CHAPTER 13
Post-Neoadjuvant Treatment Management

Timing for surgery

The pCR rate reported in the literature of up to 30% has led the group from São Paulo led by Habr-Gama to propose the strategy of "watch and wait" in selected cases.[64,82,94,104,130,149,260] This proposal was initially rejected, but in light of the obvious good results reported, NOT's strategy gained wide diffusion and acceptance. However, until today the most accepted recommendation in all international guidelines is that neoadjuvant treatment should be followed by radical resection. This is so, despite the fact that published studies have shown tumor reduction and pCR in a significant percentage of patients after this treatment, especially with the long-course regimen.

The variation observed in the number of pCRs could be explained by the application of different regimens and dosages, both of ChT and RT, as well as the fact that uniform intervals between the completion of treatment and surgery are not applied. Therefore, it is essential to establish with the greatest possible certainty whether a CRP has been achieved and not just a CRC, since in the latter case surgical treatment would be delayed until clinical evidence of tumor persistence or regrowth is obtained.The ideal waiting time for surgery after neoadjuvant treatment with long-course regimens is controversial, but a period of no less than 7 weeks is generally accepted. The randomized studies that analyