After completing the distal rectal lavage, the tightness of the anastomosis and the possible presence of subclinical bleeding foci are checked with a probe, rigid proctoscope or flexible endoscope.

- Fluorescein
As described in the corresponding chapter on fluorescein-guided surgery, its use has recently been introduced for perfusion control and identification of the appropriate site for proximal division of the colon after vascular ligation. This step is performed immediately before bowel transection. Recent evidence indicates that its application significantly decreases the rate of anastomotic dehiscence. This technology can also be used endoscopically for control of colorectal anastomosis.

- Closure of the mesocolon defect
The closure of the mesocolon resection defect can be performed with absorbable sutures. However, it has not been proven that this is necessary for left colectomies.

- Drains and wound closure
According to ERAS guidelines, there is no need to place drains in left colectomies. Their placement could be considered depending on the associated pathology, collections, peritonitis or high risk of dehiscence. Closure of 5-mm trocar wound is only necessary on the skin. In the case of trocars ≥ 10-mm, it is recommended to close the fascial plane with Endoclose® or similar. The wound closure at the specimen extraction site is done in layers, after washing with cytotoxic solutions.

Tip – Do not routinely drain. Always close the fascia of trocar sites ≥ 10-mm.

- Need for protective ostomy
Protection of the anastomosis with a transverse colostomy or loop ileostomy is recommended in the presence of:
• Patient with high surgical risk: comorbidities, sepsis, intraoperative cardiovascular events, poor general condition, etc.
• Underlying pathology: associated diffuse purulent peritonitis, fecal peritonitis, intestinal ischemia
• Anastomosis with positive air leak test, mechanical failure of the stapling device, doubt about possible ischemia of the intestinal ends.

SPLENIC FLEXURE TUMORS

Eight percent of colon tumors are located in the splenic flexure. They are generally associated with a worse prognosis because the diagnosis is usually made in advanced stages with lymphatic invasion and sometimes with colonic obstruction. Anatomically, this flexure is located in a more cranial and posterior position, and is more acute than the hepatic flexure. It is related posteriorly to the lower pole of the left kidney and anteriorly to the greater curvature of the stomach. It is attached to the diaphragm, the lateral wall of the abdomen, the lower pole of the spleen and the tail of the pancreas by the phrenic-colic ligament. Blood supply is highly variable, normally depending on the left colic artery, although in up to 10% of cases it depends on the left branch of the middle colic artery. Since the middle colic artery is absent in up to 20% of cases, an accessory middle colic artery has been described that arises from the superior mesenteric artery. Due to the great variability of vascular anatomy associated with a great variation in the arrangement of lymph nodes, there is no standardized surgical approach for the splenic flexure. For some authors, lymph node dissection should include the left branch of the middle colic artery and the root of the IMV. In tumors located in the proximal part of the descending colon, the dissection should be performed at the level of the left colic artery and at the root of the IMV. In tumors located in the flexure itself, it is necessary to ligate the middle and left colic arteries.

Four types of resections have been described:
• **Extended right hemicolectomy:** resection of the right colon, transverse colon, and part of the descending colon, ligating the right, middle, and left colic vessels, with an ileocolic anastomosis.
• **Extended left hemicolectomy:** resection of the left third of the transverse colon up to the rectosigmoid junction, ligating the inferior mesenteric vessels and the left branch of the middle colic artery.
• **Segmental resection:** trasection of the distal portion of the transverse colon and the first part of the descending colon, ligating the left branch of the middle colic vessels, the left colic vessels, and the IMV.
• **Extended resection:** indicated for large, locally advanced tumors with regional lymph node metastasis, vascular involvement, dilation of the proximal colon, or involvement of adjacent organs where en bloc resection is indicated.

The type of resection of splenic flexure tumors remains a matter of debate and is currently the subject of study.[3] Controversial issues include the type of lymphadenectomy necessary to obtain the largest lymph node harvest and the site of lymphatic drainage of the tumor. The evidence accumulated to date does not report significant differences in terms of oncological quality and short-term results between segmental resections and extended resections.[4]

- Splenic flexure mobilization
Mobilization of the splenic flexure is essential both to address tumors in that location and to ensure complete release of the left colon to achieve a tension-free and well-vascularized anastomosis. There is no consensus on whether it should be performed systematically or selectively, and this varies according to each group. It is considered a challenging moment in the surgical technique since it increases operating time, is associated with the possibility of injury to adjacent organs, and is generally the main cause of intraoperative bleeding. The technique for splenic flexure mobilization has been previously described.

TUMORS OF THE TRANSVERSE COLON

For tumors of the transverse colon, segmental colectomy with proximal and distal safety margins plus lymphadenectomy corresponding to the nutrient artery close to the tumor site is accepted. The great variability of vascular anatomy at this level makes the type of vascular ligation very irregular. If the greater omentum is involved or firmly adhered to the tumor, en bloc omentectomy is recommended.

In a tumor of the proximal and middle transverse colon, the indication is a segmental transverse colectomy, or an extended right colectomy, according to the surgeon's preference. This includes resection of the lymphovascular pedicle corresponding to the left branch of the middle colic vessels.

In cancer of the distal transverse colon proximal to the splenic flexure, irrigation and lymphatic drainage correspond to the left branch of the middle colic and distally to the left colic vessels. The middle colic vessels are usually ligated to allow anastomosis between the proximal part of the transverse colon and the proximal sigmoid colon. Malignant tumors arising from the middle transverse colon can be removed by transverse colectomy. Dissection is initiated by opening the lesser sac, dividing the gastrocolic ligament below the gastroepiploic arcade. In case of tension in the anastomosis, the hepatic and splenic flexures are subsequently released. This maneuver can be avoided if there is a

garland colon. Finally, the lymphovascular areas of the middle colic vessels are removed, leaving the colon close to the hepatic flexure as the proximal end with blood supply provided by the terminal branches of the right colic artery. Distally, the ascending branch of the left colic artery is included. Bowel transit is preferably restored with an end-to-end anastomosis.

SUBTOTAL COLECTOMY

The approach may be minimally invasive or conventional through a midline supra- and infraumbilical incision. In the conventional approach, colonic dissection begins in the cecum. After mobilization of the colon and its splenic and hepatic flexures, vascular ligations are performed.

In the laparoscopic approach, the patient is placed in the Lloyd-Davis position (modified lithotomy) with limb protectors. Five to six trocars (usually four 10-mm and one or two 5-mm) are placed in the four abdominal quadrants. Vascular control is performed using Ligasure® (Ligasure Atlas; Valleylab, Boulder, CO), or a Harmonic Shears (Ethicon, Cincinnati, OH).

The approach went through different stages until it was determined that the shortest operating time is achieved by first ligating the vascular pedicles and then releasing all segments of the colon. Whether the dissection begins from proximal to distal or in the reverse direction varies according to the preference of different surgeons.

The omentum can be separated from the transverse colon and left as a dependency of the greater curvature of the stomach. However, it is usually more effective to divide the gastrocolic ligament and remove the omentum along with the colon. In synchronous tumors, colonic resection is performed according to oncologic principles.

If it is decided not to perform an anastomosis, the terminal ileum is exteriorized as a Brooke ileostomy in the right iliac fossa and the rectosigmoid colon can be treated in several ways:

- Exteriorization as a suprapubic mucous fistula at the lower edge of the incision (benign emergency pathology)
- Closure of the sigmoid stump, leaving it supraaponeurotic and subdermal.
- Closure of the upper rectum, leaving it in the abdominal cavity (Hartmann operation).

These last two options avoid the continuous discharge of mucus and blood that occurs with a mucous fistula. Their main drawback is the risk of dehiscence, which is of course extremely serious if the colon has been left closed in the cavity, whereas this is not the case if it is placed subdermally. In this case, if a dehiscence of the stump occurs, it is sufficient to open the skin, whereas if it remains closed in the peritoneal cavity, an emergency laparotomy is necessary. In the other cases, intestinal continuity is restored by handsewn or stapled end-to-end or side-to-end ileorectal anastomosis.

In laparoscopy, the distal end is first divided intracorporeally using a laparoscopic stapler (EndoGIA®; US Surgical, Norwalk, CT). To perform the proximal intestinal transection, a small incision is made in the right lower abdominal quadrant over the 10-mm trocar site, and the terminal ileum is divided using a linear stapler (GIA®; Ethicon, Cincinnati, OH). The anvil of the circular stapler (EEA Stapler®; Ethicon, Cincinnati, OH) is then introduced into the proximal end to be anastomosed and secured with a nonabsorbable purstring (Prolene®; Ethicon, Cincinnati, OH). An end-to-end, or better yet, side-to-end, ileorectal anastomosis is then performed.

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CHAPTER 12
Special situations

This section will address synchronous tumors, those that occur during pregnancy, and advanvced tumors that may present with an obstructive, perforative, or hemorrhagic complication.

Synchronous tumors

Synchronous colon cancer is defined as cancer that is diagnosed at the same time as the primary cancer, or within 12 months of the diagnosis of the primary tumor. If the second tumor appears more than 12 months after the primary tumor, it is considered a metachronous tumor.

The synchronous tumor is different from the primary tumor in terms of histology and staging, with the primary tumor being the most advanced.

Synchronous tumors are also referred to in the literature as double tumors, twins, or multiple primaries. However, multiple primary tumors are those that simultaneously affect more than one organ and may or may not be included within multiple endocrine neoplasia syndromes.

The incidence is approximately 4-5% and they are associated with decreased OS. When located in the same segment of the colon, they are resected by segmental or standard colectomy, whereas those located in different segments may be treated with two segmental resections or a subtotal colectomy. Evidence 1B.[1] Although extended resection may not be associated with increased morbidity, it has not been shown to have benefit, and its functional outcomes significantly affect quality of life.[1]

In colon tumors associated with colonic diseases such as ulcerative colitis or hereditary syndromes, the extent of resection should consider this condition. As noted above, both hereditary cancers and those associated with inflammatory bowel disease are extended enough issues to be addressed in a separate work.

Colon cancer in pregnancy

Colon cancer during pregnancy is a diagnostic challenge. As gestational age increases, the incidence of colon cancer increases and is approximately 1/13,000. Symptoms are nonspecific and similar to those that occur during pregnancy. Diagnosis is usually made at a more advanced stage than in non-pregnant women, but survival appears to be similar. Colonoscopy during pregnancy is safe, especially from the second trimester onwards. There are no treatment guidelines or follow-up recommendations.

A multidisciplinary team must consider in each case the risk factors, the staging method, the type of oncological treatment, the risks of the therapy on the embryo or fetus, the prognosis of the mother and the urgency of starting treatment.

In advanced CRC diagnosed during the second or third trimester of pregnancy, a recent publication recommends starting 5-fluorouracil and oxaliplatin following the FOLFOX regimen with the aim of carrying the pregnancy to term, at least to 37 weeks.[2,3] Although the evidence is limited to case reports, the risk of prematurity is greater than the risk of exposure to chemotherapy prior to birth. There is a trend and recent evidence in multiple cohort studies of an improvement in outcome without an increase in neonatal, childhood or adolescent abnormalities due to fetal exposure to prenatal chemotherapy.[2,3] In these cases, there are two lives that must be considered and therefore the management decision is complex and must be multidisciplinary. In the case of Dobbs vs. Jackson Women Health Association, the US Supreme Court in 2022 ruled that each patient in association with their oncologist must have the ability to receive all possible treatment options to achieve therapeutic success.[4]

Treatment should be individualized according to the objectives and trimester of pregnancy, and the decision shared with the patient (Table 12.1).

Table 12.1. Colon cancer treatment according to the trimester of pregnancy.

Trimester	Surgery	Chemotherapy	Postponement	Early birth	Termination of pregnancy
1	Possible	Contraindicated	Possible	Contraindicated	Possible according to own laws
2	Possible	Possible	Possible	Possible ≥ 24 weeks	Possible according to own laws
3	Possible	Possible	Possible	Possible	Contraindicated

Adaptada de Cairl N, Shanker B.[2]

While surgery or postponement is possible at any time, chemotherapy is contraindicated in the first trimester. Early birth is possible only after 24 weeks, while termination of pregnancy depends on the laws of each place and can be performed during the first two trimesters, while it is contraindicated in the third.[2,3]

Advanced colon tumors

The term locally advanced colon cancer refers to infiltrating tumors, whether or not adherent to neighboring structures, in patients without distant spread. This is due to local invasion by tumor growth, the formation of adhesions, or the presence of a local perforation or fistula.[1]

T4 tumors are divided into two groups according to the TNM, AJCC:[5]

- T4a: invades the surface of the visceral peritoneum
- T4b: invades an adjacent organ or structure.

They correspond to: EIIB (T4aN0), EIIC (T4bN0), EIIIB (T4aN1/N1c) and EIIIC (T4aN2a; T4aN2b; T4bN1-2).

Resection of T4 colon tumors

T4 tumors have an incidence of 5 to 15% and are resectable in 21 to 43%.[6] In tumors that are adherent or invade adjacent organs, en bloc resection is recommended, with negative margins being achieved if the treatment is curative. Evidence 1B.[1]

Adhesions between colon tumors and neighboring organs should not be divided, since their histological analysis has shown that they contain malignant cells in 34 to 84% of cases.[7–9]

The presence of positive margins significantly worsens the outcome, in terms of progression, OS, and DFS, with an increased rate of local recurrence.[9–11]

In trained groups, both laparoscopic and robotic surgery allow adequate en bloc resection in selected cases.[12]

Extended resections

The goal of surgical treatment is radical resection of locally

advanced colon cancer. In R0 resections, a recurrence rate of 19% has been reported, while in resections with a microscopic positive margin or R1, the recurrence rate rises to 56%. The 5-year survival rate is 60% in R0 resections and 25% in R1. The R0 resection rate varies between 65 and 75% in T4a and decreases to 50% in T4b.[7,8,11]

The existence of distant metastases does not contraindicate extended resection, provided that R0 resection can be achieved. In the case of unresectable metastases, palliative colon resection is indicated in highly symptomatic patients and/or to avoid complications of the primary tumor (mainly obstruction).

Abdominal wall and soft tissue resection requires subsequent repair with or without prosthetic mesh. Invasion of large vessels contraindicates resection.[1]

If there is renal or ureteral involvement, nephrectomy should be considered, as well as resection of the ureter and subsequent repair. Invasion of the bladder requires partial or total cystectomy, with or without the construction of a neobladder. When the small intestine, other segment of the colon, or the adnexa are invaded, en bloc resection is indicated.

Involvement of the stomach, gallbladder, spleen and/or distal pancreas does not contraindicate en bloc resection, except for invasion of the hepatic pedicle or major vessels. Invasion of the duodenum may be partially resolved or require pancreaticoduodenectomy in very selected cases.

Postoperative morbidity varies depending on the type of multivisceral resection and ranges from 20 to 60%. The same occurs with mortality, which varies between 3 and 17% depending on the treatment performed. The 5-year survival rate for T4aN0 is 79%, for T4bN0 58.4% and is reduced to 40-54% for T4aN+ and 15-38% for T4bN+.[1,8,13]

Laparoscopic surgery for advanced tumors

According to the existing evidence, the feasibility of laparoscopic surgery in advanced tumors is high in centers with trained surgeons. Results similar to those of conventional surgery have been published regarding the number of resected lymph nodes, morbidity, mortality, R0 resection rate, recurrence and survival, with a conversion rate of 7% to 21%.[6,14,15]

In T4 tumors, laparoscopic surgery has longer operating time, less blood loss and shorter hospital stay, with a conversion rate of 8.2%. Absence of significant differences in mortality, recurrence and OS has been reported in R0 resections between laparoscopic and conventional surgery, with a follow-up of 40 months.[16,17]

Oophorectomy

Oophorectomy is recommended for ovaries that are macroscopically suspicious or involved by contiguous extension of the tumor. In contrast, routine prophylactic oophorectomy is not recommended. Evidence IC.[1]

However, in patients at risk of hereditary cancer, prophylactic oophorectomy should be considered in postmenopausal women after individual risk assessment. In patients with suspected or proven ovarian involvement, oophorectomy has been associated with a survival benefit and bilateral resection is indicated in these cases.[18]

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CHAPTER 13
Complications of colon cancer

In 2016, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) published a joint paper with the Association of Upper Gastrointestinal Surgery and the Association of Surgeons of Great Britain and Ireland on the future of emergency surgery. This paper was followed by a 2018 publication by the Royal College of Surgeons of England on high risk in general surgery, which raised the bar.[1,2]

Recent publications have shown that outcomes for patients with acute colon and rectal disease are better when treated by specialist colorectal surgeons. A national audit on laparotomies published in 2017 revealed that almost 50% of all emergency laparotomies are performed for colorectal pathology.[3]

The emergency presentation of CRC can occur as an initial event establishing the diagnosis, during the course of the disease as a consequence of some type of treatment, or as an end-of-life event. CRC emergency represents 20% of cases in most publications. The main presentation is obstruction (up to 80%), followed by perforation (20%) and less commonly by bleeding.[4]

Emergency surgery is associated with a worse prognosis, high levels of morbidity and mortality, and lower overall survival. This could be due to the association of emergency presentation with older age, lower socioeconomic status, comorbidities, more advanced stage of the disease, and fewer treatments with curative intent.

The treatment objectives in these situations include avoiding the negative impact of complications (sepsis, death), achieving the best possible control of the tumor, and ensuring a rapid recovery so that systemic treatment can be started.

Perioperative mortality from emergency surgery continues to decline in European Union countries. However, in the United Kingdom, 90-day mortality after emergency surgery for CRC is approximately six times higher than that after elective surgery (11.5 vs. 2%).[2]

Colon cancer obstruction

Diagnosis

Diagnostic modalities for CRC obstruction include plain abdominal X-ray, ultrasound, and contrast-enhanced CT of the abdomen and pelvis. However, performing an X-ray may lead to a delay in decision-making, such as performing a CT scan to establish a definitive diagnosis, with local and remote staging of the disease, which favors surgical tactics. When CT is inconclusive, in some stable patients in whom obstruction is not detected, colonoscopy may be useful for etiologic diagnosis by allowing biopsy to be performed, or for treatment with a stent. However, CT scan is not mandatory when the diagnosis is conclusive and surgical treatment is established as the initial plan.[2,4]

Recommendation: For the diagnosis of colon cancer obstruction, contrast-enhanced CT of the abdomen and pelvis is the modality of choice. Evidence 3B.[4]

Stent treatment

International guidelines establish that treatment with self-expanding metal stents is the modality of choice for colon cancer obstruction, because it reduces the ostomy rate, hospital stay, in-hospital mortality, the rate of admission to the intensive care unit and the time to start chemotherapy.[1,5]

The use of endoprostheses as a bridge to surgery has short-term benefits, as it allows emergency management by relieving mechanical obstruction, improving the patient's clinical condition and allowing correct staging and planning of definitive treatment. The tactic of choice should be early planned resection with a greater possibility of laparoscopic surgery and primary anastomosis and lower rates of ostomy and morbidity and mortality.[6,7]

The use of a stent as a bridge to surgery has short-term benefits, since by relieving mechanical obstruction it allows the patient's clinical condition to be improved, the disease to be staged and the definitive treatment to be adequately planned.. After stent placement, the tactic of choice is early resection with a greater possibility of laparoscopic surgery and primary anastomosis, and lower rates of ostomy, morbidity and mortality.

The use of stents has increased due to their lower immediate morbidity and mortality compared with emergency surgery. The short-term success rate ranges from 80% to 90%.[8,9] Success tends to be higher for stents placed as a bridge to surgery than for palliative stents.[10,11] The Dutch colorectal audit demonstrated a technical success rate of 87.4% and a clinical success rate of 79.7%.[12]

The use of stents is contraindicated in the presence of perforation or peritonitis. This contraindication particularly affects the group of patients receiving antiangiogenic therapy with bevacizumab, in whom the risk of perforation during treatment is higher. This risk does not appear to be increased in patients receiving other therapeutic agents such as cetuximab.[12–15]

Stents can also be used in patients with colonic obstruction due to extraluminal malignancy and peritoneal carcinomatosis, although with a lower success rate, greater technical difficulty and a higher complication rate.

Recommendation 1: Self-expanding metal stents for the treatment of colon cancer obstruction can be used for palliation and as a bridge to surgery. Evidence IA.
Recommendation 2: Self-expanding metal stents should not be used in the presence of perforation, peritonitis, or systemic toxicity and are relatively contraindicated in patients treated with antiangiogenic agents. Evidence IIIC.[2]

Technical risks

There is debate about recurrence and poorer survival secondary to stenting, due to the dissemination of tumor cells and perforations. Some randomized studies have shown a worse oncologic prognosis with higher mortality. Other studies report higher recurrence in this group of patients. Guidelines do not recommend its routine use, reserving it for patients with metastatic disease or poor general condition and high risk of operative mortality. There is a wide variation between the different recommendation guidelines, so it is suggested that this treatment be selected individually for each patient.[2–4]

A recent meta-analysis of randomized controlled trials compared stenting with emergency surgery and found an overall higher risk of recurrence in the stenting arm (37 vs. 25.9%).[16] One retrospective study and two systematic reviews found equivalent 5-year oncologic outcomes.[17] The Dutch colorectal audit demonstrated equivalent 3-year oncologic outcomes in patients with left-sided colon cancer obstruction, with the stenting arm having a higher perforation rate, higher recurrence (18 vs. 11%; $p = 0.432$), worse 3-year DFS (49 vs. 59.6%; $p = 0.717$), and worse OS (61 vs. 75.1%; $p = 0.529$), but no statistical significance was found in any case.[18]

Balloon dilation prior to stent placement is not recommended because it may result in worse oncologic outcomes secondary to perforation.[2]

Recommendation: Self-expanding metal stents appear to be oncologically as safe as emergency surgery. Locoregional recurrence at 3 and 5 years and OS are comparable between these two groups. The risk of stent perforation represents a high risk of local recurrence. Evidence IA.[3]

ComplicationsShort- and long-term complications secondary to stent placement have been reported in up to 30%. The main complications include perforation (up to 12%), placement failure, migration and restenosis. Less frequent are pain, bleeding, tenesmus, fistula, late perforation, incontinence and hyperthermia. Reobstruction can be treated with the placement of a new stent.[19,20]

Stent perforation may be clinically evident, identified by the guidewire, or silent (microperforation). According to recommendations of the endoscopic audit group, the incidence of perforation should not be greater than 10%, ideally less than 5%. In recently published studies it ranges between 1.6 and 5%, reflecting greater training in the technique.[21,22]

Recommendation: The technical success rate in stent placement for obstructive colon cancer should exceed 90%. Evidence IA.[2]

Palliation

A 2011 Cochrane review demonstrated improved clinical outcomes of emergency surgery compared with stenting in a palliative setting.[23] However, subsequent studies have shown that stenting has significant benefits in terms of quality of life, with reduced ostomy rate, hospital stay, time in the intensive care unit, time to initiation of chemotherapy, and morbidity and mortality.[24]

It has therefore become the technique of choice for left-sided colonic obstructions. In contrast, stenting for right-sided colonic obstructions is technically more challenging, and the recommendation for its implementation depends on the training of each group. The ASCRS recommends considering stenting as a palliative treatment for right-sided obstructions.[4]

A diverting colostomy may be an alternative to stenting in patients with left-sided colonic obstruction. A recent Dutch population-based study compared initial stoma with decompressive stenting and demonstrated that ostomized patients have a higher rate of laparoscopic resection (57 vs. 9%; $p < 0.001$), more primary anastomoses (88 vs. 41%; $p < 0.01$), lower 90-day mortality (1.7 vs. 7.2%; $p = 0.03$), improved 3-year survival (79 vs. 73%; HR 0.36, 95% CI 0.20–0.65), and a lower rate of permanent ostomies (22 vs. 42%; $p < 0.001$).[25]

Recommendation: Self-expanding metal stents should be the palliative treatment of choice in patients with unresectable primary disease or metastases associated with colonic obstruction. Stent placement in this group of patients is associated with a better quality of life, a shorter hospital stay, and a lower rate of ostomies, compared with palliative surgery. Evidence IA.[3]

Stent as a bridge to surgery

Emergency surgery for colon cancer obstruction has a higher incidence of morbidity and mortality, including anastomotic leak, when compared with elective surgery. These complications adversely affect oncologic outcome. International guidelines vary widely in recommending the use of stents as a bridge to surgery. Furthermore, these results are variable when comparing left-sided versus right-sided tumors. While the UK and European guidelines do not favor the use of right-sided stents, American guidelines recommend it.[4]

Most studies focus on left-sided obstruction. Meta-analyses have shown that stenting as a bridge to surgery is associated with lower morbidity, lower ostomy rate, higher number of primary anastomoses, and similar mortality rate.[11,14]

A systematic review of right-sided obstruction comparing stenting with surgery showed lower morbidity and mortality in the former group, but cautioned that most of the studies reviewed were retrospective.[26]

Recommendation: There is good evidence supporting the use of self-expanding metal stents as a bridge to definitive surgery for malignant colon obstructions distal to the splenic flexure, particularly in high-risk patients. The decision should be individualized between the patient and physician. Evidence IA. This recommendation can be applied to right-sided obstructions, although its practical application is more limited. Evidence IIIC.

Time to surgery after stent placement

The European Society of Gastrointestinal Endoscopy recommends surgery within 5 to 10 days of stent placement, although current evidence is weak.[9] With longer waiting times, a 20% increase in complications, such as migration and perforation, has been reported during this period and an increase in recurrence. Further studies are needed for a definitive conclusion on this matter.

Recommendation: In the absence of strong evidence, surgical resection appears appropriate immediately after improvement of the patient's clinical condition, radiological staging and the decision of the multidisciplinary committee. Evidence IV.

Coated stents

Coated stents are associated with a higher rate of migration in retrospective series. Migration is likely to be facilitated by less tumour growth incorporating into the stent, resulting in less anchorage. The European Society of Gastrointestinal Endoscopy and the American Society for Gastrointestinal Endoscopy do not recommend this type of stent.[9,27]

Recommendation: Uncoated stents should be used as a bridge to surgery due to reduced migration. In palliative care patients, the evidence on coated versus uncoated stents is inconclusive. Evidence IIIB.

Surgical treatment

Antegrade lavage

There is no relevant evidence on the benefit of applying antegrade lavage in obstructive colon cancer surgery. According to Mattacheo,[28] the best evidence comes from the study by Lim et al,[29] which compares lavage with manual decompression and shows a difference only in lavage time and similar results regarding time to recovery of bowel function, length of stay, surgical site infection and anastomotic dehiscence.

Antegrade lavage is performed using the appendicular orifice (post appendectomy) or an enterostomy to infuse more than 4 liters of saline solution. The fluid is recovered through a colostomy proximal to the tumor, or more commonly, through the proximal colon after the tumor has been removed. Obviously, this technique is only used in the conventional approach. Transanastomotic lavage through a corrugated tube or by colonoscopy has also been described, which requires a significant increase in operating time without considerable advantages in postoperative variables.

Surgical tactics

In patients with proximal obstruction of the ascending and transverse colon, who are stable and at low surgical risk, it is reasonable and safe to perform resection with primary anastomosis.[30,31]

The European Society of Coloproctology audited 3208 patients and found an increased rate of dehiscence in different types of stapled anastomoses in this group of patients, suggesting that a hand-sewn anastomosis is preferable in this setting.[32]

The incidence of dehiscence after emergency right hemicolectomy for obstruction varies widely between 7 and 16.4%, with a tendency to be higher in proximal than in distal anastomoses. Advanced age, ASA II-IV classification and preoperative renal damage are factors associated with a worse postoperative outcome in colon cancer obstruction. Therefore, in patients with low surgical risk or high anastomotic risk, it is reasonable not to perform a primary anastomosis and to consider resection and ileostomy.[33,34]

Elective surgery after stenting does not adversely affect oncologic outcome and reduces the rate of ostomy.[17] A meta-analysis of 8 studies with 444 patients (219 stents vs. 225 surgeries) found that 7 studies showed no difference in the rate of ostomy and 3 randomized controlled trials showed no difference in mortality or anastomotic dehiscence but did show a difference in overall morbidity. Stenting is no more advantageous than emergency surgery for left-sided colon obstruction due to malignant tumor.[34]

In left-sided obstructive cancers, multiple options exist, including primary resection and anastomosis with or without diverting stoma, or a defunctioning stoma alone. In a meta-analysis, no difference was found between one-stage resection versus two-stage or three-stage resection.[35] Primary resection and anastomosis, a technique used for many years, is safe even in selected elderly patients and should be the preferred option if the clinical condition is good.[31]

If possible, segmental resection is preferred over subtotal colectomy or extended colectomy because of its better functional results.[36] Subtotal colectomy with a minimal portion of distal ileum should be reserved for cases of proximal colonic damage due to distal obstruction or for synchronous tumors. Anastomotic leak varies between 2.2 and 12%.

The LaCes trial, which compared conventional surgery with laparoscopic surgery, showed that the latter is feasible, acceptable and safe, with a conversion rate of 39%.[37]

The proportion of emergency laparoscopic resections in the UK between 2000 and 2016 ranged from 15.1% to 30.3%, with a conversion rate of around 18.7%. This approach was associated with shorter operating time, hospital stay and mortality.[38]

In a recent study published by the Dutch Snapshot Research Group,39 between 2009 and 2016, 158 patients were selected from 2002 patients who underwent laparoscopic resection for left colon obstruction due to cancer and compared with 474 patients who underwent open surgery. Complications at 90 days were 26.6 vs. 38.4%, with no difference in mortality (5.1 vs. 7.2%). OS and DFS at 3 years were better in the laparoscopic surgery group (81 vs. 69.4% and 68 vs. 52%, respectively). They conclude that laparoscopic surgery in obstructive colon cancer decreases complications and increases survival. This study suggests that intentional emergency laparoscopic resection might improve short- and long-term outcomes in patients with left-sided obstructive colon cancer compared with emergency open resection, warranting confirmation in future studies. Adequate patient selection for intentional laparoscopic resection is required if relevant experience of the surgical team is available, to avoid emergency open resection.

Recommendation: The surgical decision should be based on the patient's physiological condition, the extraction site, and the characteristics of the proximal colon. In case of obstruction proximal to the transverse colon, resection and primary anastomosis is preferable, except in a markedly deteriorated patient, in whom the accepted treatment is resection with terminal ostomy and mucous fistula. In case of obstruction of the colon distal to the transverse colon in physiologically stable patients, resection and primary anastomosis is preferable. The presence of comorbidities and poor general condition determines resection with terminal colostomy. Evidence IIIB.[4]

Recently, it has been shown that tumor obstruction of the transverse colon can be successfully treated with a stent in selected patients. The success rate of right-sided stenting ranges from 87 to 96%.[40]

In the Japanese National Database Study of 1500 patients, emergency surgery was compared with stenting as a bridge to surgery and in the latter case a higher indication for laparoscopic surgery was observed (50 vs. 25%; $p < 0.001$), as well as a lower rate of ostomy (1.7 vs. 5.1%; $p < 0.01$) and a shorter hospital stay (13 vs. 15 days; $p < 0.001$).[41]

A 2022 systematic review and meta-analysis on emergency colectomy or stenting as a bridge to surgery for right-sided obstructive colon cancer demonstrated that stenting is associated with reduced postoperative complications and mortality.[42]

In a meta-analysis by Veld et al.[43] of 18 studies and 1518 patients, early complications were found in 13.6% with stenting and 25.5% with surgery, whereas late complications were lower with surgery (23.2 vs. 9.8%), including reobstruction (16.7%), migration (6.9%), and perforation (5%). There were 14.3% ostomies in the stenting group and 58.4% in the surgery group, and mortality was 3.9% vs. 9.4%, respectively.

Some studies suggest a better prognosis in patients whose primary tumor is resected compared to those treated with a stent without resection.[44]

In summary, the stent:

- Is a safe option, particularly for severely deteriorated patients.
- Has a high rate of early and late complications.
- May avoid unnecessary resection.
- May have a worse prognosis than surgical resection of the primary tumor.

Recommendation 1: In patients with left-sided colon obstruction and potentially curable disease, endoscopic stenting or oncologic colectomy with primary anastomosis with or without protective stoma should be individualized. Evidence IB.[4]

Recommendation 2: In markedly deteriorated patients with significant preexisting comorbidities, loop stoma alone is reasonable. Evidence IIIC.[4]

Recommendation 3: In patients with right-sided colon or transverse colon obstruction with curative disease, initial colectomy with or without anastomosis, with or without protective or definitive stoma, and/or decompression with endoscopic stenting with immediate subsequent colectomy are all valid therapeutic options. Evidence IC.[4]

Colon cancer perforation

Perforation accounts for 18.6-28.4% of all colon cancer complications. It may occur at the cancer site (65-92%) and proximal to the cancer (3-35%).[2,4] These data are based on mostly retrospective, single-center studies with corresponding bias. In population-based studies, 1.6-4.1% of all cancers presented with perforation.[5,45]

Mortality depends on the site of perforation. Perforation proximal to the tumor site in an obstructed colon leads to diffuse peritoneal contamination and septic shock, with subsequent perioperative mortality. A perforation at the tumor site results in local contamination with a lower risk of severe peritonitis, although these data are not supported by strong evidence. Mortality, reported as high as 62%, is associated with age, comorbidities, and stage IV.[46] However, more recent studies have reported perioperative mortality of between 0 and 20%.[4]

The influence of perforation on oncologic outcome has not been clearly determined. There is heterogeneity according to the site of obstruction, the site of perforation, emergency surgery, immediate vs. delayed surgery, and other factors that lead to confusing conclusions. A worse oncologic prognosis has been reported in patients with emergency vs. elective surgery. The worse oncologic outcome would be related to perioperative mortality and advanced-stage oncologic disease.[47] However, other authors have reported a similar 5-year OS in perforated patients with complete resection compared to those without perforation. In more recent population-based studies, locally perforated cancers had a higher local recurrence (15.7 vs. 7.8%; $p = 0.0021$) and greater peritoneal carcinomatosis (13.8 vs. 6.3%; $p = 0.036$), although there was no difference in the incidence of distant metastasis (17.7 vs. 18.6%; $p = 0.099$). Perforation was an independent risk factor for local recurrence and peritoneal carcinomatosis ($p = 0.004$). However, after excluding postoperative mortality, perforation was not a significant prognostic factor in the multivariate analysis regarding survival ($p = 0.54$).[48] On the other hand, the Erlangen CRC registry found a lower 5-year DFS (42.9 vs. 72.8%) and lower OS (47.3 vs. 66.9%) in perforated patients, demonstrating that perforation was an independent negative prognostic factor.[49] It has also been shown in the multivariate analysis that although patients with colon cancer with local perforation had a significantly lower DFS than those with nonperforated obstructive cancers, there were no differences in OS.[49]

According to ASCRS, patients with perforation tend to have fewer primary anastomoses and higher postoperative morbidity and mortality. In addition, they have significantly lower 5-year OS and DFS, with an increased risk of metachronous peritoneal metastases. Patients with free perforation have a worse OS than those with sealed-off perforation.[4]

Recommendation: Patients with perforated cancer should be warned about an increased incidence of local recurrence and peritoneal carcinomatosis, but not of distant metastasis. The long-term oncologic outcome of patients treated urgently with curative intent for obstruction or perforation is equivalent. Level of evidence IIIB.[4]

The goals of emergency surgery for perforated colon cancer are to control the immediate negative impact of complications such as sepsis and death, to achieve the best possible local control of the tumor, and to ensure a prompt recovery in order to initiate systemic adjuvant therapy. The preferred treatment when possible is standard oncologic resection. Patient safety must be balanced with prompt local control of sepsis and optimization of oncologic control of the disease. Subtotal colectomy is generally indicated for patients with perforation proximal to the tumor, while perforations at the tumor site can be treated with segmental resections.

Perforated patients and those with a higher ASA classification have the lowest chance of having a primary anastomosis. This depends on the clinical condition of the patient and the balance between the risks associated with an anastomotic leak vs. those associated with an end ostomy. The anastomotic risk in patients with emergency surgery is higher than in those undergoing elective surgery and has an average incidence of 15.8%.[47,48]

In selected patients with minimal peritoneal contamination, healthy tissue, and hemodynamic stability, consideration should be given to performing an anastomosis with or without a protective stoma. The threshold for performing a staged procedure in this setting should be low, although ostomies performed in emergency situations are often not reversed. In patients with free perforation complicated by peritonitis, oncologic resection with an end stoma should be considered therapeutic.

Recommendation: Surgical tactics should be individualized taking into account physiological factors, comorbidities, and tumor characteristics. If possible, the choice is to perform an oncologic resection that includes the perforation site, with or without anastomosis, with or without diverting ostomy. In proximal perforations, simultaneous resection of the tumor and the perforation is required. Evidence IIIB.[4] In the context of a macroscopic or imminent perforation, oncologic resection is recommended, with a low threshold for performing a staged procedure. Evidence IC.[4]

Bleeding

CRC is the cause of 6.1 to 7.4% of all cases of lower gastrointestinal bleeding.[2] However, this rate may be underestimated due to the lack of diagnosis at the time of presentation and early discharge of patients without study or without diagnosis, which reaches up to a third of cases. Acute bleeding from a newly diagnosed colon cancer should initially be managed with a nonsurgical approach. Evidence IC.[4]

For the British Society of Gastroenterology, colonoscopy is the initial investigation method for minor or major acute lower gastrointestinal bleeding in stable patients. In unstable patients, CT-guided angiography is the option. The latter achieves the diagnosis of bleeding in 49.7 to 55.8% of cases. It should be performed in a triphasic manner, involving the acquisition of the arterial phase, the portal venous phase and the delayed phase.[50] In addition to the localization of bleeding, CT angiography allows locoregional assessment and staging of a potential tumor. It has been shown to be superior to nuclear medicine for the diagnosis of the bleeding site (sensitivity 85 vs. 20-60%, respectively).

Conventional angiography detects bleeding in 40-90% of patients and allows treatment with embolization, achieving cessation of bleeding in 70-90% of cases.

Emergency colonoscopy without preparation detects the site in 20-40% of patients with acute bleeding and has the advantage of being both diagnostic and therapeutic. If possible, stabilization of the patient and bowel preparation within 12 hours of admission is preferred.[51,52]

Surgery is indicated in cases of hemodynamic instability despite transfusion of 6 U of red blood cells, persistent bleeding requiring more than 3 U per day, inability to stop bleeding by an endoscopic or endovascular procedure, or recurrent episodes of low-grade bleeding.

If surgical resolution is required, resection should be performed using oncologic principles if possible. The performance of a primary anastomosis or a diverting or definitive ostomy should be individualized according to the patient's condition and the surgical team's judgment. Infrequently, in the case of unresectable neoplasms with significant bleeding, endovascular stents can be successfully placed.[2,4]

Adjuvant treatment in complicated colon cáncer

Patients with complications from colon cancer are indicated for adjuvant therapy, however, the high presence of comorbidities and prolonged hospitalization determine that only 50% receive systemic treatment.[53]

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CHAPTER 14
Neoadjuvant treatment in colon cancer

Surgical treatment is essential for a good prognosis of the disease, since local recurrence is low if surgery is effective. This should be oncologically adequate, which implies en bloc resection, central vascular ligation, extensive lymphadenectomy and complete excision of the mesocolon. Oncological results are directly related to surgical results. The main form of recurrence is systemic.

The 5-year DFS ranges from 35 to 88% with adjuvant therapy and from 14% to 79.6% with surgery alone. The absolute benefit of adjuvant chemotherapy ranges from 8.7 to 22%.[1]

Indications for neoadjuvant therapy

According to NCCN, neoadjuvant therapy is indicated for bulky T4b and N+ tumors, which define at-risk patients.[2] The latest ESMO guidelines do not clarify the indication.[3]

Published trials include patients with bulky or extensive T3-T4 tumors, with or without N, right colon tumors, and patients too frail for initial surgery.

Fundamentals of adjuvant therapy

These concepts are extensively developed in the chapter on adjuvant treatment, but in summary:

- The 2009 MOSAIC study demonstrated a 5-year DFS of 73.3% and a 6-year OS of 72.9% with FOLFOX.[4]
- The NSABP R04 study reported a 5-year DFS of 66-67% and a 5-year OS of 80-81%. Overall recurrence was 11.2-12.1% and in R0 resections 3.1-5.1%.[5]
- Survival is related to distant micrometastases for which chemotherapy is the only treatment. Since survival is related to systemic relapse, it is worth asking why not starting neoadjuvant therapy earlier.

In patients with locally advanced colon tumors, neoadjuvant chemotherapy or radiotherapy may produce tumor regression and facilitate resection with negative margins. Evidence IIB.[6]

Neoadjuvant chemotherapy may facilitate complete resection of locally advanced colon cancer.[7–9] Current NCCN guidelines consider the use of neoadjuvant oxaliplatin (OXA) in patients with T4b colon tumors.[2] A comparative analysis of the oncologic outcome of surgery with or without neoadjuvant therapy is shown in Table 14.1.

In a 2020 systematic review of six studies, neoadjuvant chemotherapy resulted in tumor volume reduction in two-thirds of patients and major pathologic regression in 4 to 37% ($p = 0.005$). It also resulted in improved 3-year DFS in patients who responded to treatment compared with non-responders (94 vs. 63%) and a 23% lower 3-year mortality rate in patients with cT4b tumors, but no benefit in those with cT3 and cT4a tumors.[9]

The potential advantages of neoadjuvant therapy are:

- Effective and well-established strategy in other tumors of the digestive tract and other organs.
- Opportunity for early systemic treatment.
- Improving surgery through downstaging and downsizing.
- Lower risk of incomplete resection or higher rate of R0 resection.
- Lower risk of tumor cell spread.
- Early treatment of micrometastatic disease.
- Improve tolerance and compliance with less treatment loss.
- In vivo sensitivity test of pathological response, assessing regression as a factor for better prognosis.
- Rehabilitation: preparation period for surgery to improve the risk of morbidity and mortality with treatment.
- Potential and theoretical non-surgical management of colon cancer.

Obviously, there is controversy about this approach due to what could be considered disadvantages:

- Local and distant progression (15-20% of patients progress in the first 3 months of systemic treatment).
- Overtreatment (low-stage, non-responder patients).
- Toxicity that potentially affects surgery.
- Potentially higher rate of postoperative complications.
- Lower rate of complete surgery due to potential disease progression.

Key findings from the major published studies are detailed below.

The FOxTROT trial,[10] a prospective randomized study of 1053 patients from the UK, Denmark, and Sweden, compared patients with non-metastatic T3-T4 tumors, not at risk of obstruction, treated with 6 weeks of FOLFOX followed by surgery to those treated with surgery plus adjuvant therapy. The primary endpoint was the absence of recurrent or persistent disease after 2 years. Secondary endpoints included safety, histologic stage, completeness of resection, and OS.

Neoadjuvant therapy was feasible in 90% of patients, with a higher proportion of patients receiving adjuvant therapy than in the control group. Data related to surgery, especially morbidity and mortality, were similar to those of the control group. Patients receiving neoadjuvant chemotherapy had a significant reduction in T and N tumor stage, a 3.8% complete pathologic response, and a tendency to present less recurrence and persistence of the disease at 2 years (14 vs. 17.5%).

The 2-year recurrence decreased by 28%, there was a higher rate of R0 resection (94 vs. 81%), less incomplete surgery due to the presence of R2 or residual metastasis (5.1 vs. 10.3%) and less findings of T4 (21 vs. 31%), N0-1-2 (59, 25 and 15% vs. 48.8, 25 and 25.9%) and apical N + (3.8 vs. 7.5%), all with significant difference.

Patients with tumor regression or better histopathological response had fewer recurrences, with an obviously better prognosis. Patients with dMMR did not respond to chemotherapy and had a worse prognosis. MMR status would seem to predict resistance to chemotherapy, since the response in patients with dMMR, as measured by tumor regression, is lower than in the MMR proficient group (7 vs. 23%; $p < 0.001$). This also supports MSI testing before starting neoadjuvant therapy in colon cancer.

According to the FOxTROT trial, neoadjuvant therapy is safe, well tolerated, does not increase perioperative morbidity, and has a trend toward a lower rate of serious complications. Evidence of histopathologic regression was observed in 59%, including complete pathologic response. There was a clear reduction in histologic staging and a reduction in incomplete resections (94 vs. 89%). Less residual or recurrent disease was demonstrated at 2 years (16.9 vs. 21.5%). Tumor regression was strongly associated with lower recurrence. Panitumumab did not demonstrate benefit in neoadjuvant therapy. In addition, there was little benefit in dMMR tumors. They conclude that neoadjuvant therapy improves oncologic and surgical outcomes and should be considered as a treatment for colon cancer.[1,11]

Table 14.1. Comparison of oncological outcome of surgery with and without neoadjuvant therapy.

Oncological outcome	Neoadj + Sx + Adj	Sx + Adj	P value
R0 resection (%)	90.6	85.9	0.001
3-year DFS (%)	81.2	76.3	0.001
3-year OS (%)	83.8	79.4	0.001

Neoadj: Neoadjuvant therapy. Sx: Surgery. Adj: Adjuvant therapy. DFS:Disease-free survival. OS: Overall survival.

The PRODIGE 22 trial, a French multicenter randomized study of 104 patients with T3-T4, N0-2 tumors treated with perioperative FOLFOX versus surgery plus adjuvant therapy, showed that patients in the neoadjuvant group were more likely to have tumor regression (44 vs. 8%) and significant downstaging of pTNM.[12,13] However, there was no difference in 3-year OS (90.3 vs. 90.4%) or DFS (76.8 vs. 69.2%). A limitation of this study was clinical upstaging in one-third of patients, indicating possible overtreatment in the experimental group.[12]

Along with FOxTROT, both studies randomized a control group with surgery and adjuvant chemotherapy vs. the experimental group with neoadjuvant therapy followed by surgery and adjuvant chemotherapy. While neither found an OS advantage, a 2018 retrospective analysis of the National Cancer Database found a 3-year OS advantage (74 vs. 66%; $p < 0.001$) in cT4b patients treated with neoadjuvant therapy compared with adjuvant chemotherapy. In this subgroup, OS was 23% higher.[14]

In the OPTICAL study conducted in China, patients with T3-T4, N1-2 tumors were randomized to receive FOLFOX or CAPOX followed by surgery and adjuvant chemotherapy for 3 months versus surgery and optional chemotherapy. Results, presented but not published, showed that 26% of patients in the control group had low-risk stage II, indicating overtreatment. As in FOxTROT, 94% of patients received 6 weeks of neoadjuvant therapy, but only 69% completed it. There were no differences in rates of laparoscopic surgery, R0 resection, and postoperative morbidity.[15] In the study group, there was a significant improvement in 3-year OS (94.9 vs 88.5%). At 20 months, the survival curve separated and was maintained at 5 years. However, the 2% (78.7 vs 76.6%) improvement in 3-year DFS was not significant, except in women (84.2 vs 74.7%). The neoadjuvant group had a 7% complete pathologic response. There was a 10% reduction in pT4 and a 5% reduction in pN2. Patients with dMMR were more resistant to chemotherapy with 51% poor or no response.[15]

The Scandinavian NeoCol study included 250 nonmetastatic patients with T3-T4, N0-2 tumors randomly assigned to 4 cycles of FOLFOX or 3 cycles of CAPOX followed by surgery with adjuvant chemotherapy for 3 months vs upfront surgery with adjuvant chemotherapy. There was no difference in 5-year DFS (85%) or OS (90%). Complete response was 3%. There was little reduction in pT4 with 3 cycles, but node-negative disease was more common with neoadjuvant therapy (59 vs 48%), as was lymphovascular invasion (25 vs. 39%). R0 resection was higher in the study group (93 vs. 90%), which also had more laparoscopy and less anastomotic dehiscence.[16]

In summary, three randomized controlled trials demonstrated the safety of preoperative chemotherapy, with excellent 6-week compliance. It is not applicable to dMMR tumors due to lack of response. Efficacy varies between trials. FOxTROT demonstrated improvement in recurrent or residual disease, OPTICAL demonstrated benefit in OS, while NeoCol found no difference at 5 years in OS or DFS. Unlike NeoCol, FOxTROT and OPTICAL demonstrated downstaging (Table 14.2).

Table 14.2. Analysis of tumor regression and survival achieved with neoadjuvant therapy.

Trial	T	N	TR (%)	3-year DFS (%)
FOXTROX	+	+	93 vs. 88	80.7 vs. 75.8
PRODIGE 22	+	+	94 vs. 98	76.8 vs. 69.2
OPTICAL	+	+	97 vs. 95	78.7 vs. 76.6
NeoCol	+	+	93 vs. 90	p = NS

TR: Tumor regression. DFS: Disease-free survival. NS: Not significant.

An analysis of the period 2003–2023, with 2729 patients in 8 studies (4 randomized controlled trials and 4 retrospective studies) of neoadjuvant surgery in colon cancer, demonstrated a complete pathological response of 4.6% and proved that surgery can be performed with good oncologic principles, obtaining better R0, DFS, and OS rates. It was concluded that it is a practical approach supported by evidence in the literature.[17] Table 14.3 summarizes the results of neoadjuvant treatment studies in colon cancer.

Table 14.3. Results of published trials on neoadjuvant therapy in colon cancer.

Trial	N	Age	rT4	rN+ (%)	Neoadj (%)	Safe Sx	Endpoint
FOXTROX	1052	65	25.5	75.3	90	+	R2 2-year recurrence
PRODIGE 22	104	63	11.5	76.9	96	+	TRG
OPTICAL	738	56	75.4	77.2	93.5	+	3-year DFS
NeoCol	250	66	26%			+	3-year DFS

Radiotherapy

Neoadjuvant radiotherapy is not widely used. A single-center study and a National Cancer Database study concluded that neoadjuvant radiotherapy may be associated with greater tumor downstaging, higher R0 resection rate, and improved OS.[18,19]

Neoadjuvant immunotherapy according to MMR status

Immunotherapy in pMMR tumors

The mismatch repair (MMR) system is responsible for repairing small sequence errors (1 to 4 base pairs) produced during DNA replication. The state of this system can be proficient (pMMR) or deficient (dMMR) and this has therapeutic implications.

The NICHE 1 study suggests a potential role for neoadjuvant immunotherapy in non-metastatic patients with locally advanced or potentially resectable tumors. Thirty-one pMMR patients treated with neoadjuvant ipilimumab plus nivolumab were studied versus a control group treated with 2 doses of celecoxib (cyclooxygenase and PGE2 inhibitor). Mild toxicity was observed in 13%. The results were impressive in 9 patients, with 4 complete responses, 3 major responses with less than 10% viable tumor, and 2 partial responses with less than 50% remaining tumor. The remaining 22 patients did not respond to treatment with more than 50% viability. There were only 2 patients with recurrence, classified as non-responders. Considering that metastatic pMMR patients have a poor response to checkpoint inhibitors, the efficacy achieved by immunotherapy in NICHE 1 has unprecedented results and suggests that the immunological context in the early stages of the primary tumor is more sensitive to immunotherapy than in the metastatic context. The presence of CD8 and PD1 expressing T cells improved the response, resulting in a predictive biomarker of response to immunotherapy to be validated.[20]

The NEST1 trial (NCT05571293) evaluated neoadjuvant immunotherapy with botensilimab (anti-CTLA4 enhanced agent) plus balstilimab (anti-PD1) in stage I-III in proficient tumors. A dramatic pathologic response was reported in 2 patients.[21] A similar situation occurred in the NICOLE study with the use of antiPD1, where 2 of the 18 patients had a major pathologic response and 1 of them a complete response.[22]

Neoadjuvant therapy is ideal for evaluating the efficacy of therapies targeting early-stage disease with mutated BRAF V600E or amplified HER2.

Immunotherapy in dMMR tumors

Metastatic dMMR tumors are rare (5%) and are more commonly seen in patients with earlier stages (15-18% in stage II and 11% in stage III). They have a more favorable prognosis but are less sensitive to chemotherapy, so adjuvant chemotherapy is not recommended for stage II dMMR tumors. Both FOxTROT and OPTICAL demonstrated a lack of response or resistance to neoadjuvant chemotherapy in these cases.[11,15]

In the NICHE1 study, the dMMR group (47% T4 and 78% N+) had excellent clinical and pathological response. After a 32-month follow-up, recurrence-free survival was 100%.[20] The NICHE2 study included 113 patients with non-metastatic resectable dMMR tumors, treated with the same neoadjuvant regimen. Most patients were high risk (63% T4, 62% N2, and 48% T4N2). Major pathological response was observed in 95% with 67% complete pathological response. One-hundred percent had R0, with no impact on oncological surgical outcome. With a 13-month follow-up, recurrence-free survival was 100%. Immunotherapy was extremely well tolerated with no related mortality.[23]

The PICC trial conducted in China, studied a group with neoadjuvant therapy with immune checkpoint inhibitors compared to a control group with celecoxib. Thirty-four patients were included, 17 with toripalimab (anti-PD1) for 3 months and 17 with celecoxib. All had R0 and complete response was 88 vs. 65%, respectively. After a 15-month follow-up, OS and DFS were 100%.[24]

The NICHE3 study, recently presented at the European Congress of Oncology, evaluated the treatment of resectable patients with dMMR tumors with 2 doses of nivolumab with relatlimab (anti-LAG3 antibody). Tolerance was excellent and the outcome was impressive, with a major pathological response of 89% and a complete pathological response of 79%. It included unstable T4N2 patients who did not require emergency surgery, who received 2 applications of nivolumab (antiPD1) and ipilimumab (antiCTLA4). All were resected and were R0. Toxicity was minor, with only 4% serious adverse events. Complete pathological response was 100% in dMMR and 27% in pMMR.[25]

Between the NICHE1 and NICHE2 studies, a 67% tumor disappearance and 95% regression were observed, with no recurrence.

The evidence for neoadjuvant immunotherapy in non-metastatic colon tumors is compelling. Only the NICOLE study did not find a complete pathological response. Therefore, according to the NICHE study, it is recommended that patients with cT4b,
antiPD1 could be used if the approach is nonsurgical. Monotherapy is less toxic, but the combination would seem to be more effective.

Final comments

Despite the existing evidence, neoadjuvant therapy should not be considered as standard therapy for colon tumors. However:
- Six-week chemotherapy treatment has been shown to be safe with a reduction in the recurrence rate at 2 years.
- It may be considered, particularly for locally advanced tumors (T4 or N2), with a higher risk of surgery or incomplete resection.
- In the case of MSI, do not consider the application of chemotherapy without associated immunotherapy.

Neoadjuvant therapy in locally unresectable tumors

Neoadjuvant therapy is recommended in some situations of advanced tumors. The described regimens are FOLFOX and CAPOX. When a locally advanced tumor is initially unresectable, it is suggested to evaluate its conversion to resectable by using preoperative chemotherapy and radiotherapy (conversion neoadjuvant therapy). A 23% decrease in the risk of death at 3 years was reported in patients with T4b who received neoadjuvant therapy.[9,24]

A prospective randomized study of patients with T3-T4, N0-N2 treated with preoperative FOLFOX found a 59% histopathologic regression and a 3.5% complete pathological response. In addition, a lower rate of incomplete resection, a higher rate of R0 resection, and a lower 2-year recurrence were observed, although there was no significant difference in 2-year DFS.[11]

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CHAPTER 15
Adjuvant therapy

General principles

Systemic adjuvant therapy consists of chemotherapy administered after surgical treatment to prevent postoperative recurrence and improve the prognosis of patients after R0 resection. It is also indicated to treat unresectable colon cancer.[1,2]

The rationale for adjuvant therapy is to treat tumor disease at a time when it is of smaller size and most likely to be eradicated. If a regimen is effective in reducing tumor size or progression, it can also effectively treat residual microscopic disease after surgery. Curability is greatest when the number of cells that make up the tumor population is smaller. A cycle of chemotherapy allows this population to be reduced, although it is recovered by cell growth between cycles. Adjuvant therapy for CRC began in the 1970s with regimens based on 5-fluorouracil (5FU), a drug useful in the treatment of advanced disease.[3,4]

The high incidence of lymph node involvement at the time of surgery and recurrence rates of over 50%, support the need to add therapy after removal of macroscopic disease. Micrometastatic disease exists in operated patients considered free of lymph node disease by traditional pathology techniques.

Adjuvant therapy is based on the treatment of residual microscopic disease, theoretically considered a preventive treatment, depending on the risk of disease persistence or recurrence.

The American cooperative group National Surgical Adjuvant Breast and Bowel Project (NSABP) published the first prospective study showing a significant difference in survival of patients operated on for CRC who received postoperative chemotherapy.[5]

Most drugs are common to all countries but immune or molecular therapy varies according to each national health institute, or drug approval system. The main drugs for the chemotherapy treatment of colon cancer are:

- Cytotoxic drugs: 5FU, leucovorin (LV), Capecitabine (Cape), Irinotecan (Iri), Oxaliplatin (OXA).
- Molecular targeted drugs: bevacizumab (Bev), cetuximab (Cetu), panitumumab (Pani), regorafenib (Reg), aflibercept (AFL), ramurizumb (Ram).
- Immune checkpoint inhibitors: pembrolizumab (Pembro).

Chemotherapy regimens

The most commonly used regimens with proven benefits are:

- Monotherapy with fluoropyrimidine: Cape, 5FU + LV.
- Combined therapy with OXA: FOLFOX (5FU ± infusional LV + OXA), CapeOX or CAPOX: (Cape + OXA)
- Combined therapy with Iri: FOLFIRI (5FU + LV + Iri)

Other regimens are:

- FLOX: 5FU ± weekly infusional LV + biweekly OXA
- UFT+LV - tegafur uracil + LV- S-1: tegafur-gimeracil-oteracil potásico

The usual treatment period is 6 months, but it is adapted to each case and each patient.

The guidelines used in different regions of the world can be seen in Table 16.1.

Indications for adjuvant therapy

The principles of adjuvant therapy indication include:

- Stage II colon cancer with increased risk of recurrence.
- Stage III colon cancer with R0 resection: (T1-4 N1-2 M0 of the TNM classification and T1-4 N1-3 M0 of the Japanese classification).
- Stage IV colon cancer after surgical resection.
- Patient recovered from a postoperative complication.
- Patient with performance status PS 0-1.
- Patient without alteration of organ function.
- Patient without other associated complications.

Table 16.1. Chemotherapy regimens by region: Japan (a), USA (b), Europe (c).

JSCCR (a)[6]	NCCN (b)[7]	ESMO (c)[3]
UFT ± LV	FOLFOX	FOLFOX
Cape	CapeOX	CapeOX
S-1	FLOX	Cape
5FU ± LV	Cape	5FU ± LV
FOLFOX	5FU ± LV	
CapeOX		

Elderly patients or those over 70 years of age

Elderly patients or those over 70 years of age with high-risk stage II have not had benefits in OS and DFS with the addition of OXA to the treatment regimen.[1,3,4]

Timing of adjuvant chemotherapy initiation

The timing of adjuvant treatment initiation after surgery remains a matter of debate. Based on the evidence, it is relevant to initiate chemotherapy treatment as soon as possible, ideally no later than 8 weeks after surgery. Evidence IIB.[1,4]

A meta-analysis of 14 studies demonstrated that a delay of more than 8 weeks in the initiation of adjuvant chemotherapy is associated with a higher relative risk of death (HR 1.02; 95% CI 1.15-1.26; p = 0.001).8 Likewise, Japanese guidelines recommend starting adjuvant chemotherapy within 4 to 8 weeks of surgery and continuing it for 6 months.[6]

Although other studies have shown that adjuvant therapy may be useful even if started at 5 or 6 months, the benefit is apparently minimal or virtually nonexistent if treatment is started after 6 months postoperatively.[9]

According to ASRCS, adjuvant chemotherapy should begin within 8 weeks of colon resection. Evidence IB.[4]

Recommendations from Asian guidelines[2]

- The combination of fluoropyrimidine, either 5FU or Cape with OXA, constitutes the basis for adjuvant treatment of stage III colon cancer. Evidence IA.
- Adjuvant treatment of stage III colon cancer based on OXA, can be indicated for 3 to 6 months in the CAPOX regimen and 6 months for the FOLFOX regimen, following the evidence from the IDEA study. Evidence IA.
- According to the IDEA study, adjuvant treatment can be individualized according to 3 risk subgroups: 1) in T1-3 N1: 3 months of CAPOX, 2) in any T4 or any N2: 6 months of

CAPOX and 3) in any of the previous scenarios: 6 months of FOLFOX.
- For patients with intolerance to OXA, Cape or 5FU + LV for 6 months constitute acceptable regimens. Evidence IA.
- It is important to start chemotherapy as soon as possible after surgery, ideally not later than 8 weeks. Evidence IA.

Evaluation of recurrence risk and benefits of adjuvant therapy

TNM staging remains the relevant criterion for postoperative oncologic risk assessment. Five-year survival after surgical resection is 99% for stage I, 68-83% for stage II, 45-65% for stage III, and about 20% for stage IV.[1,2,4]

Recurrence risk assessment is relevant and is estimated taking into account clinical and histological findings and the MMR/MSI status of the tumor.

Adjuvant systemic therapy with 5FU decreases the risk of death by 3-5% in high-risk stage II tumors and by 10-15% in stage III tumors. Adding OXA to the treatment adds 4-5% improvement. Evidence IA.[4]

Stage I tumors usually have a cure rate of more than 90% with surgery, so they do not require adjuvant treatment. The risk is so low that the absolute value of the potential benefit is negligible and the risk/benefit equation due to treatment complications contraindicates therapy.[4]

In stage II and stage III tumors, the risk of residual microscopic disease increases depending on the depth of tumor invasion and the involvement of regional lymph nodes. The risk is variable and in some cases, greater than 50%, so adjuvant treatment is especially relevant.[4]

The particular situation of patients with stage II is highlighted, as they are divided into two groups of low and high risk of recurrence. The definition of the risk of patients with stage II includes other parameters that greatly influence their prognosis. The major prognostic parameters are lymphatic mapping with less than 12 nodes and pT4, including perforation. The minor prognostic parameters are: high grade of tumor differentiation, vascular, lymphatic, or perineural invasion, tumor obstruction and high preoperative CEA level.

In a Memorial Sloan Kettering Cancer Center multivariate analysis of patients with stage II, only 3 factors had independent prognostic influence: T4, elevated preoperative CEA, and lymphovascular or perineural invasion. The 5-year specific survival rate for patients with 1, 2, or more than 2 factors was 95%, 85%, and 57%, respectively.[10]

There is a subgroup of patients with stage II tumors (10-15%) with a very low risk of recurrence, in whom the benefits of fluoropyrimidine have not been demonstrated, and who should therefore not receive adjuvant chemotherapy. Evidence IA.[4]

Molecular aspects in risk assessment

According to NCCN guidelines, all new colon cancers should be evaluated for expression of DNA repair proteins and to rule out MSI (MMR) status.[7]

Five to fifteen percent of colon tumors have this mutation mechanism as the only one related to their pathogenesis, while 3-5% are associated with Lynch syndrome, the most common form of hereditary cancer. They tend to be tumors with greater chemoresistance and their preferred treatment is based on immunotherapy. Another peculiarity is that the incidence decreases as the stage is more advanced; while it is 15% in stage II, it is only 5% in metastatic disease.

Clinically, these tumors are located in the right colon, occur in younger patients (under 45 years of age), are poorly differentiated, mucinous, with signet ring cells and present peritumoral lymphocytic infiltration (marker of MSI-H). They have a better prognosis in stage II, but do not benefit from chemotherapy with 5FU, have a worse prognosis and chemoresistance in stage IV.

MMR/MSI status is the most validated prognostic molecular marker for deciding on adjuvant therapy, in association with other clinical prognostic factors. The dMMR status can be identified by immunohistochemistry (IHC), detecting the loss of MMR protein expression (MLH1, MSH2, MSH6, PMS2), or by polymerase chain reaction (PCR) that determines the MS status and microsatellite mutation. The determination of the MMR/MS status in localized colon tumors has two objectives: to characterize the prognosis and predict the benefit of adjuvant therapy, and on the other hand, to determine the genetic predisposition.[11]

MSI/dMMR is more prevalent in stage II than in stage III (21 vs. 14%). dMMR tumors are typically located in the right colon, have a mucinous histology with tumor-infiltrating lymphocytes, and have a better prognosis than tumors with microsatellite stability (MSS).[12,13]

Determination of MMR/MS status is important to rule out Lynch syndrome. Loss of MSH2 and/or MSH6 protein on IHC indicates suspicion of Lynch syndrome, whereas loss of MLH1 and PMS2 requires investigation of the BRAF mutation or hypermethylation of the MLH1 promoter region, since the identification of some of these mutations suggests a high probability of an acquired alteration of the somatic MLH1 gene rather than Lynch syndrome.[14] In addition to the implication of the diagnosis of Lynch syndrome, dMMR/MS status defines a subgroup of patients with a better prognosis and less benefit from chemotherapy.[15]

MMR/MS status determination should be requested in all cases based on the following premises according to the stage:
- Stage I: The determination of instability does not modify the approach. Its advantage is to perform individual and family genetic screening.
- Stage II: Unlike what happens in stable patients, the prognosis of unstable patients worsens with fluoropyrimidine-based chemotherapy, so to decide on adjuvant chemotherapy, especially in patients with a high risk of recurrence (less than 12 nodes examined, perineural or lymphovascular invasion), it is necessary to know the MMR status. dMMR patients do not benefit from chemotherapy with 5FU.
- Stage III (pT3N+M0): The standard is surgery followed by adjuvant therapy with FOLFOX or CAPOX/XELOX. The determination of MSI does not modify the indication for chemotherapy. However, early studies such as NICHE (neoadjuvant therapy in early colon cancer) showed an almost complete pathological response and minimal residual disease in unstable patients, so it could be a validated future therapy, even in localized tumors.
- Stage IV: According to the Keynote 177 study, determining stability first should be the standard, reserving immunotherapy with pembrolizumab for unstable tumors due to the better outcomes achieved.

Biomarkers

Currently, for routine assessment of resistance risk in non-metastatic patients, the study of MSI/MMR status and other genetic markers such as RAS and BRAF and their mutations is recommended.

Other biomarkers, such as genetic signature, Immunoscore, CD-X2 and postoperative circulating DNA, have shown some benefits in determining prognosis.[16–18]

Genetic signatures

Genetic signatures have emerged for prognostic stratification in locoregional disease, i.e. for an accurate and personalized assessment of the risk of relapse and the benefits of chemotherapy. The best documented validated tool is Oncotype DX and the FxColon gene. They are obtained from formalin-fixed, paraffin-embedded tumor samples.

The Oncotype DX is a test that quantifies the expression of 5 reference genes and 7 recurrence risk genes, with a prognostic classification that establishes the low, intermediate and high probability of recurrence of colon cancer. It is used in tumor samples from patients with stage II. The Cancer and Leukemia Group B (CALGB) study showed an average recurrence index of 31.4 (range: 2-78). An increase of 25 points in the index was significantly associated with the risk of recurrence.[19]

In a similar analysis from the National Surgical Adjuvant Breast and Bowel Project (NSABP C-07), in patients with stage II, a high recurrence index was associated with a higher recurrence rate (HR 2.11; $p < 0.001$), and lower OS and DFS when compared with a low recurrence index, with an increased benefit of OXA in the chemotherapy regimen.[20]

This was corroborated by the QUASAR study (13-gene study) which reported a 3-year recurrence of 12, 18 and 22% in stage II patients classified as low, intermediate and high risk, respectively.[21]

ColorPrint is a multigene assay that studies the expression of 18 genes and quantifies the high or low probability of cancer recurrence. In a study of 206 patients with stage II-III colon cancer, the 5-year recurrence-free survival rate was 88% for those with low probability and 67% for those with high probability.[22]

ColDx is a multigene assay that uses 634 helper tests to identify patients with stage II colon cancer at high risk of recurrence. In one study, those identified by this assay had a high risk of recurrence and decreased recurrence-free survival compared to those at low risk.[23]

Following the above-mentioned studies, genetic signature analysis could be considered to complement histopathological findings in order to determine chemotherapy treatment in stage II patients. For example, treating T3N0 patients, classified as high risk based on their genetic signature, and avoiding chemotherapy in T4N0 patients classified as low risk. Evidence IIC. However, this has not been validated by any regulatory entity and according to ASCO, NCCN and ESMO there is insufficient data to recommend the use of multigene panels to determine adjuvant therapy.[1,7,24]

Immunoscore

The Immunoscore involves quantification of the T cell population, particularly CD3+ and CD8+, in the center of the tumor and at the invasion margins, using histopathology. It is both a prognostic and predictive test.

The Immunoscore was recently validated in a prospective cohort of over 2500 patients with stage I-III. It was a strong predictor of time to recurrence, OS, and DFS, independently of age, sex, MSI status, and other prognostic factors.[25]

A study from the Society for Immunotherapy for Cancer, in an international consortium of 14 centers in 13 countries, retrospectively evaluated a standardized Immunoscore assay in patients with stage I-III. stage I-III. primary colon tumors, demonstrating that it provides reliable evidence on the risk of recurrence.[26]

A comparative evaluation of the outcome of patients receiving adjuvant chemotherapy vs. observation demonstrated a survival benefit of chemotherapy only in patients with a high Immunoscore.[27]

Retrospective analysis of evidence from the French study, which included patients with stage III colon cancer at low and high clinical risk, demonstrated that an intermediate and high Immunoscore significantly predicts the benefit of administering 6 vs. 3 months of adjuvant therapy with FOLFOX regimen.[28]

Retrospective analysis of the French study, which included patients with stage II colon cancer at low and high clinical risk, demonstrated that an intermediate and high Immunoscore significantly predicts the benefit of administering 6 vs. 3 months of adjuvant therapy with FOLFOX regimen.[2]

The Immunoscore could be used as an additional prognostic information to identify high-risk stage II and stage III subgroups of patients and redefine the benefit of adjuvant chemotherapy. Evidence IIIC-IVB.[2]

CD X2

CDX2 is a transcription factor that has recently been shown to be important in identifying high-risk stage II colon cancer patients who may benefit from adjuvant chemotherapy. Patients with CDX2-negative tumors had a significantly lower 5-year DFS than those with CDX2-positive tumors. In turn, the incidence of 5-year DFS was higher in CDX2-negative patients treated with adjuvant chemotherapy than in those without treatment (91 vs. 56%; $p = 0.006$; respectively).[16]

According to the ASCRS in its latest publication of practice parameters, multigene assays, CDX2 expression analysis and circulating tumor DNA (ctDNA) or liquid biopsy, should be used to complement the multidisciplinary decision in stage II and stage III colon cancer patients. Evidence IB.[4]

Circulating tumor DNA (ctDNA) or liquid biopsy

Liquid biopsy is the determination of tumor DNA fragments that are in the bloodstream and can be used as markers of residual or recurrent disease. The presence of ctDNA can be used both for risk assessment and to identify patients at high risk of recurrence.

Liquid biopsy may also be useful in follow-up after surgical resection and adjuvant chemotherapy, to detect recurrences earlier than with current follow-up procedures.

A correlation between decreased ctDNA and tumor response has been demonstrated during systemic therapy for metastatic colon cancer. Thus, ctDNA is being studied to determine whether it could be a useful marker for monitoring adjuvant treatment.[29]

There are some studies worth highlighting, such as a prospective analysis of patients with stage II colon cancer, in which the detection of ctDNA immediately after completing adjuvant chemotherapy was associated with a lower recurrence-free survival.

In a similar study, patients with stage III colon cancer with detectable ctDNA after completing adjuvant treatment had a recurrence-free survival of 30% compared with 77% in those without detectable ctDNA.[30] An additional study reported a 17-fold increased risk of recurrence if ctDNA remained detectable after completing adjuvant chemotherapy.[17]

In another study, in patients not treated with chemotherapy, positive ctDNA was detected in 7.9%, with a recurrence rate of 79%. Recurrence occurred in only 9.8% of patients with negative ctDNA, with a statistical difference in patients treated with chemotherapy. Positive ctDNA after completion of chemotherapy was associated with a lower DFS.[31]

Postoperative determination of ctDNA in stage II patients has been shown in these early studies to provide direct evidence of residual disease, and to identify patients at very high risk of recurrence. Two trials (CIRCULATE-IDEA and CIRCULATE-EUROPE) are under development to determine the role of liquid biopsy.

In the recently published study by Hofste et al.[32] on 53 patients with colorectal metastases resected with curative intent, mutation analysis of 15 specific tumor genes and determination of ctDNA were performed preoperatively and one week after surgery. ctDNA was detected in preoperative samples in 88% of patients who did not receive preoperative systemic treatment, 55% of patients with chemotherapy, 75% of patients with no pathological response, and 0% of patients with good pathological response ($p < 0.06$). Postoperatively, ctDNA was found in 80% of patients with incomplete resection and 0% of patients with complete resection ($p = 0.003$).

The DYNAMIC study was based on the premise that postoperative ctDNA predicts very low recurrence-free survival, whereas its absence predicts a low risk of recurrence. Patients with a positive postoperative liquid biopsy received adjuvant chemotherapy, whereas those with a negative result did not receive treatment. The 3-year recurrence-free survival was 86.4 and 92.5%, respectively. Liquid biopsy reduced the use of adjuvant chemotherapy in patients with stage II, without compromising recurrence-free survival.[33]

There are numerous trials in development (9NCT04068103 COBRA, NCT 04120701 CIRCULATE, ACTRN12615000381583 or DYNAMIC-II) that may answer whether ctDNA can be successfully used as a marker of survival, recurrence, or effectiveness of adjuvant therapy.

Current NIH guidelines through NCCN state that these assays can report the risk of cancer recurrence on other risk factors, but consider that there is insufficient evidence to recommend the use of liquid biopsy in daily clinical practice to determine adjuvant treatment.[7] The same situation occurs with the guidelines of the European Society of Medical Oncology (ESMO).[1,34] The Japanese guidelines only include the determination of the MSI/MMR status.[6]

Recommendations

- The risk of recurrence after surgery for colon cancer should be assessed by integrating the TNM system, MMR/MS status, and the number of lymph nodes examined. Evidence IIIA.
- To redefine the risk of recurrence in patients with stage II, other additional clinical-pathological factors should be used, such as the histological subtype and its grade of differentiation, venous, lymphatic, or perineural invasion, lymphoid inflammatory response, involvement of resection margins, and CEA level. Evidence IIIA.
- The patient's age has no predictive value for indicating or not adjuvant therapy; other situations such as life expectancy and comorbidities should be considered. However, it can be generalized that the combination of fluoropyrimidine and OXA seems to have a more limited benefit with a greater possibility of toxicity in elderly patients.
- MS/MMR status is the only molecular marker validated and used in the decision of adjuvant treatment in patients with stage II. In stage III, its use is limited to identifying Lynch syndrome. Evidence IVA.
- Determination of dihydropyrimidine dehydrogenase deficiency, both genotypically and phenotypically, is recommended before adjuvant fluoropyrimidine-based treatment, in order to avoid adverse effects. Evidence IIIA.
- Gene expression signature is not routinely recommended in practice given its lack of predictive value for the benefit of chemotherapy. However, it can be used to complement the clinical-pathological evaluation in patients with intermediate-risk stage II. Evidence IIC.
- The Immunoscore could be considered together with the TNM to redefine the prognosis of early colon cancer and adjust the decision of adjuvant treatment in patients with stage II, or low-risk stage III. Evidence IIIC.

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CHAPTER 16
Systemic treatment according to the tumor stage

Stage II

Better progression -free survival and OS have been demonstrated in patients in stage II and stage III treated with fluoropyrimidine-based adjuvant chemotherapy compared to those treated with surgery only.[1–4]

The Quasar study randomized 3238 patients in stage III treated with chemotherapy based on 5FU vs. observation, finding only one tendency towards a better 5 -year OS (83.9 vs. 81.5%, respectively).[5] The Impact B2 study found a small but not statistically significant improvement in DFS and OS at 5 years with the adjuvant treatment.[6]

On the other hand, Cancer Care Ontario found a small but significant improvement (5-10%) in DFS.[7]

In 2004, an expert panel of the American Society of Cancer Oncology (ASCO) concluded that the evidence does not support the routine use of adjuvant chemotherapy for colon cancer in stage II.

The Intergroup included data from 3302 patients with stage II and stage III colon cancer from 7 randomized trials comparing surgery and 5FU vs. surgery alone. For stage IIdisease, there was a statistically significant improvement in 5-year DFS in favor of chemotherapy (76% vs. 72%), but there was no statistically significant improvement for OS (81% vs. 75%).[8]

The Accent group analyzed a group of patients with stage II over the long term, finding that adjuvant chemotherapy was associated with a 5% absolute improvement in OS at 8 years (72 vs. 66.8%).[1–3]

According to ASCRS, there is controversy regarding the treatment of all patients with stage II, so they have been classified as low and high risk based on 5-year DFS, which reaches 90% in patients with well-differentiated T3 tumors and 74% in those with poorly differentiated T4b tumors.[9] Most evidence suggests that there is minimal benefit from adjuvant chemotherapy in patients with low-risk stage II colon cancer

The MOSAIC trial initially demonstrated that the addition of OXA to patients with high-risk stage II was beneficial. However, a recent analysis of this same trial did not demonstrate any benefit with OXA, regardless of whether the patient was in high- or low-risk stage II.[10]

In general, the prognosis of patients with stage II is better than that of patients with stage III. However, subgroups of stage II with MSI, deletion of chromosome 18q or elevation of CEA have been identified, with an aggressive biological behavior similar to or even worse than that of some stage III subgroups. In this subgroup of high-risk or poor-prognosis patients, the relative benefit of adjuvant treatment would be clearly superior.[11–14]

Patients with high-risk stage II colon cancer are defined as those with perforation, obstruction, lymph node count less than 12, positive resection margin, T4b, poor cell differentiation, lymphovascular or perineural invasion, high-grade tumor budding, with or without MSI.[13,14] These patients, with one or more of these factors present, have a similar risk of recurrence to patients with stage III and are currently considered for routine adjuvant chemotherapy, as it may offer a survival benefit. Evidence IIB.[1–3]

Stage II risk groups

There are major and minor clinical and pathologic factors that affect the time to recurrence of stage II colon cancer. The presence of major factors such as T4 (including perforation) and lymph node count less than 12 nodes increases the risk of recurrence, while other additional factors are less significantly associated. Surveillance is an option for low-risk stage II patients, but chemotherapy is recommended for those at intermediate and high risk. Level of evidence IB.[1–3,15]

Although the Gramont regimen with fluoropyrimidine and LV is the only one that has demonstrated efficacy in this scenario, Cape is also an option, especially when the use of central lines is contraindicated. Evidence IB.[1–3,15]

In the Japanese phase III SACURA study, tumor budding and histologic grade were independent prognostic factors in stage II. The budding score was significantly correlated with recurrence in the liver, lungs, lymph nodes, and peritoneum, so they recommend its evaluation in all cases. They also found that in patients with high tumor budding, the fluoropyrimidine monotherapy regimen was associated with improved relapse-free survival.[16,17]

In a retrospective study, Shin et al.[18] evaluated 1390 patients operated on between 2007 and 2013 for stage II colon cancer, defining high-grade tumor budding as the presence of $\geq$ 10 cellular nests. They found that 10.5% of those with high-grade tumor budding also had advanced T stage, poor cell differentiation, lymphatic invasion, and perineural invasion. There were no differences in 5-year OS, but DFS was lower in this group (81.3 vs. 93.5%; $p < 0.03$) and there was no benefit from adjuvant therapy. They concluded that high-grade tumor budding associated with vascular and perineural invasion, and adjuvant treatment were independent factors for worse prognosis.

In intermediate- and high-risk patients, there is a trend towards improved chemotherapy benefit with the addition of OXA. Evidence IB.[1–3]

The IDEA trial demonstrated that in the high-risk group the optimal duration of treatment with CAPOX regimen is 3 months and with FOLFOX 6 months.[19]

The presence of MSI/MMR indicates a better prognosis and less benefit from adjuvant therapy, so chemotherapy with OXA should be indicated with caution in this group.[11,20]

For ASCO, NCCN and ESMO, in high-risk stage II patients, poorly differentiated histology represents an adverse feature only if they do not have MSI and lack a BRAF mutation.[21]

The addition of aspirin reduces the risk of polyp formation and may improve survival in approximately 20% of patients with colon cancer. However, this claim remains under study in ongoing trials.

OXA in stage II

No study has achieved statistical power to consider the addition of OXA as standard in stage II, although this could be argued for high-risk groups. There is little evidence to support that patients considered high risk are more likely to benefit from chemotherapy than from surgery alone plus observation. The long-term results of the MOSAIC and NSABP studies did not demonstrate any clinical benefit of the addition of OXA to a 5FU regimen for the treatment of patients with colon cancer in stage II.[21,22]

MOSAIC compared adjuvant 5FU/LV for 6 months vs. FOLFOX in patients with stage II (40%) and stage III colon cancer (60%) and in an initial analysis the addition of OXA demonstrated a small but significant increase in 6-year OS (79 vs. 76%) limited to stage III patients. In stage II patients, 5-year DFS was not significantly longer with FOLFOX (84 vs. 80%) and 6-year OS was identical (87%).[10] In 2015, an updated analysis demonstrated a greater absolute OS benefit for OXA in stage III (57% vs. 59%) while FOLFOX demonstrated absolutely no survival benefit over 5 FU/LV for stage II (78% vs. 79%). This study suggests that patients

with high-risk stage II (e.g. T4b) might benefit from the addition of OXA with regard to DFS, although it is underpowered.[21]

NSABP C-07 compared the Roswell Park regimen (5FU/LV) vs. the FLOX regimen (5FU ± weekly infusional LV + biweekly OXA) for stage II and stage III. With 8-year follow-up, in stage III, the 5-year DFS significantly favored FLOX (69 vs. 64%), but the OS was not significantly different (80 vs. 78%). However, there was no benefit in stage II.[22]

Improvement in OS has been shown in high-risk stage II, but this benefit is limited to those patients with intestinal perforation, obstruction, T4 tumors or less than 12 nodes evaluated.[23]

Despite the lack of studies with sufficient evidence, major guidelines suggest considering the high-risk subgroup when deciding on adjuvant chemotherapy. FOLFOX and CAPOX remain the current standard of care for this group of patients. The FLOX regimen has a higher incidence of diarrhea and is therefore not currently considered. Irinotecan (Iri), cetuximab (Cetu) and bevacizumab (Bev) have not demonstrated clinical activity in localized disease and should therefore not be included in adjuvant treatment in this setting.[24–27]

In a 2010-2016 study of high-risk stage II patients (T4, perineural invasion, poor cell differentiation, and less than 12 nodes on histological analysis), 3 groups were evaluated: 1) without high-risk factors (18,056 patients), 2) with 1 factor (9,426 patients), and 3) with ≥2 factors (3,503 patients) and compared with 34,842 stage III patients. The 3- and 5-year survival rates were 59.1 and 68.1%, respectively, in stage III. In stage II without risk factors, it was 74.9 and 90.7%; with 1 risk factor, 67.1 and 82.4%; and with ≥ 2 factors, 49.2 and 59.5%, showing that this subgroup of stage II patients with multiple high-risk factors have a worse survival rate than those with stage III..[28]

Lymphatic, vascular, and perineural invasion are known to be prognostic factors for colon cancer. However, their prognostic significance based on the location of vascular invasion (intra- or extramural) in stage II remains unclear. This finding was evaluated in a cohort of 1130 patients who underwent radical surgery at Seoul National University Hospital between 2003 and 2015. The DFS and OS of patients with extramural invasion were significantly worse than those of patients without invasion or with intramural invasion. Multivariate survival analysis confirmed that extramural (as opposed to intramural) invasion is a highly significant independent prognostic factor associated with a worse prognosis in stage II colon cancer.[29]

Mucinous adenocarcinoma is a rare histological feature of CRC, with different oncological properties from adenocarcinoma. In a retrospective cohort study, 2532 patients in stage II and stage III were studied between 2010 and 2015. At 86 months, DFS and OS were significantly lower in the mucinous adenocarcinoma group. When evaluating subgroups, multivariate analysis demonstrated that mucinous adenocarcinoma was a poor prognostic factor for DFS and OS only in stage III patients. Therefore, in stage II patients, mucinous adenocarcinoma could not be considered an independent risk factor requiring chemotherapy for favorable oncological outcomes. However, for stage III colon cancer, patients with mucinous adenocarcinoma require close observation.[30]

Choice of chemotherapy régimen

The 5FU/LV regimen is the most commonly used. Cape is an option, although there are no data on the benefit of this drug in patients with stage II since the X-ACT study was conducted in patients with stage III.[31]

Some guidelines such as the NCCN, in patients with MSI or MSS (proficient DNA repair system, pMMR) tumors, recommend Cape alone as an alternative to FOLFOX or the 5FU/LV regimen. The FOLFOX regimen is an alternative to fluoropyrimidines for patients with high-risk stage II tumors with MSI (dMMR), since it can overcome the chemoresistance of these tumors.[32]

ESMO Recommendations:[1]

- In patients with low-risk stage II colon cancer, follow-up is recommended.
- In patients with intermediate-risk stage II colon cancer (MMR/MSS and any risk factor except pT4 or less than 12 nodes evaluated), a regimen with flouropyrimidine is recommended.
- Patients with high-risk stage II colon cancer (pT4 or less than 12 nodes, or with multiple intermediate risk factors, regardless of MSI), are candidates for treatment with OXA.
- In patients with high-risk stage II colon cancer, treatment with 3 months of CAPOX or 6 months of FOLFOX is recommended, according to the results of the IDEA study.

Fig. 16.1 outlines ESMO recommendations for adjuvant treatment of stage II colon cancer.

NCCN Recommendations:[32]

- Patients with T3-4N0M0, dMMR/MSI tumors should only be given observation.
- Patients with T3N0M0, MSS and no high-risk factors, should be given observation or consider fluopyrimidines for 6 months.
- Patients with T3N0M0, high-risk factors or T4N0M0 with stable MSS/pMMR tumors should be given a regimen with fluorpyrimidine, or OXA-based chemotherapy (CAPOX, FOLFOX) or observation without clarifying the duration of treatment.

Recommendations from Pan-Asian guidelines:[2,3]

- In patients with stage II colon cancer, clinical follow-up is recommended. Evidence IA.
- For stage II patients with intermediate risk and no MSI/MMR mutation associated with any of the risk factors except pT4 or evaluation of less than 12 lymph nodes, the recommended treatment is 6 months of fluoropyrimidines. Evidence IB.
- An acceptable alternative in patients in good general condition is treatment with 3 months of CAPOX.
- In patients with high-risk stage II, pT4, perforation, less than 12 evaluated lymph nodes, or multiple intermediate risk factors regardless of MMR status, given the high risk of relapse, the addition of OXA to the base regimen should be considered. Evidence IC.
- Patients with high-risk stage II can follow a 3-month CAPOX regimen according to the non-inferiority analysis of the IDEA study, or a 6-month FOLFOX regimen. Evidence IIB.

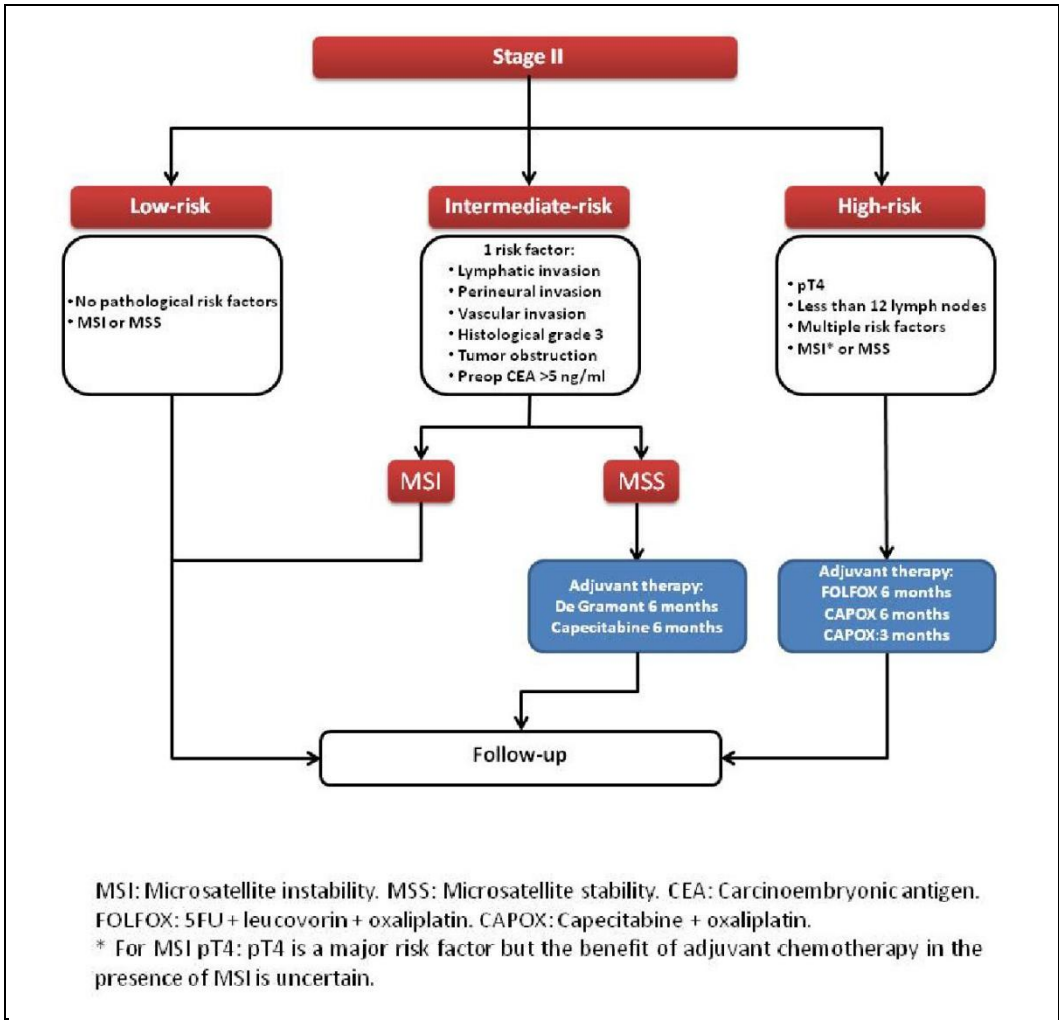

Figure 16.1. *Adjuvant treatment of stage II colon cancer recommended by ESMO.*

Stage III

In 1990, the NIH developed a consensus establishing adjuvant chemotherapy as the new standard of care for patients with resected stage III colon adenocarcinoma. This was based on a study showing that 5-year DFS in patients with positive lymph nodes was 44% with surgery alone vs. 61% when 5FU and levamisole were added, representing a 39% reduction in mortality ($p < 0.0001$).[1]

Levamisole was progressively replaced by LV (folic acid analog), a 5FU biomodulator with demonstrated clinical benefit in advanced disease. The NSABP conducted its C-03 study comparing 5FU + LV vs. MOF (semustine, vincristine, 5FU). The results showed superiority of the weekly 5FU/LV regimen with regard to DFS.[33]

Subsequently, the NSABP C-04 included 2151 patients with stage II and stage III, randomized into 3 groups: 5FU/LV, 5FU/LV/levamisole, and 5FU/levamisole. The 5-year DFS was 65% vs. 60% ($p = 0.04$), concluding that the addition of levamisole did not add benefit.[34] A similar finding was obtained by the INT-0089 Intergroup, concluding that the addition of levamisole does not add anything to the treatment. Therefore, 5FU/LV-based regimens are considered standard for adjuvant treatment in colon cancer.[35]

In patients with stage III colon cancer, adjuvant therapy is generally recommended. Evidence IA.[4]

In patients stage III, large multi-institutional studies have shown a survival benefit with OXA-based adjuvant chemotherapy. Cape is a safe and efficient alternative and can be used in combination with OXA (CAPOX).[1,4,27] In 2018, the International Duration Evaluation of Adjuvant Therapy collaboration (IDEA) published similar findings regarding outcome in patients with T1-T3 and N1 who received 3 or 6 months of OXA, with a 3-year DFS of 83%. However, in patients with T4 or N2, DFS was superior with 6 months of treatment.[19]

The current era of adjuvant therapy is based on studies that demonstrated benefit in OS by adding 5FU/LV to surgical treatment compared to surgery alone, with a 30% decrease in recurrence and 25-32% in mortality.

The current standard of care for adjuvant therapy in stage III is the combination of a fluoropyrimidine and OXA. This regimen is independent of MSI status. The significant DFS benefit of this combination over fluoropyrimidine monotherapy was demonstrated in three pivotal trials: MOSAIC, NSABP C-07 and NO16968.

In the MOSAIC study, the survival benefit (67 vs. 59%) was maintained at 10 years. The FOLFOX regimen was approved for adjuvant therapy of stage III colon cancer based on this study.[21]

The NSABP C-07 study randomized 2407 patients with stage II and stage III colon cancer, comparing a 5 FU/LV + OXA (FLOX) regimen vs. 5FU/LV for 6 months. With an 8-year follow-up, 5-year DFS favored the FLOX regimen

(69 vs. 64%), although the difference in OS was not statistically significant (80 vs. 78%).[36]

Study NO16968 compared 5 months of treatment with 5FU/LV (Roswell Park regimen) with CAPOX in 1886 stage III patients. At 74 months follow-up, both 7-year DFS (63 vs. 56%) and OS (73 vs. 67%) were significantly superior with CAPOX.[37]

NSABP C-07 used a bolus of fluoropyrimidine in both arms (5 FU/LV/Iri/OXA), whereas the XELOXA study used a bolus of fluoropyrimidine vs. a CAPOX regimen. The MOSAIC and NSABP C-07 studies included patients with colon cancer in stage II and stage III, whereas NO16968 included only stage III.

Although the chemotherapy regimens were different in the three studies, the addition of OXA resulted in a similar risk reduction (23% in MOSAIC and 20% in the other two studies). With long-term follow-up, all three trials demonstrated an improvement in OS with a reduction in the risk of death of 16% in MOSAIC, 12% in NSABP C-07, and 17% in NO16968. However, the improvement in OS was significant only in stage III.

In stage III colon cancer, CAPOX and FOLFOX regimens remain the current standard of care. The addition of Iri, Cetu, and Bev has not demonstrated relevant clinical significance in patients with localized cancer, so they should not be included in adjuvant treatment regimens in these cases. Evidence IE.[4]

Choice of chemotherapy regimen and treatment duration (IDEA Collaboration)

Cumulative sensory peripheral neuropathy toxicity is greater with 5FU + OXA. A 6-region, international, prospective, collaborative noninferiority study (IDEA) evaluated 12,834 patients with inflammatory bowel disease-associated colon cancer randomly assigned to receive 3 or 6 months of treatment with FOLFOX or CAPOX.[38]
According to the results of this study, the duration of treatment depends on the choice of regimen. In patients receiving the CAPOX regimen, 3-month treatment was non-inferior to 6-month treatment (3-year DFS 75.9 vs. 74.8%, respectively). In contrast, the 3-month FOLFOX regimen was definitely inferior (3-year DFS 73.6 vs. 76%). Therefore, non-inferiority was only demonstrated for a 3-month CAPOX regimen.

A subgroup analysis was also performed: lower risk (T1-T3 + N1) and higher risk (T4, N2, or both). For the higher risk subgroup, 3-month treatment was inferior.

After a follow-up of 72 months, 5-year OS was similar (82.4 vs. 82.8%). For low-risk patients, the difference in 5-year OS with 3 vs. 6 months of treatment was 89.6 vs. 88.9%, while for high-risk patients it was 72 vs. 74%. In patients treated with CAPOX, there was no significant difference in the 3- vs. 6-month regimen, but the results were inferior with 3 months of FOLFOX (5-year OS 68.4 vs. 71.7%).[19]

In the Asian ACHIEVE study, the HR for 3 months of treatment vs. 6 months of treatment was 1.07 for FOLFOX and 0.9 for CAPOX, similar to the findings of the IDEA study. This study recommends 3 months of CAPOX as the most appropriate therapy in low-risk stage III patients (T1-3 + N1).[39]

In conclusion, both the 3-month CAPOX regimen and the 6-month FOLFOX regimen can be recommended as adjuvant chemotherapy for patients with stage III colon cancer. Evidence IA.[1]

Fig. 16.2 outlines ESMO recommendations for adjuvant treatment of stage III colon cancer.

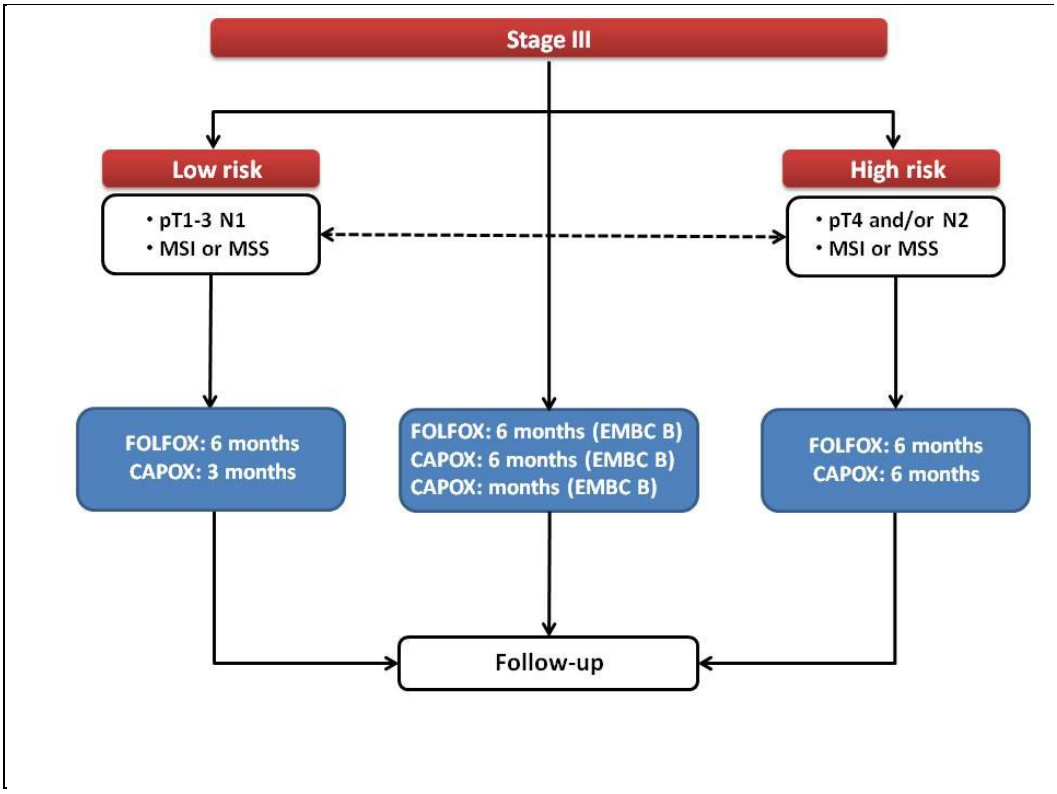

Figure 16.2. *Adjuvant treatment of stage III colon cancer recommended by ESMO.*

High and low risk groups in stage III

Although based on low-quality evidence, the IDEA study established high- and low-risk subgroups in EII. Evidence IVB.

In the low-risk subgroup (T1-T3 with N1), 3 months of adjuvant treatment would seem to be sufficient, when the CAPOX regimen is implemented. Evidence IIB.[4]

In the high-risk subgroup (T4, N2, or both), 6 months of treatment is necessary, especially when the regimen is FOLFOX, although the same is true for the CAPOX regimen. Evidence IIB.[1]

Final recommendations

- The combination of fluoropyrimidine, either 5FU or Cape, associated with OXA constitutes the basis for adjuvant treatment of EIII colon cancer. Evidence IA.
- The duration of OXA-based treatment can be 3 to 6 months for the CAPOX regimen and 6 months for the FOLFOX regimen, according to the evidence from the IDEA study. Evidence IA.
- Adjuvant treatment can be individualized by subgroups, with caution and strict analysis of each case: 3 months of CAPOX for T1-3 + N1, 6 months of CAPOX for any T4 or any N2, or 6 months of FOLFOX for any of these scenarios, according to the IDEA study.
- For patients unsuitable or intolerant to OXA, either Cape or 5FU/LV constitute acceptable regimens with a duration of 6 months. Evidence IA.
- It is important to start chemotherapy as soon as possible after surgery, ideally not later than 8 weeks. Evidence IA.

Stage IV

Adjuvant therapy in stage IV will be discussed in detail because it has multiple aspects related to resectability, the possibility of cure, conversion to resectable disease, and treatment aimed at controlling progression and symptoms.

Stage IV in colon tumors is associated with synchronous distant metastases in organs such as the liver, lung, peritoneum, brain, and lymph nodes not related to the primary tumor and in other less frequent organs (bone, spleen, adrenal glands). The incidence of synchronous metastases according to the Japanese Society registry[27] is shown in Table 16.1.

Table 16.1. Incidence of colon cancer metastasis by site. Registry of the Japanese Society for Cancer of the Colon and Rectum.[27]

Site of metastasis	Liver	Lung	Peritoneum	Bone	Brain	Virchow's lymph node	Other
%	11.8	2.2	5.7	0.3	0.01	0.1	1.3
N = 15391	1815	338	875	47	6	23	205

According to the ESMO 2023 guidelines, in general terms the strategy and planning of treatment for metastatic colon cancer can be summarized as follows (Fig. 16.3):[40]

- If both the primary tumor and distant metastases are resectable, curative resection of the primary tumor is indicated and resection of the metastases is considered.
- If the primary tumor is resectable but the metastases are unresectable, resection of the primary tumor is indicated based on the clinical picture and its impact on prognosis.
- If the primary tumor is unresectable and the metastases are resectable, another therapeutic option is considered instead of initial surgical resection.

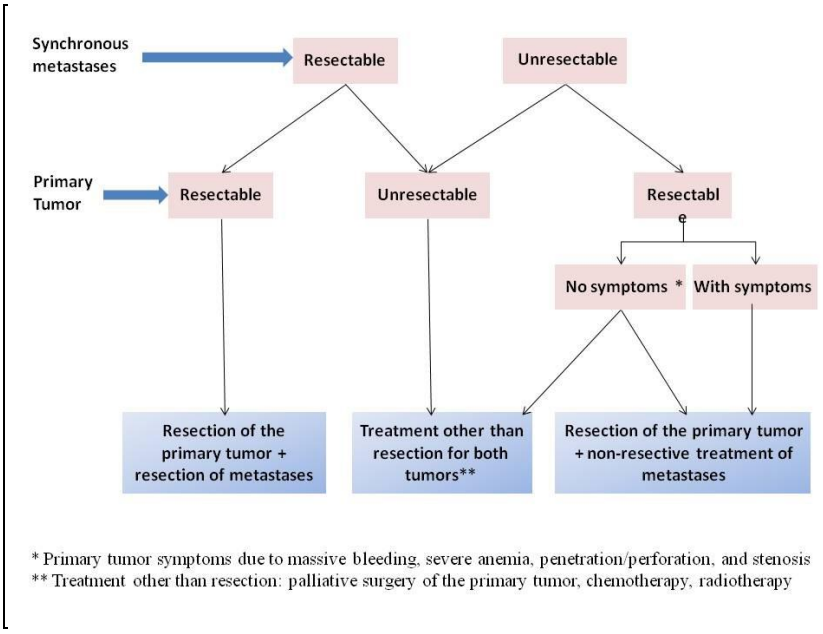

Figure 16.3. *Treatment strategies for metastatic colon cancer according to ESMO 2023 guidelines.*[40]

Stage IV resectable or potentially resectable

Before planning treatment, it is important to clearly distinguish resectable metastatic disease from that which can potentially be converted to resectable disease after preoperative chemotherapy. Conversion to resectable disease is based on the standard chemotherapy regimen with the combination of Bev or Cetu.

In patients with resectable lung or liver disease with curative intent, resection of the primary tumor should be considered, particularly in patients with good performance status,[4,41] This algorithm is summarized in Fig. 16.4.

The treatment of patients with stage IV colon cancer should be approached in a multidisciplinary context, as with most complex cases. Evidence IB.4 The multidisciplinary approach has been shown to increase the rate of metastasectomy and improve survival in patients with stage IV colon cancer.[40]

Patients with resectable liver metastases can be treated with neoadjuvant chemotherapy followed by surgical resection or initial surgery, depending on the type of metastasis and the experience of the team. Evidence IIB.[4] According to ESMO, if the liver metastasis is resectable, it should be resected after confirming radical excision of the primary tumor. Resection of the primary tumor and the metastases can be performed simultaneously or synchronously depending on the difficulty and complexity of the liver resection. If the complexity is greater, the recommendation is metachronous resection. There is still controversy about whether resection has an impact on the prognosis of the disease depending on whether it is simultaneous or deferred. [4,40]

In patients with resectable metastases, favorable prognostic criteria, and good surgical approach, systemic perioperative treatment may not be necessary. Evidence IIB.[4]

In left colon tumors with wild type (KRAS-wt) or non-mutated KRAS, conversion chemotherapy should be indicated when the goal is R0 resection. A perioperative regimen based on OXA, associated with anti-EGFR monoclonal antibodies, is recommended. Evidence IIA.[4]

In patients with right colon cancer and/or mutated KRAS, the FOLFIRINOX regimen, also called FOLFOXIRI (5FU/LV + OXA + Iri), associated with Bev should be considered as the best treatment option. Evidence IA.[4]

The role of systemic chemotherapy in the setting of resectable liver metastases was evaluated in the EORTC 40983 trial in patients with up to 4 resectable liver metastases. They randomized treatment with surgery alone vs. 6 cycles of neoadjuvant FOLFOX, followed by metastasectomy and then 6 cycles of adjuvant therapy with the same regimen. Complications of liver resection were higher (25 vs. 16%) in the chemotherapy arm. At 3 years, there was a 7% higher progression-free survival (35 vs. 28%) in the perioperative chemotherapy arm. With a follow-up of 8.5 years, 5-year OS did not differ significantly between the two groups (51 vs. 48%). Based on evidence of improved disease-free progression with perioperative chemotherapy, the investigators recommend this approach.[41]

Current NCCN guidelines recommend two approaches for patients with resectable synchronous or metachronous liver metastases from colon cancer: initial surgery, or neoadjuvant therapy followed by surgery and then adjuvant therapy.[32]

According to ESMO, the initial recommendation for patients with oligometastatic disease is to perform systemic treatment and then assess response. If the disease is progressive, assess whether to continue with systemic treatment or perform local treatment of the metastases. If there is response to systemic treatment, continue with local treatment of the metastasis.[40]

The decision to perform a single or combined procedure should be individualized. In patients with resectable liver metastases, combined single-stage surgery is recommended if possible for relatively low-complexity cases and sequential or staged surgery for more complex cases. Evidence 2B.[4]

A multicenter study that included 475 staged procedures and 135 combined surgeries demonstrated that the addition of minor liver resection to colon resection surgery did not result in increased severe morbidity (12.5 vs. 14.5%). However, the addition of major liver resection resulted in increased severe morbidity compared with major liver resection surgery alone (36 vs. 15%), with major hepatectomy being an independent predictor of severe morbidity.[42]

In 2015, a US National Surgical Quality Improvement Program (NSQIP) study provided evidence in favor of combined surgery for relatively low-complexity cases and staged surgery for more complex cases. In this study, cumulative postoperative morbidity was 25% for low-risk colectomy (right colectomy) combined with low-risk hepatectomy (left hepatectomy) and 39% for high-risk colectomy (total colectomy) combined with high-risk liver resection (right hepatectomy).[43]

In a recent retrospective study of 145 simultaneous vs. 53 staged surgeries, morbidity was comparable in both groups, even in the group undergoing major liver resection. Total hospital stay was significantly shorter for simultaneously resected patients, suggesting that simultaneous resections may be safe even in complex cases and should be performed at referral centers with extensive experience in colon cancer surgery and major liver surgery.[44]

Schubert et al.,[43] found that the mortality of synchronous resection increases as the risk of a complex colectomy and a major hepatectomy increases by up to 5%. Clearly, the lowest mortality rate is given by a minor hepatectomy associated with a low-risk colectomy. Reverse surgery (initial approach to the metastases and later to the primary tumor) is indicated in patients with significant liver disease and asymptomatic primary tumors (without intestinal obstruction).

Barros Scheloto,[45] in his conference on hepatic metastases of colonic origin offered at the Asociación Argentina de Cirugía, recommended to discriminate each case according to the form of presentation of the colon tumor (with or without symptoms) and the resectability of the metastases, in order to decide on the course of action. Considering these elements, 4 scenarios may arise to decide on the treatment of synchronous liver metastasis:

1) Symptomatic colon cancer with resectable metastasis: it is surgical at the start.
2) Symptomatic colon cancer with unresectable metastasis: it is not surgical.
3) Asymptomatic colon cancer with unresectable metastasis: it is not surgical.
4) Asymptomatic colon cancer with resectable metastasis: it could be surgical at the start.

Seen from another perspective, according to the same author, both liver and colon surgery can be high or low risk and there are also 4 scenarios:

1) Low-risk colon surgery with low-risk liver surgery: synchronous resection is possible
2) High-risk colon surgery but with low-risk liver surgery: attempt resection
3) Low-risk colon surgery but high-risk liver surgery: synchronous surgery is not possible.
4) High-risk colon surgery and high-risk liver surgery: synchronous surgery is contraindicated.

The NSQIP review reported mortality from synchronous colorectal liver resections according to the extent of colonic and liver resection:[43]

- Low-risk colectomy and minor hepatectomy: 1.4%
- High-risk colectomy and minor hepatectomy: 0.9%
- Low-risk colectomy and major hepatectomy: 3.4%
- High-risk colectomy and major hepatectomy: 5%

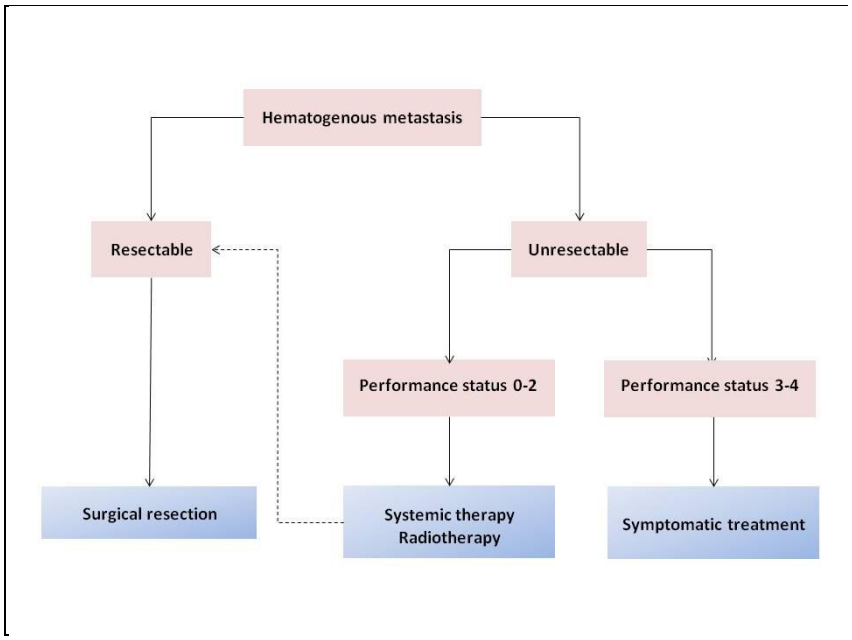

Figure 16.4. *Therapeutic approach to hematogenous metastases*

Initial unresectable liver metastases

Patients with colon cancer and initially unresectable liver metastases should be considered for neoadjuvant chemotherapy to attempt to convert them to a resectable state. Evidence IB 3.[40]

A 2017 systematic review and meta-analysis of 11 studies demonstrated that neoadjuvant therapy with 5FU combined with OXA (FOLFOX) or Iri (FOLFIRI) combined with Bev achieved conversion in 39% (27-53%) of patients with colon cancer with initially unresectable liver metastases and in these converted patients R0 could be achieved in 28% (18-41%) of cases.[24]

Neoadjuvant treatment with FOLFOX, FOLFIRI, or FOLFIRINOX plus Bev or Cetu for KRAS-wt tumors resulted in a 55-85% response, a 10-61% conversion to resectable tumors, and an R0 of up to 54%.[3,40]

In addition to systemic chemotherapy and immunotherapy, other approaches exist to increase the resectability of liver metastases, such as systemic chemotherapy combined with hepatic artery infusion chemotherapy. Level of evidence IB (Fig. 16.5).[40]

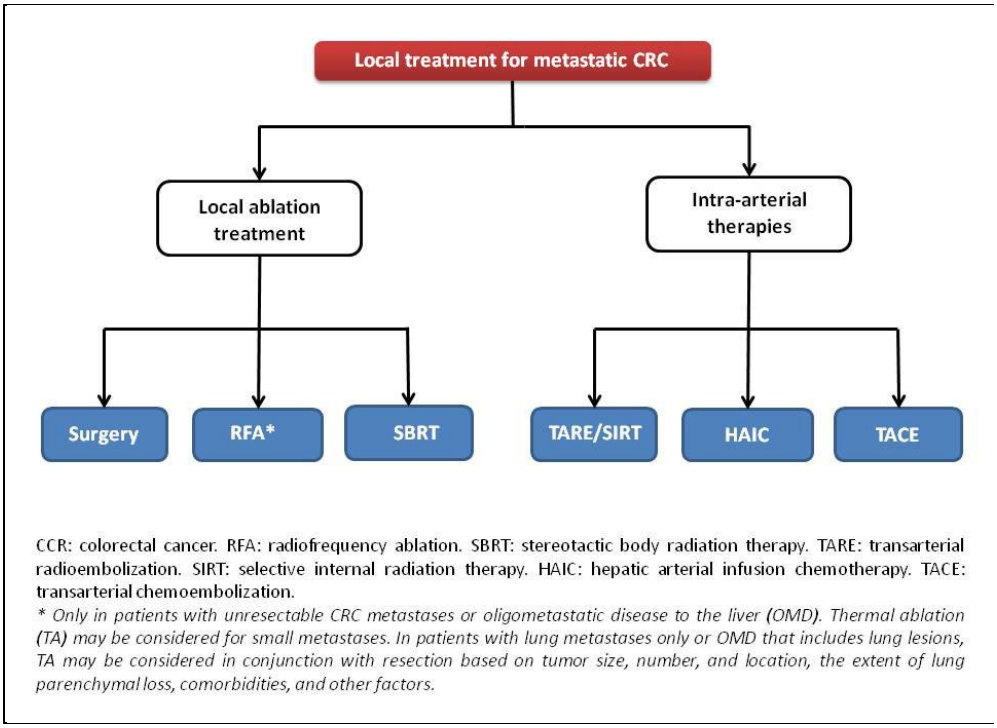

Figure 16.5*. Therapeutic strategies in metastatic colon cancer recommended by ESMO.*[40]

Lung metastases

In patients with resectable colon cancer and lung metastases, resection of lung metastases should be considered because it may prolong survival. Evidence IIB.[4]

A Japanese national study of 553 patients reported a 5-year recurrence-free survival of 80% and 68% for patients undergoing segmentectomy or wedge resection.[46]

In the Spanish national registry of 522 patients, DFS and specific survival were 28 and 55 months, with better outcomes in those treated with major lung resections and lymphadenectomy.[47]

The Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) cohort study randomized patients with resectable lung metastases comparing surgical vs. nonsurgical treatment and reported an OS of 3.5 vs. 3.8 years, so nonsurgical treatment should also be considered in these patients.[48]

Stereotactic radiation therapy (SBRT) could also be considered in these cases, but is less effective than resection in terms of disease-free progression and OS.[3,40]

According to ESMO, if the lung metastasis is resectable, its resection should be considered after resection of the primary tumor. Delayed resection is generally the usual approach.[40]

Peritoneal metastases

The risk of peritoneal metastasis after an advanced tumor is approximately 30%. Patient survival without treatment is 5 months and with systemic treatment between 5 to 12 months.49 Twenty-five percent of patients with metastatic disease will have disease limited to the peritoneum.[50]

According to the ASCRS, in patients with resectable colon cancer and peritoneal metastases, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered after a complete multidisciplinary decision. Evidence IB.[4]

In this group of patients, initial treatment includes systemic chemotherapy, with or without resection of peritoneal involvement, with or without intraperitoneal chemotherapy.

Systemic therapy based on modern chemotherapy agents and targeted biological therapy has improved the course of carcinomatosis associated with CRC, with an average survival of 16 to 24 months. Five-year survival with OXA-based therapy is less than 5% and there is minimal benefit with the addition of Bev.[51,52]

The surgical approach includes the combination of cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C or OXA, with or without hyperthermia. The first randomized trial of cytoreduction plus HIPEC vs. standard systemic OXA demonstrated an improvement in OS for the first group. After a median follow-up of 21.6 months, the median survival was 22.3 months in the experimental group vs. 12.6 months in the control group (log rank test, $p = 0.032$).[53]

The COLOPEC study evaluated cytoreduction plus HIPEC as adjuvant therapy in patients with high-risk primary tumors. Patients with clinical or pathological T4N0-2M0 tumors or perforated colon cancer were randomly assigned to an experimental cytoreduction plus HIPEC arm vs. a standard systemic chemotherapy control arm. After 5 years of follow-up, there were no differences in OS (69.6 vs. 70.9%, log-rank; $p = 0.692$), or in DFS (55.7 vs. 52.3%, log-rank; $p = 0.875$).[54] Current guidelines state that there is insufficient evidence to recommend HIPEC in these situations.

In 2021, the multicenter randomized controlled trial PRODIGE-7 analyzed 132 patients with cytoreductive surgery vs. 133 patients with cytoreduction plus HIPEC and reported more adverse events after HIPEC, with no benefit in OS, with 41 to 42 months in both arms.[55] However, there was a favorable difference in OS in the subgroup of patients with PCI (peritoneal carcinomatosis index) of 11 to 15.

The 2020 Chicago consensus, based on this study, recommended preoperative systemic therapy, with or without the addition of immunotherapy for MSI-H tumors, in high-risk patients and initial cytoreductive surgery, with or without the use of intraperitoneal chemotherapy, in low-risk patients.[56]

Complete resection is recommended when the tumor is easily resectable. ESMO recommends complete cytoreductive surgery. The addition of HIPEC should only be considered in experimental studies. There is no current recommendation in this regard.[40]

Distant lymphatic metastases

The treatment of distant lymphatic metastases remains controversial, as there are no comparative trials demonstrating therapeutic benefit. However, in recent years, resection of metastatic para-aortic lymph nodes has been linked to a potential improvement in long-term survival and radical treatment of the disease.

Metastasis in other sites

Although reports have been published on the resection of multiple metastases in other sites, such as bone, brain, spleen, etc., there are no clear benefits in survival.

In the case of multiple metastases that usually involve the liver and lung, resection should be considered if it is possible to remove the primary tumor.

Given the high rate of recurrence after radical surgical treatment, adjuvant chemotherapy is recommended.

Author's comment

Strategies and techniques for the treatment of distant metastases (liver, lung, etc.) constitute a chapter in themselves, so this report will not address these aspects. In fact, the treatment of metastatic involvement of each organ separately could be considered as a topic for a future report.

Biomarkers

The molecular classification of patients with colon tumors has therapeutic implications. The genes involved include: KRAS, BRAF V600 E, MMR, Her2.

KRAS/NRAS gene

KRAS/NRAS gene mutations are detected in approximately 40-50% of patients with unresectable or metastatic colon tumors. There is a high concordance between the characteristics of the primary tumor and synchronous metastases, while in metachronous metastases the discordance can reach 20%. The most common mutation is that of exon 2 (in codons 12 and 13) of the KRAS gene.

Anti-EGFR antibody therapy such as Cetu and panitumumab (Pani) has been reported to be ineffective in tumors with these mutations. For this reason, it is recommended that this mutation be determined prior to first-line therapy for patients who are to receive systemic treatment.[32]

There is specific therapy aimed at this mutation, such as the use of sotorasib, with a progression-free survival of 4 months and follow-up at 12 months.57 Another option is the combination of Cetu with adgrasib, which improves the response rate and disease control, all in phase II studies.[58]

BRAF V600E gene

The BRAF gene mutation is detected in approximately 5-10% of patients with unresectable colon tumors. The most frequent mutation is in codon 600 (V600E, valine for glutamic acid). This mutation is more frequent in right colon tumors and has a tendency to peritoneal dissemination. It is

associated with smoking and is a poor prognostic factor. Mutations in other codons may have a better prognosis. The use of anti-EGFR (Pani, Cetu) alone does not confer an adequate response.

According to the Tribe study, in a subgroup of patients, first-line therapy with FOLFOXIRI plus Beva was superior for mutations in this gene. The use of 2 or 3 lines of treatment for mutated BRAF V6000E results in longer OS, higher progression-free survival and pathological response rate, all at the expense of higher toxicity, which for triple therapies is around 60%.[59]

In patients with BRAF-mutated metastatic colon cancer, NCCN currently recommends the combination of encorafenib plus Cetu. It is also recommended to test for this mutation in patients with dMMR and in those with suspected Lynch syndrome.[32]

MMR genes

MMR (dMMR) deficiency, or deficiency of DNA repair proteins, is seen in Lynch syndrome patients carrying a germline mutation of genes associated with MMR proteins and also in sporadic colon cancer caused by acquired methylation of the MLH1 gene.

Testing for dMMR includes analysis of microsatellite instability (MSI) and immunohistochemistry for MMR proteins. There is a high rate of concordance between positive MSI and MMR protein testing by immunohistochemistry.

MSI is recognized in approximately 5% of patients with unresectable colon cancer. There is no established specific systemic therapy for these patients with dMMR. Under these circumstances, treatment regimens are similar to those indicated for patients with sporadic colon tumors. Recently, the efficacy of anti-PD-1 antibody therapy such as pembrolizumab (Pembro) and nivolumab (Nivo) was reported in this subgroup of patients.[3,4,40]

HER-2 gene

HER-2 overexpression or amplification occurs in 5% of patients with CRC and is determined by immunohistochemistry. It is associated with non-mutated RAS/BRAF-wt, with expression being less than 1% in mutated patients. It is more frequent in tumors of the left colon.

In this group of patients, there are multiple phase II studies evaluating the response rate (30 to 40%) with drugs such as trastuzumab, lapatinib, pertuzumab and tucatinibe.[3,4,40]

Stage IV unresectable

In patients with incurable colon cancer, the goals of planning should be symptom control and quality of life. Palliative therapy consists of initial systemic chemotherapy, or palliative surgery for intractable bleeding or obstruction, including colectomy, ablative procedures, and definitive ostomy.

In these cases, the goal of adjuvant systemic therapy is to prolong life and control symptoms associated with the tumor, delaying disease progression. Individualized treatment of these patients should be considered based on life expectancy.

In patients without any type of systemic therapy, the median survival is approximately 8 months. Recently, systemic therapy has increased survival to 30 months..[60,61]

In patients with incurable stage IV colon cancer and asymptomatic primary tumor, initial systemic chemotherapy is recommended. Evidence IB.4

The choice of strategy depends on the primary objective, i.e. tumor shrinkage or control of progression, clinical presentation of the tumor and its characteristics, presence or absence of metastases and their location, progressive or non-progressive nature of the disease, RAS gene status, patient-related factors (very symptomatic or asymptomatic disease, presence of comorbidities) and possibility of conversion with successful systemic therapy.

Randomized controlled trials in patients with good performance status demonstrate that systemic therapy is associated with significantly longer survival times.[62,63]

For patients without severe comorbidities and with good performance status, considered tolerant to first-line therapy, the first choice is a regimen containing OXA or Iri (FOLFOX, FOLFIRI or CapeOx) associated with monoclonal antibodies based on genetic determination. Patients with severe comorbidities or inadequate performance status are vulnerable or inappropriate for intensive systemic therapy and are considered intolerant to first-line therapy.

In patients considered appropriate for systemic therapy, determination of RAS (KRAS/NRAS) and BRAF (V600) mutations should be performed before the start of first-line therapy.

Cetu and Pani are monoclonal antibodies that act by binding to the epidermal growth factor receptor tyrosine kinase (EGFR). They are only indicated for patients with non-mutated KRAS/NRAS-wt.

Bev is a monoclonal antibody that binds to a protein called vascular endothelial growth factor (VEGF) and is indicated for patients with mutated KRAS/NRAS. Pani is indicated for patients with high-frequency microsatellite instability (MSI H).

The Tribe study demonstrated the superiority of the FOLFOXIRI + Bev regimen over the FOLFIRI + Bev regimen, with respect to progression-free survival and response rate.[59]

The OLIVIA trial demonstrated that FOLFOXIRI + Bev improved R0 resection compared with FOLFOX + Bev in patients with unresectable colon cancer and liver metastases.[59,62]

For patients not amenable to intensive systemic therapy, NCCN guidelines added the anti-PD-1 (anti-programmed death) checkpoint inhibitor antibodies Nivo and Pembro, especially for dMMR or MSI-H disease.[32]

In patients with incurable stage IV colon cancer and asymptomatic primary tumor, controversy exists regarding management. An argument in favor of initial nonsurgical treatment was prospectively evaluated using initial therapy with FOLFOX and Bev. At 21 months of follow-up, 14% of patients experienced primary tumor-related morbidity and only 12% required surgery, with obstruction being the most common cause. The probability of requiring unplanned surgery at 6 to 12, 12 to 24, and > 24 months was 8.1, 6.7, and 5.3%, respectively.[64] Risk factors for unplanned surgery were female sex, left-sided tumors, and young patients.[63]

In 2021, a study of 165 patients demonstrated no survival benefit when comparing resection of the symptomatic primary tumor with chemotherapy. OS was 26 months in the group with initial surgery vs. 26.7 months in the group with chemotherapy.[65]

In contrast, there is insufficient evidence to indicate early surgery. This comes from a single-center retrospective study published in 2016 and a 2019 meta-analysis. Both concluded that resection of the primary tumor is associated with better survival compared to chemotherapy, although it has higher morbidity.[3,40]

Thus, based on the existing evidence, the most important argument is to indicate initial chemotherapy, evaluate response, estimate prognosis and re-evaluate in a multidisciplinary context. Two ongoing prospective studies (CAIRO 4 and GRECAR 8) may clarify the management to follow in these patients.

In patients with obstructive colon cancer and incurable metastases, when life expectancy is less than one year, endoscopic decompression or diverting colostomy is preferred over colectomy. Evidence IB.[4] In this group of patients, endoscopic decompression has been shown to have lower mortality, fewer permanent ostomies and a shorter interval to start chemotherapy, with no difference in survival. Likewise, the stent was associated with a shorter hospital stay when compared to surgery, although reinterventions at

one year were more frequent in the stent group and readmissions were similar in both groups.

In case of tumor growth through the stent, the replacement of a new one has been shown to be safe and effective in most patients.

There is evidence of a higher perforation rate in patients with stents treated with Bev compared with those treated with standard chemotherapy (12% vs. 7%).[3,40]

Table 16.2 shows the chemotherapy regimens for unresectable colon cancer recommended by different international guidelines.

Table 16.2. Comparison of chemotherapy regimens for unresectable colon cancer recommended by different major guidelines.

Japonese Guidelines[27]	NCCN[32]	ESMO[40]
Intensive chemotherapy		
FOLFOX+Beva	FOLFOX+Beva	FOLFOX+Beva
CapeOX+Beva	CapeOX+Beva	CapeOX+Beva
FOLFIRI+Beva	FOLFIRI+Beva	FOLFIRI+Beva
SOX+Beva	-	-
FOLFOX+Cetu/Pembro	FOLFOX+Cetu/Pembro	FOLFOX+Cetu/Pembro
FOLFIRI+ Cetu/Pembro	FOLFIRI+ Cetu/Pembro	FOLFIRI+ Cetu
FOLFIRI+Beva	FOLFIRI+Beva	FOLFOXIRI
FL/cape/5FU+LV/S1/Beva	FL/cape+Beva	IRIS
Cetu/Beva		
Non-intensive chemotherapy		
FL/cape/5FU+LV+beva	FL/cape+beva	5FU+LV/cape+beva
Cetu/Pembro	Cetu/Pembro	FOLFOX
	Nivolumab/Pembro	capeOx
		FOLFIRI
		IRIS

FOLFOX: 5-Fluorouracil + Oxaliplatin; Beva: Bevacizumab; CapeOX: Capecitabine + Oxaliplatin; FOLFIRI: 5-Fluorouracil + Irinotecan; SOX: S1 + Oxaliplatin; Cetu: Cetuximab; Pembro: Pembrolizumab; FOLFOXIRI: 5-Fluorouracil + Oxaliplatin + Irinotecan; Cape: Capecitabine; FL: 5-Fluorouracil infusional; IRIS: S1 + Irinotecan; 5FU+LV: 5-Fluorouracil + folinic acid/leucovorin.

Immunotherapy

The frequent diagnosis of advanced stages and the high risk of systemic toxicity, poor response and low efficacy have led to the development of new therapies and better therapeutic options, with specific selectivity directed to the tumor.

Targeted therapies provide an alternative for patients with metastatic colon cancer. These therapies work by blocking specific molecules involved in the growth and spread of cancer.

Over the past 20 years, many potential therapies with different mechanisms of action have been studied:

- Inhibition of the epidermal growth factor receptor (EGFR).
- Suppression of the RAS-Raf-MEK-ERK gene pathway, responsible for tumor growth and proliferation.
- Inhibition of tumor angiogenesis (neoangiogenesis) promoted by epithelial endothelial growth factor A (VEGF-A).
- Inhibition of immune controls or checkpoints (PD-1, PD-L1, CTLA-4), the most recent therapy.

Bev, the first anti-VEGF-A monoclonal antibody, was approved in 2004. The FDA has also approved aflibercept (a VEGF-A inhibitor), ramucirumab (a fully humanized monoclonal antibody against VEGFR-2), and regorafenib (a VEGF-2 inhibitor) for the treatment of metastatic colon cancer.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies directed against activating T-cell receptors, particularly the programmed cell death receptor 1 (PD-1), including programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) expressed on T cells and antigen-presenting cells. In patients with MSI-H and dMMR cancers, these antibodies have shown encouraging responses. However, in cancers with microsatellite stability (MSS) or low microsatellite instability (MSI-L), which represent 95% of colon tumors, the role of these antibodies is not defined.

These therapies have started a new and promising chapter in the treatment of colon cancer. Currently, PD-1 and PD-L1 inhibitors could have significant potential in patients with metastatic colon cancer with MSI-H/dMMR. The role of drugs such as Pembro (anti PD-1) and atezolizumab (anti PD-L1) has been studied in trials such as KEYNOTE-177, KEYNOTE-164 and ATOMIC, in comparison with standard chemotherapy in patients with MSI-H/dMMR, demonstrating an improvement of 32-41% in progression-free survival up to 12 months, constituting an alternative for this subgroup of patients with lack of response to standard chemotherapy with FOLFOX or FOLFIRI.[66–68]

Regorafenib is likely involved in the induction of the pathway responsible for macrophage activation and the production of inflammatory cytokines responsible for the activation of cytotoxic T cells. The combination of regorafenib with Nivo also appears promising in non-randomised small cohort studies.[69]

According to ASCRS, immunotherapy with PD-1 and PD-L1 inhibitors should be considered in patients with MSI-H/dMMR colon cancer. Evidence IA.[4,69] However, these therapies are ineffective in patients with non-microsatellite instability/MMR-proficient colon cancer.

Immunoprevention

Immunoprevention of CRC consists of administering vaccines based on DNA repair protein deficiency (dMMR) that generate neoantigens consisting of peptides or fragments of the DNA chain. Different types of vaccines are proposed: those based on peptides, those guided by a viral vector, those based on dendritic cells and those based on RNA.

The obstacles to the application of these vaccines are related to effectiveness, tolerance and the possibility of early identification of the chains and achieving sufficiently broad coverage to include the entire chain.

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CHAPTER 17
Application of enhanced recovery after surgery (ERAS) for colon cancer

With the collaboration of Marcelo Viola Malet and Marcelo Laurini Zanola

Why does the surgeon need to audit his results?

In medicine and in all health teams, there is an implicit need to offer patients the best care, relying on the knowledge and tools available at the time in which our activity is carried out. Over time, and specifically in the last 30 years, the anesthetic-surgical community has attempted to improve perioperative care by defining different parameters that together allow achieving the gold standard.

In the mid-1990s, Professor Henry Kehlet began to talk about what he called Fast Track or Accelerated Recovery protocols in colorectal surgery. In his first publication in 1997, he referred to the fact that the morbidity of surgery is fundamentally linked to the organic response to surgical stress, mediated by metabolic/endocrine changes that lead to the activation of the inflammatory cascade. Therefore, by understanding these changes, it is possible to try to modulate this response and minimize complications.[1]

In 2002, Kehlet and Wilmore2 defined the three factors that contribute to delayed postoperative recovery: inadequate pain management, bowel dysfunction, and immobilization. They concluded that understanding perioperative pathophysiology and implementing care regimens that seek to reduce surgical stress accelerate patient rehabilitation, which is associated with shorter hospital stay and greater satisfaction and safety after discharge. The greatest challenge for healthcare teams is to develop and improve multimodal rehabilitation protocols to achieve a "pain-free and risk-free" perioperative period.

More than 230 million major surgical procedures are performed worldwide each year, so surgical care impacts the lives of millions of people. At least 7 million patients a year may suffer postoperative complications, and about 1 million die in the perioperative period. Surgery-related complications cause disability or increase hospital stay in 3–25% of patients, depending on a variety of factors, primarily surgical complexity and hospital setting.[3]

According to the World Health Organization, the vast majority of surgeries performed annually around the world are not recorded, making it very difficult to truly assess the problem. The *Safe Practices Save Lives* initiative is a collaboration between more than 200 ministries of health, national and international medical societies and health professional organizations and aims to reduce deaths and complications related to surgical care.

Improving access to surgical care and the safe delivery of related services is crucial to ensuring its effectiveness. No less than half of complications and deaths associated with surgery could be avoided by following a series of basic standards of care.

In this regard, and concerned about the morbidity and mortality of anesthetic-surgical procedures, the ERAS (Enhanced Recovery After Surgery) collaborative group was created in 2001, led by surgeons and anesthesiologists from five countries (Denmark, Sweden, Norway, Scotland and the Netherlands). In those early years, they discovered that there was a variety of traditions in use in different centers, but also large discrepancies between actual practices and what was already known to be best practice, according to the literature. This led the group to examine and lead the process of changing tradition to best clinical practice.

In 2005, they published the first consensus protocol for patients undergoing colon surgery. Two years later, the same group in a new publication stated that the implementation of a multimodal action protocol is not sufficient to allow hospital discharge upon recovery of functionality, but that good organization and experience are required.[4]

Finally, the ERAS Society was founded in Amsterdam in 2010. This is a non-profit multidisciplinary, multiprofessional, academic-medical society that spans all continents and involves a wide range of health disciplines. Its mission is to develop perioperative care and improve postoperative recovery by promoting research, education, the implementation of practices based on the best scientific evidence and the auditing of results.[5,6]

The ERAS implementation program introduces the use of the ERAS Interactive Audit System (EIAS) created and developed by the company. This audit system provides real-time quality control and is a very powerful research tool. Data is updated hourly and available online, helping teams to continuously monitor their results and processes, as well as benchmark against other hospitals to standardize practice and improve outcomes.

In short, ERAS refers not only to the use of action protocols (ERAS guidelines), but also to the implementation of a standardized program to homogenize the actions of all teams and also to the interactive audit system (EIAS), all of which implies a new way of understanding and executing perioperative care.

Nowadays, the concept of "value in health" is gaining great importance in healthcare, involving the quality of care, healthcare costs, objective results and patient satisfaction. Value in health relates the quality of care to costs (Value = Quality/Costs). Quality of care is defined by two parameters: clinical results and the patient's perception of the care received and the results that can be objectified. On the other hand, health costs involve those derived directly from healthcare and those indirectly resulting from that care. Therefore, we can affirm that value in health is an indicator of quality of care towards which all providers must tend to improve their administrative management and clinical results. This new way of working proposed by the ERAS Society is in line with the improvement of quality indicators of care and management, since it promotes quality improvement with patient-centered protocols, based on the best clinical evidence and seeks to reduce direct and indirect costs.

The role of the surgeon in an accelerated perioperative recovery protocol

One of the major problems in gastrointestinal surgery has always been the management of postoperative pain and the reduction of postoperative ileus, nausea and vomiting, which ultimately cause a delay in patient recovery and hospital discharge.

For more than 2 decades, surgeons have tried to acquire technical skills and develop minimally invasive procedures as the only way to improve postoperative results. In recent years, two changes have occurred that have revolutionized the results of elective colorectal surgery. On the one hand, the introduction of minimally invasive surgery on a routine basis, and on the other, the development of protocols for optimized recovery after surgery (ERAS), which represented a paradigm shift in surgical practice. The surgeon ceased to be the central axis in patient care and became one more link in a correctly structured chain. The patient is the center of attention and each member of the team contributes from their place to try to achieve care efficiency. In this way, the surgeon must learn to work as a team and understand that,

although his role is important, the final result depends not only on an adequate surgical technique, but also on the set of perioperative measures.[7]

One of the strengths of this new way of working is the possibility of auditing the results and knowing the advantages, failures and possible improvements. This is known in the program as the ERAS Interactive Audit System® (EIAS) and allows efforts and changes in the way of acting to be directed, in order to improve the results through permanent auditing and evaluation.[6]

Below are some of the actions proposed in the ERAS guidelines for colon surgery related to the surgeon's performance:

Mechanical bowel preparation (MBP)

In terms of surgical practice, among the preoperative measures, one of the most resisted and controversial is the MBP. Classically, colon surgery was not permitted without MBP and this remains the case even today. MBP is stressful for the patient, leads to adverse effects such as dehydration and is associated with an increase in postoperative ileus.[7,8]

The dogma of MBP prior to elective colon surgery has been strongly challenged. In the 2011 Cochrane review for colon surgery, which included 18 prospective randomized trials and 5805 patients, no significant differences were found between patients with and without MBP, or with MBP vs. rectal enema alone, in terms of anastomotic leak, mortality, reoperation, and operative wound infection.[9] Furthermore, it was shown that laparoscopic colectomy can be safely performed without MBP.[10]

Patron Uriburu conducted a study on MBP in 60 patients with 2 branches of 30, not randomized. Malignant pathology was 70%. Laparoscopic surgery and anastomosis were similar. There was morbidity in a quarter of patients, somewhat less in those who were not prepared. He concludes that surgery without MBP is safe and similar in infectious complications and hospitalization time.[11]

Leiro and Bianchi[11]published a prospective, randomized study of 129 elective patients with benign and malignant colonic pathology divided into two groups: one with MBP and antibiotics and the other with antibiotic prophylaxis. In the MBP group, there was a 21.9% rate of surgical site infection and 5.7% rate of anastomotic dehiscence. In the group without MBP, there was a 21.5% rate of surgical site infection and 15.2% rate of anastomotic dehiscence, with no significant difference, although in this group there were more extraperitoneal anastomoses. According to this study, MBP did not influence infectious complications or anastomotic dehiscences, while extraperitoneal anastomoses in middle and lower rectal cancer had a better outcome with preparation. The authors recommend the possibility of performing colon anastomoses in patients without MBP.

On the other hand, the justification is to avoid dehydration and hydroelectrolytic alterations that MBP entails, in addition to the discomfort for the patient. In any case, MPP is recommended in the case of small lesions that cannot be palpated and require intraoperative colonoscopy, although it is preferred to mark the lesion preoperatively with India ink.

According to the 2013 ERAS guidelines, the recommendation is not to routinely perform MBP in colon surgery, with a high level of evidence and a strong degree of recommendation.[7]

Another point in which both surgeons and anesthesiologists must modify their behavior is related to preoperative fasting and carbohydrate loading. The classic 8-hour fast is sometimes a difficult measure to modify. The patient must arrive at the operating room in a state as close to euvolemia as possible, with electrolyte disturbances corrected and euglycemic or slightly hyperglycemic. The most physiological way to achieve this objective is through oral replacement, since prolonged fasting and intravenous replacement cause excess fluid to leave the intravascular space towards the interstitium, producing visceral edema. Prolonged fasting causes the patient to arrive at surgery hypovolemic and hypoglycemic and has not been shown to reduce the risk of aspiration during anesthetic induction. Several prospective and randomized studies have shown that clear liquids can be administered up to 2 hours before surgery and a light meal up to 6 hours before.[12,13]

Preoperative administration of complex carbohydrates, such as 12.5% maltodextrin, 285 mOsm/k (approximately 100 g maltodextrin in 800 ml water) on the night before surgery and 50 g maltodextrin in 400 ml water 2–3 hours before anesthetic induction, reduces the catabolic response generated by prolonged fasting. It also improves patient well-being and reduces peripheral insulin resistance.[14]

Current ERAS guidelines recognise the advantages of minimally invasive approaches to colon cancer, including faster recovery, fewer overall complications, lower wall morbidity and fewer adhesions, without compromising oncological outcomes, which in some cases may even improve. The level of evidence for the superiority of minimally invasive surgery over conventional surgery is high and the grade of recommendation is strong.

Early restart of feeding

Historically, preoperative instructions for gastrointestinal surgery involved *"nothing by mouth from the night before until bowel function is restored"* which may occur several days after surgery. In addition, routine prophylactic use of a nasogastric tube was also indicated. Currently, there is evidence that early refeeding is safe and well tolerated in 80-90% of patients, improves postoperative comfort, and promotes early discharge.[15–17]

The resumption of intestinal transit is also favoured by the administration of prokinetics, as well as by rapid and active mobilisation. The postoperative hospitalization time is related to the resumption of intestinal transit, oral tolerance and postoperative analgesia. An anastomotic dehiscence usually appears between the 5th and 7th postoperative day, so even if the patient is discharged he or she should be strictly monitored during this period. The warning signs are the appearance of hyperthermia, abdominal distension, lack of progression of intestinal transit, abdominal pain and vomiting.

Fluid administration

Perioperative fluid administration has been a topic of debate in recent decades, and multiple prospective randomized studies have attempted to compare a volume-free vs. a restrictive regimen. Currently, the trend is not to overhydrate patients parenterally and to actively restart oral diet, particularly with carbohydrate solutions initially, then to resume soft diet and progressively general diet.

Surgeons and anesthesiologists have for decades been inclined to use a free regimen to prevent hypotension and hypoperfusion of tissues, particularly the anastomosis.[18,19] However, excess fluids, especially saline, lead to pulmonary edema, metabolic acidosis, renal failure, and splanchnic edema, events that can compromise the safety of the anastomosis. On the other hand, it is important to know that both volume overload and extreme restriction are harmful and have a negative impact on complications and hospital stay.

The goal of ERAS programs is appropriate volume management, with goal-guided therapy that achieves a balance close to zero and minimal body weight gain.

Surgical considerations

The incidence and duration of postoperative ileus appears to be related to the degree of surgical trauma, which is less in minimally invasive procedures.[20,21]

With regard to wounds, it is important to monitor the site of extraction of the specimen due to the possibility of infection of the surgical site.[8] After discharge, it is suggested to carry out a follow-up at 7, 15 and 30 days postoperatively to evaluate the clinical progression and tolerance to the oral diet, which should be fractionated, progressive and restricted as appropriate.

Analgesia

Non-opioid analgesia, or a short-acting opioid, should be used both intraoperatively and postoperatively. This allows for early re-feeding and mobilization. It is essential that each team has its own pain management strategy, based on the lowest possible use of opioids.

Drains and tubes

It is advisable to restrict or not routinely use the nasogastric tube in the postoperative period and avoid the placement of drains, since both delay recovery and do not improve results.

Finally, we can conclude that with the new perioperative optimization protocols, several paradigms of classical surgery have been destroyed. The surgeon must adapt to the changes, but fundamentally must understand that it is one more link in a care process that not only requires an adequate surgical technique.

Importance of auditing in the implementation and development of the ERAS protocol

The word audit comes from the Latin *audire*, meaning to hear, and is generally used to refer to the examination of an entity's financial management.

In health, the term began to be applied to the retrospective evaluation of medical performance based on the analysis of generally poorly organized available records, essentially the medical history. Currently, it is understood that it is a process that begins with the analysis of carefully selected data and its comparison against well-defined standards. The audit is part of an efficient cycle of data use to implement changes that objectively improve the quality of care.[22]

Structures, care processes, and results are the subject of audit. In our case, the structure is a surgical team made up of surgeons, anesthesiologists, nurses and nutritionists. The care processes are the guidelines we agree on to care for our patients. The results refer to objective variables such as the reacquisition of normal functions, complications, and hospital stay.

One of the pillars of the ERAS program is the exhaustive audit of all these elements, and one of its advantages is that it makes the methods and the tool available to the team through the EIAS.[23]

When the program is officially introduced into daily clinical practice, the entire team is committed to the audit process, each person has a specific responsibility for one of the parts and has defined a time in their agenda to complete the task. In other words, the audit is incorporated as another aspect of the care because the entire group understands the positive impact of knowing the result of their actions.

To produce improvements, the audit process cannot stop at the analysis of the data collected, but extends through a repetitive cycle of planning, action, analysis and corrections.[24]

There is controversy about the final impact of this process. Among the elements that predict significant improvement are the existence of a team leader, verbal and written communication, repetition over time (iterations), and the level of specification of the objectives and the action plan.[25]

The EIAS audit program is organized in such a way that it contemplates all these elements and includes numerous guidelines that the evidence considers necessary for the process to produce continuous improvement. Some of them are:

- Have a very structured program (previously defined).
- Have a selection of criteria based on evidence.
- Audit the process and the results.
- Be applied by a multidisciplinary team that has a leader.
- Be executed repetitively once a week.

Why implement an ERAS program?

Protocols derived from evidence-based medicine are the standard of care in referral centers, whether or not they have an ERAS program. As noted above, the EIAS audit system is based on methods that have proven their usefulness, and impact studies show that it is effective in producing significant changes, profoundly and positively transforming health services with low adherence to good practices.26 A benefit is also reported in the professional performance of team members and in their level of satisfaction, as evidenced by the fact that it motivates them to seek excellence, greater adherence, and better results.[23]

The weekly team meeting includes a time slot to review the audit and plan problem resolution, and another time slot to review the status of each patient who entered the program. Problem resolution primarily consists of introducing a change to improve adherence to the protocol when noncompliance is detected.[27]

As noted above, ERAS offers an online audit system that is built on evidence to produce improvements. There are numerous publications that denounce audit systems that do not produce improvements, due to the selection of incorrect indicators, erroneous readings of data and deficiencies in the training and functioning of teams. Other times, institutional realities such as the lack of dedication of professionals or support from administrators, conspire against the virtuous circle of audit-corrective action.[22]

Among the emerging properties of an audit system of this nature are the unification of the language used to compare the results and the alerts that are generated as a product of the association of practices and results.

The first case is exemplified by the comparison of the percentage of complications that occur. The definition of complications, or their choice for drawing up a list, is practically unreproducible among current publications. In ERAS, the comparison between the complications of one centre and another is immediate and faithful because they are perfectly defined and weighted in the same way. For a hospital and its professionals, the mere fact of confirming that their complications do not exceed the standard is of great value. The fact that this information goes unnoticed is detrimental to the assisted population and an additional cost that can be several times higher than that of the implementation of the programme. In the second case, alerts are generated when practices associated with results that deviate from the average are identified. These indicate entry points for carrying out prospective studies and improving protocols.

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CHAPTER 18
Evolution of colon cancer in the last 15 years

In a recent study, Horesh et al.[1] analyzed colon cancer treatment outcomes in the United States over 15 years and found a significant and alarming increase in patients with metastatic disease, approximately 20% over the period. Furthermore, it was found that while the proportion of patients treated with systemic chemotherapy remained stable over time, the use of multiple chemotherapeutic agents increased by 61%, which is likely the main reason for the improved 5-year OS in stage III patients. Another significant change was the increase in the use of immunotherapy from 3 to 7.6%, highlighting its benefits, especially in patients with metastatic CRC. The authors cite improved progression-free survival in patients with dMMR, known as unstable (78 vs. 11% in the control group). In addition, they found that immunotherapy was more frequently used in left-sided tumors.

Regarding surgical technique, one of the most significant changes in the last decade has been the increased use of minimally invasive surgery by laparoscopic and robotic means, with demonstrated superiority in the short term (shorter hospital stay, fewer readmissions, lower incisional hernia rate) and in the long term (lower morbidity and mortality).[2,3]

According to the authors, these changes in colon cancer treatment have contributed to improved long-term outcomes, probably with a greater benefit in patients with stage III and stage IV. This latter finding was also confirmed by a study from the Netherlands for patients with stage III and in another population-based study from Scandinavian countries between 1990 and 2016.[4,5]

When considering colon tumors by location, the adoption of minimally invasive surgery did not differ between the right and left colon, while the application of robotic surgery was significantly higher for tumors in the left colon.

Follow-up for the diagnosis of recurrence or metastatic disease has also improved significantly thanks to new biomarkers, which have high sensitivity and specificity for the diagnosis of neoplasia and allow for more accurate long-term assessment.

Finally, they conclude that the increased use of chemotherapy drugs, immunotherapy and the advancement of minimally invasive surgery have led to an improvement in the outcome of patients, especially in those with advanced disease. The authors consider that a personalized approach to the treatment of colon cancer should be promoted.

Survival

According to Japanese guidelines, the 5-year OS of colon cancer after curative resection for stages p0-IV is 72.8%. Survival according to stage is: I: 92.3%, II: 85.4%, IIIA: 80.4%, IIIB: 63.8% and IV: 19.9%.[6]

The 5-year OS according to tumor location is 68.2% for the cecum, 71.4% for the ascending colon, 74% for the transverse colon, 75.4% for the descending colon, and 73.7% for the sigmoid colon.

Follow-up

The recommended follow-up protocol includes:

- Up to 3 years after surgery:
  - Clinical examination and CEA every 3 to 6 months.
  - CT scan of the chest and abdomen every 6 to 12 months.
  - Colonoscopy every 3 to 5 years starting the first year after surgery.
- From 3 to 5 years after surgery:
  - Clinical examination and CEA every 6 to 12 months
  - CT scan of the chest and abdomen every 12 months
  - Colonoscopy every 3 to 5 years if there are no findings
- After 5 years: evaluate to end follow-up, except:
  - Colonoscopy every 5 years until 75 years of age or individualized according to life expectancy.

Recurrence

The diagnosis and treatment of locoregional recurrence of colon cancer are beyond the scope and objectives of this report. Given the importance of the topic, it is suggested that it be included in a future report.

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CHAPTER 19
Analysis of surgical results of colon cancer in Northwestern Argentina (NOA)

A survey was conducted of all patients operated on for colon cancer in the last 5 years in the main health care centers in the northwest of our country, including those who had complete and sufficient data. These were collected by members of the Argentine Society of Coloproctology who work in the provinces of Jujuy, Salta and Tucumán, both at the public and private level. They were:

San Salvador de Jujuy, Jujuy

- ***Hospital Pablo Soria***

- Dr. Pablo Jorge, MAAC, MSACP, MATCP
- Dr. Lucia D. Lamas, MAAC

Public and private practice

Salta

- ***Hospital San Bernardo***

- Dr. Vicente Borquez, MAAC, MSACP, MATCP
- Dr. Pablo Tacchi, MAAC, MSACP, MATCP
- Dr. Alejandro Sanchez Ruiz, MAAC, MSACP, MATCP

- ***Nuevo Hospital del Milagro***

- Dr. Martin Garcia, MAAC, MSACP, MATCP

Public and private practice

San Miguel de Tucumán, Tucumán

- ***Hospital Central de Salud***

- Dr. Susana Bruzzi, MAAC, MSACP, MATCP
- Dr. Audel Closas

Public practice

- ***Sanatorio Modelo***

- Dr. Paula Casares, MAAC, MATCP
- Dr. Hugo Amarillo, MAAC, MSACP, MATCP

Private practice

The results of this survey are shown in Table 19.1. Patients with metastases were excluded in order to concentrate the data according to the location of the tumor in the colon and because it was considered that patients with colorectal metastases should be part of a report in itself. Data were recorded for 788 patients, 261 from Salta, 71 from Jujuy and 456 from Tucumán. As reported in most of the literature, there was a slight predominance of the male sex (52.5%), except in Jujuy which had an equal distribution by sex.

Table 19.1. Characteristics of colon cancer cases treated in the NOA.

		Salta	Jujuy	Tucumán	Patients (N)
Patients (N)		261	71	456	788
Sex	M F	142 119	35 36	237 219	414 374
Ostoma	Yes No	46 215	30 41	115 341	191 597
Emergency	Yes No	40 221	16 55	71 385	127 661
Type of complication	Perforation Obstruction Bleeding	167 26 5	6 10 0	14 56 1	187 92 6
Endoscopic treatment	Yes No	1 260	3 68	5 451	9 779
Laparoscopy	Yes No	216 45	31 40	324 132	571 217
Location of the tumor	Splenic flexure Left colon Right colon Transverse colon	17 62 116 66	1 51 13 4	19 231 202 4	37 344 331 74
Type of surgery	Segmental colectomy Extended colectomy Right colectomy Left colectomy Hartmann´s	64 21 83 69 0	3 1 13 35 5	7 52 215 138 82	74 74 311 242 87
Adjuvant chemotherapy	Yes No	180 81	31 40	276 180	487 301

The need for emergency surgery was 16% (Salta 15%, Jujuy 22.5%, Tucumán 15%) and the incidence of elective and emergency ostomies was 25.3% (Salta 17%, Jujuy 42%, Tucumán 25%).

The most frequent complication was perforation (23.7%), followed by obstruction (11.6%) and bleeding (0.7%). When complications were considered proportionally, the incidence was 65.6% for perforation, 32.3% for obstruction and 2.1% for bleeding. The frequency of complications varied in the 3 regions, while in Jujuy and Tucumán obstruction was the first complication, similar to what has been reported in the literature, in Salta there was a strikingly high incidence of perforation (63%).

Colon cancer treatment was primarily surgical. Endoscopic treatment was possible in only 9 cases (1.1%) in the entire region. The initial approach was laparoscopic in 72% (Salta 82.7%, Jujuy 43%, Tucumán 71%).

The most frequent location was the left colon, followed by the right colon, transverse colon and splenic flexure. However, it was different by region. In Salta, the most frequent location was the right colon (44%), followed by the left colon, transverse colon and splenic flexure. In Jujuy, the left colon predominated (71%), followed by the right colon, transverse colon and splenic flexure. A similar distribution was found in Tucumán, with the left colon (50.6%), followed by the right colon, splenic flexure and transverse colon.

The type of surgery was right colectomy (39.3%), left colectomy (30.7%), Hartmann´s procedure (11%) and the same rate of segmental and extended colectomy (9%).

According to stage, stage I was the least frequent in the region, accounting for 3% of all treated cases, similarly for all sites, with slight variation. Early tumors were not frequent, according to the literature (Table 19.2).

The distribution of stage II was similar in all sites and subtypes, although there was a slight tendency towards a higher frequency of Stage IIC or T4b, which was the most frequent in Salta and Tucumán.

Stage IIIC was the most frequent stage III at all sites, with the distribution of cases across all sites being almost similar for stage IIIA and stage IIIB.

Table 19.2. Tumor stage of patients treated for colon cancer in the NOA.

		Salta	Jujuy	Tucumán	Patients (N)
Patients (N)		261	71	456	788
Stage I	T1- T2 N0 M0	10	2	25	25
Stage IIA	T3 N0 M0	13	3	45	61
Stage IIB	T4 N0 M0	14	3	43	60
Stage IIC	T4b N0 M0	24	1	63	88
Stage IIIA	T1-T2 N1 M0 T1 N2 M0	69 6	2 3	179 9	250 18
Stage IIIB	T3-T4 N1 M0 T2- T3 N2 M0 T1- T2 N2 M0	22 14 15	4 10 10	67 61 63	93 85 88
Stage IIIC	T4 N2 M0 T3- T4 N2 M0 T4 N1-N2 M0	8 66 24	6 7 1	35 184 8	49 257 33

CHAPTER 20
Survey on current treatment of colon cancer

A survey was conducted consisting of 21 multiple choice questions, 20 with a single option and one with an open answer. The survey was sent via email and social networks of the Sociedad Argentina de Coloproctología, Revista Argentina de Coloproctología, Asociación Argentina de Cirugía and different communication and dissemination channels through social networks.

Survey

1. In your surgical practice, you perform:
   a) General surgery
   b) General surgery and coloproctology
   c) Only coloproctology

Answers:

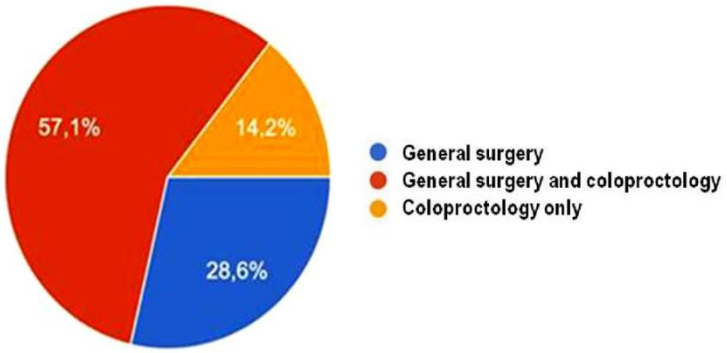

Figure 20.1

2. Are you a specialist in coloproctology?
   a) Yes
   b) No

Answers:

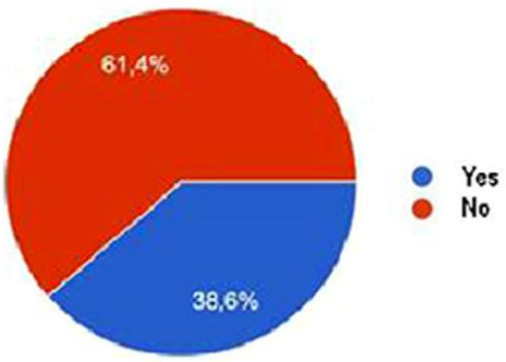

Figure 20.2

3. How do you manage colon cancer in your institution?
   a) Multidisciplinary team or committee
   b) Surgeon approach + oncologist

Answers:

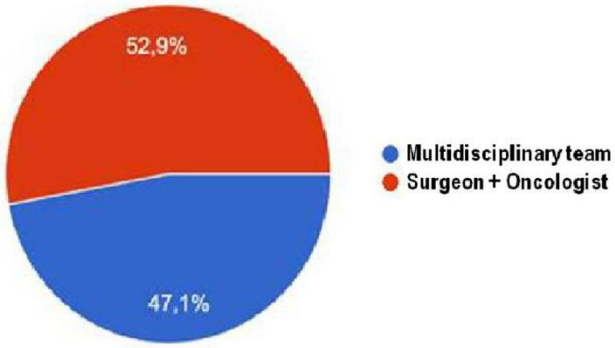

Figure 20.3

4. Is endoscopic treatment of early colon cancer (malignant polyp-T1) performed by surgeons at your institution?
   a) Yes
   b) No

Answers:

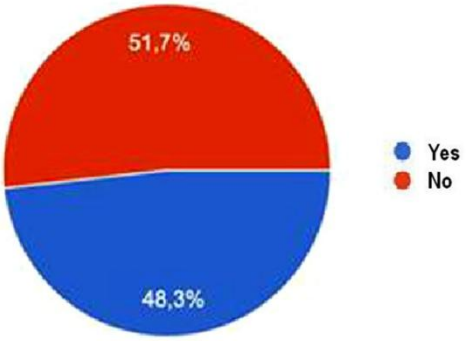

Figure 20.4

5. In early colon cancer, what is the treatment of choice in your department?
   a) Endoscopic treatment + tattoing and eventual surgery according to the histopathology.
   b) Surgery

Answers

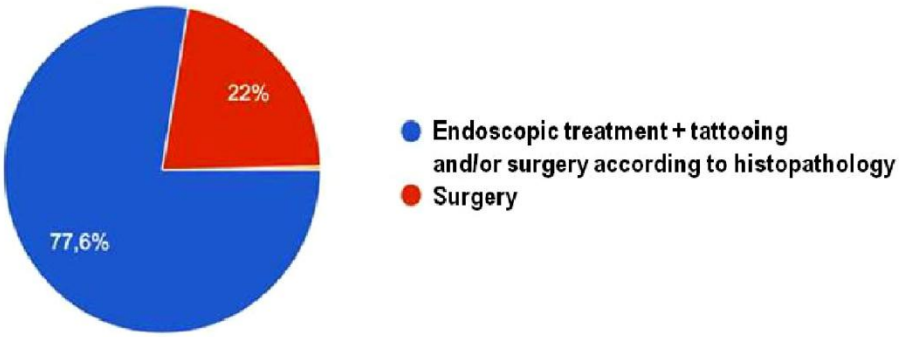

Figure 20.5

6. What is your approach to adjuvant therapy for stage II colon cancer?

a) Surgery is sufficient
b) Add adjuvant therapy
c) It depends on histological factors, genetic stability, status of DNA repair genes

Answers
:

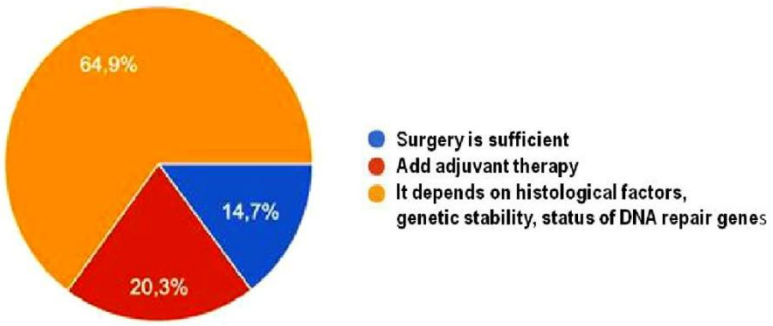

Figure 20.6

7. In right colon cancer, you perform a colectomy with total excision of the mesocolon:
a) Routinely
b) Selectively
c) Occasionally
d) Never

Answers:

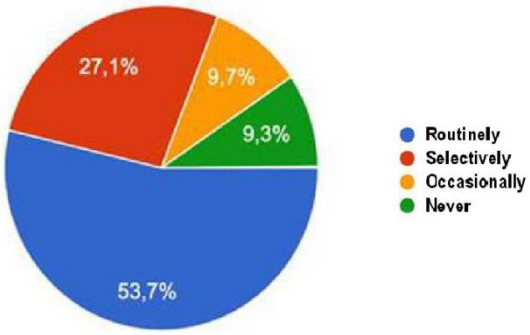

Figure 20.7

8. In locally advanced right colon cancer, you routinely perform a colectomy with:
a) D1 lymphadenectomy
b) D2 lymphadenectomy
c) D3 lymphadenectomy

Answers:

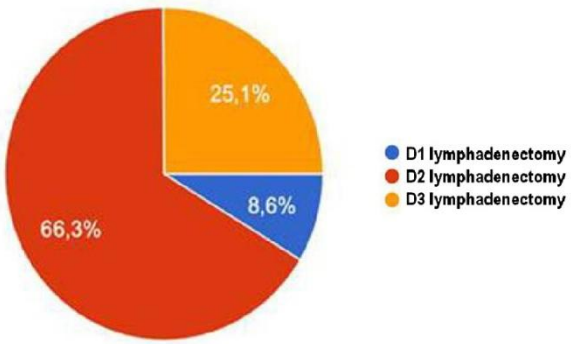

Figure 20.8

9. For the treatment of transverse colon cancer without involvement of the colonic

flexures, you decide to perform:
a) Segmental colectomy
b) Extended colectomy (right or left depending on the location)

Answers:

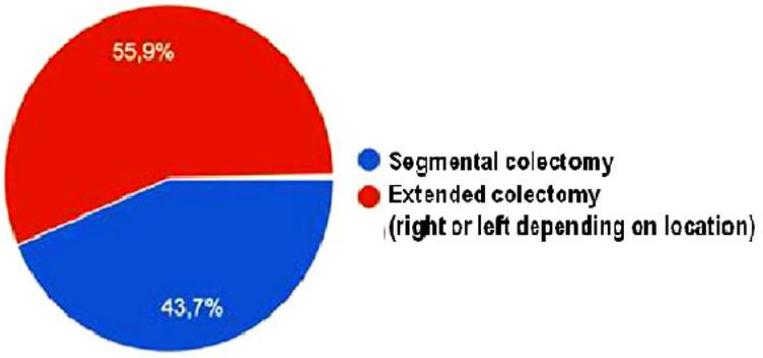

Figure 20.9

10. For the treatment of splenic flexure cancer, you indicate:
a) Segmental colectomy
b) Extended colectomy (extended right colectomy, extended left colectomy, subtotal colectomy)

Answers:

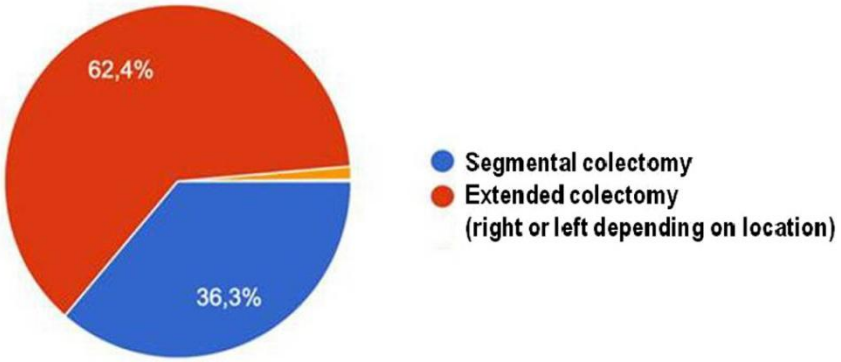

Figure 20.10

11. For elective treatment of colon cancer, you usually perform:
a) Open surgery
b) Laparoscopic surgery
c) Robotic surgery

Answers:

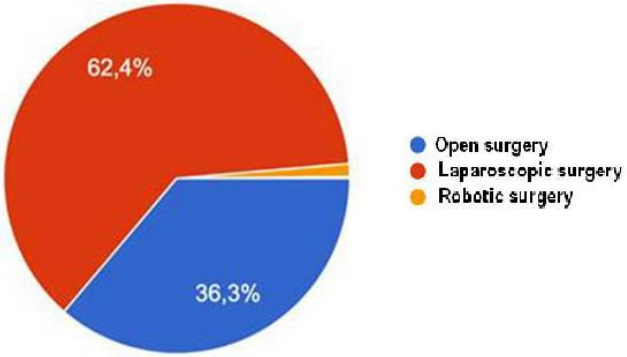

Figure 20.11

12. Do you think that robotic surgery has or will have a role in the elective treatment of

colon cancer in our setting?
a) Yes
b) No

Answers:

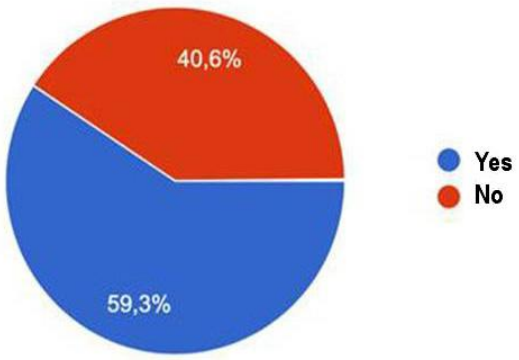

Figure 20.12

13. When do you indicate neoadjuvant therapy in colon cancer?
a) T3-T4 Nx
b) Tx N+
c) M+ (Systemic treatment)
d) Never

Answers:

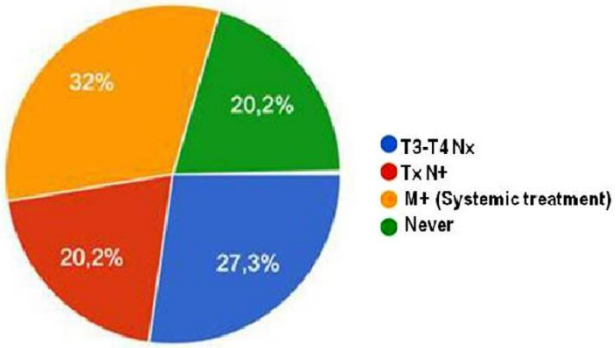

Figure 20.13

14. Do you or your multidisciplinary team use liquid biopsy in daily practice?
a) Yes
b) No

Answers:

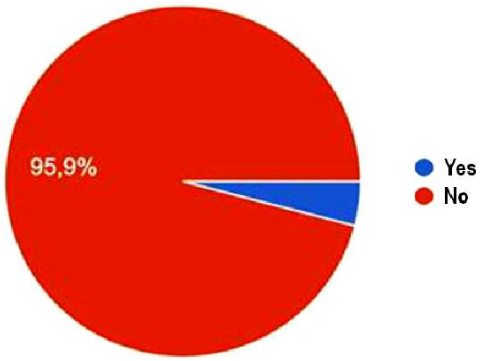

Figure 20.14

15. Do you test for microsatellite or chromosomal instability in your patients?
    a) Yes
    b) No

Answers:

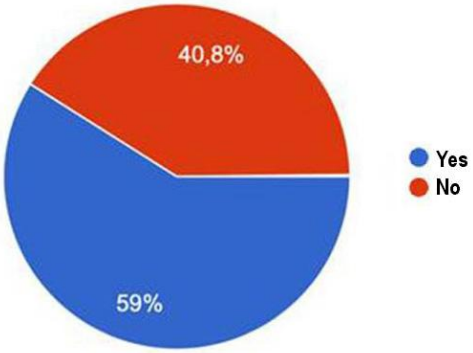

Figure 20.15

16. For the treatment of colon cancer in an emergency, you usually indicate:
a) Open surgery
b) Laparoscopic surgery

Answers:

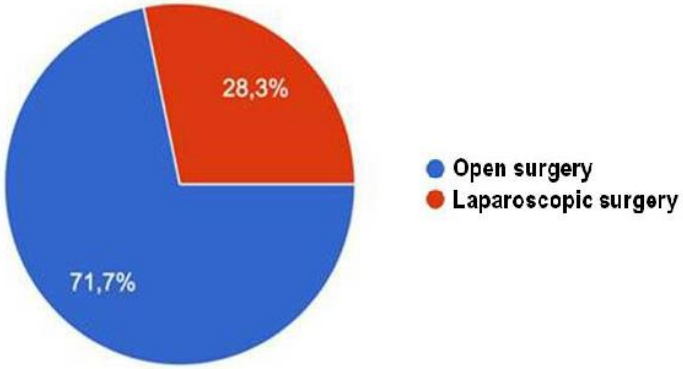

Figure 20.16

17. In occlusive cancer of the left colon, you usually opt for:
    a) Endoscopic/radiological stent
    b) Ostomy
    c) Extended colectomy, with or without anastomosis
    d) Hartmann's procedure

Answers:

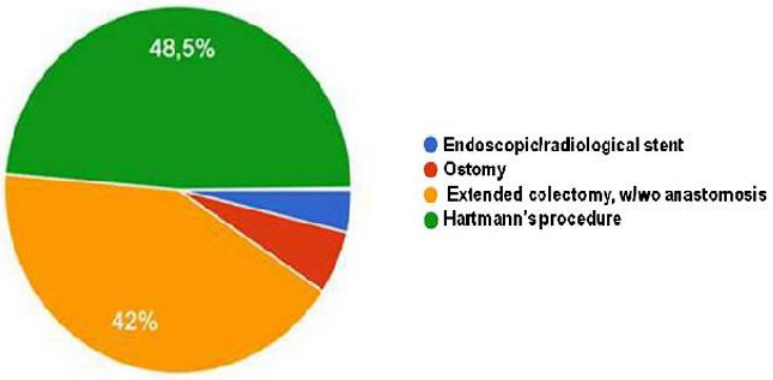

Figure 20.17

18. For occlusive cancer of the right colon, you usually opt for:

a) Ileostomy
b) Colectomy with anastomosis
c) Colectomy + ileostomy

Answers:

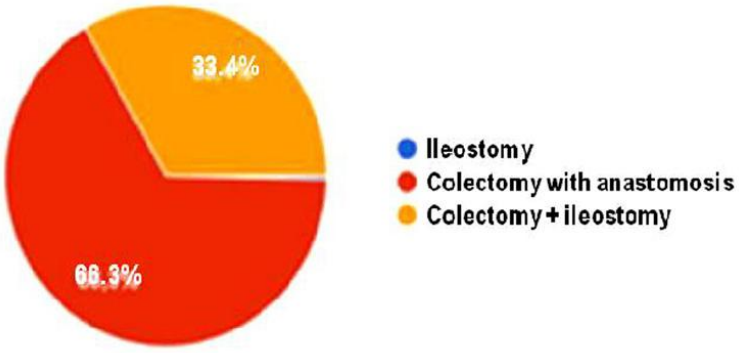

Figure 20.18

19. In a patient with resectable or potentially resectable synchronous liver metastasis, you:
    a) Treat both the primary tumor and the metastases
    b) Refer to a hepatobiliary surgeon
    c) Refer to another center of greater complexity
    d) Refer to an oncologist

Answers:

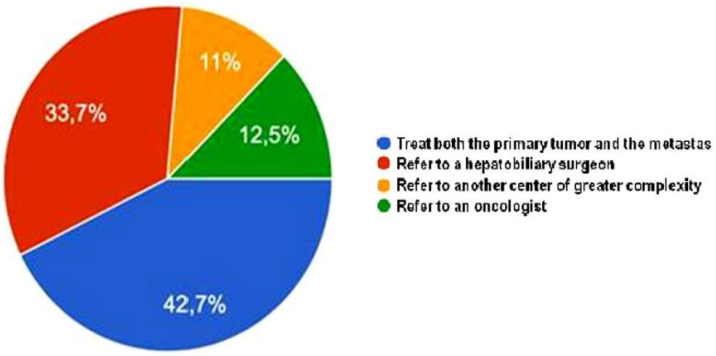

Figure 20.19

20. Your age is:

    a) < 40 years
    b) 40 to 60 years
    c) > 60 years

Answers:

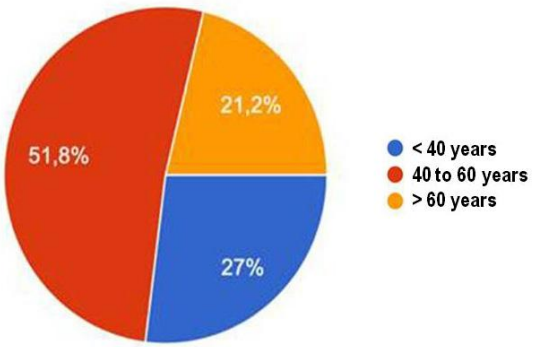

Figure 20.20

21. What is the province of Argentina/country where you practice surgery?

Answers:

Argentina 513
- Buenos Aires 169
- CABA 103
- Catamarca 2
- Chaco 10
- Chubut 2
- Córdoba 34
- Corrientes 8
- Entre Rios 16
- Formosa 4
- Jujuy 10
- La Pampa 4
- La Rioja 1
- Mendoza 14
- Misiones 4
- Neuquén 7
- Rio Negro 12
- Salta 8
- San Juan 16
- San Luis 7
- Santa Cruz 3
- Santa Fe 42
- Santiago del Estero 4
- Tierra del Fuego 2
- Tucumán 30

Rest of Latin America 77
- Uruguay 28
- Paraguay 11
- Chile 9
- Ecuador 6
- Venezuela 5
- Mexico 4
- Panama 2
- Brazil 2
- Bolivia 2
- Guatemala 1
- Peru 2
- Colombia 1
- El Salvador 1
- Nicaragua 1
- Dominican Republic 1
- Costa Rica 1

Survey analysis

Five-hundred ninety responses were received. The questions were answered by surgeons dedicated only to coloproctology (14.2%), only to surgery (28.6%) or to both specialties (57.1%) (Fig. 20.1). Two hundred twenty-eight (38,6%) respondents said they were specialists in coloproctology (Fig. 20.2).

It is relevant that 52.9% manage patients with colon cancer individually with the oncologist, without having a multidisciplinary team or Tumor Committee, as recommended (Fig. 20.3). A similar proportion (51.7%), do not personally manage the malignant polyp en6oscopically, but refer it to an endoscopist or treat it surgically (Fig. 20.4). Regarding the management of early colon cancer, 77.6% of respondents perform endoscopic treatment with marking and only 22% decide on the initial surgical approach (Fig. 20.5).

For the treatment of stage II, 64.9% consider risk factors when deciding whether to add adjuvant therapy to surgical treatment. However, 20.3% always indicate it and 14.7% never do so and only perform surgical treatment. (Fig. 20.6).

In right colectomy, 53.7% routinely perform total mesocolon excision, 27.1% do so selectively, and 9.3% never do so. (Fig. 20.7).

For the treatment of lymph node invasion in locally advanced right-sided colon cancer, 66.3% add a D2 lymphadenectomy to the right colectomy and 25.1% a D3 lymphadenectomy. However, the remaining 8.6% perform a D1 lymphadenectomy. (Fig. 20.8).

For transverse colon cancer without flexure involvement, 55.9% of respondents indicate extended colectomy including the flexures, depending on the location. The remaining 43.7% perform segmental colectomy (Fig. 20.9). For the treatment of splenic flexure cancer, 62.2% indicate extended colectomy and 37.8% indicate segmental colectomy. (Fig. 20.10).

Elective treatment for colon cancer is routinely performed laparoscopically in 62.4% of respondents, while 36.3% use the conventional route. Only 1.2% (7 surgeons) use robotics from the start. (Fig. 20.11). However, 62.4% think that robotic surgery will play a relevant role in our environment, while 36.3% are skeptical about its }}applicability in colorectal surgery. (Fig. 20.12).

The indications for neoadjuvant therapy are varied and all are used in similar proportions. Thus, 32% indicate it for metastasis, 27.3% for T3 and T4 Nx tumors, 20.2% for TxN+, and another 20% say they never use neoadjuvant therapy and operate without prior treatment in any of these circumstances. (Fig. 20.13).

Only 4.1% responded that they use liquid biopsy in their daily practice for the oncological follow-up of their patients (Fig. 20.14) and 59% answered that they do not evaluate chromosomal or microsatellite stability, while 40% determine it systematically. (Fig. 20.15).

For the emergency treatment of colon cancer, 71.7% indicate open surgery and 28.3% indicate initial laparoscopy. (Fig. 20.16).

In occlusive left colon cancer, 48.5% of the surgeons surveyed recommended a Hartmann´s procedure, 42% an extended colectomy with or without anastomosis, and 5.6% only a colostomy. Only 3.7% suggested the placement of an stent. This means that more than half of the surgeons surveyed resolve a left colon obstruction with a colostomy. (Fig. 20.17). If the obstruction is in the right colon, 66.3% opt for a resection with primary anastomosis and 33.4% without anastomosis. (Fig. 20.18).

In the setting of a synchronous, resectable or potentially resectable liver metastasis from a colon tumor, 42.7% approach the case surgically simultaneously, 33.7% refer or consult a liver surgeon, 12.5% refer to an oncologist, and 11% refer to a more complex center. (Fig. 20.19)

Regarding the age group of the surveyed surgeons, 51.8% are between 40 and 60 years old, 27% are under 40 years old and 21.2% are over 60 years old (Fig. 20.20). Eighty-seven percent come from Argentina, the majority from the Province of Buenos Aires and CABA, followed by Santa Fe, Córdoba and Tucumán and the rest of the Argentine provinces, which were fully represented. Thirteen percent come from different Latin American countries, mostly from Uruguay, followed by Paraguay and Chile and to a lesser extent from other countries in the region.

CHAPTER 21
Final considerations

The update in the treatment of colon cancer includes multiple aspects that have been developed in recent years and that have resulted in an improvement in OS, DFS and quality of life, considering the variability between different stages and risk groups.

Sometimes, treatment includes not only colon resection, but also resection of organs affected by direct invasion, locoregional involvement or metastasis. Therefore, it is essential to create a work team that includes specialists related to diagnosis and staging (imaging specialist, pathologist), in addition to those involved in treatment (colorectal or general surgeon, liver surgeon, thoracic surgeon, oncologist, radiotherapist) to define in a personalized way the best therapeutic option for each patient.

In our opinion, the current approach to the treatment of colon cancer depends on the stage and clinical presentation, with or without complications. Special situations that arise with advanced tumors, multiple tumors, and those that occur during pregnancy should also be considered.

Significant advances in recent years include genetic-based classification, the determination of stable or unstable tumors, and a large number of tools (e.g. liquid biopsy, Immunscore) whose implementation is the subject of multiple studies and whose clinical applicability seems imminent. This advance was fundamental for the inclusion of immunotherapy as part of the treatment. In addition, technical advances have been made such as complete mesocolic excision and oncological strategies such as neoadjuvant therapy as a new therapeutic approach, with outstanding results.

In the last chapter prior to these conclusions, data from recent years on the diagnosis and treatment of colon cancer in the main healthcare centres in the Northwest of Argentina have been collected, with very interesting results for understanding the local problems and their differences with the rest of the country. In addition, the opinion of almost 600 colleagues from all over Latin America completes the data included in this publication.

This report aims to present the largest amount of evidence and information available, both from the healthcare and research point of view, which is highly relevant today for the clinical-surgical implementation of colon cancer treatment.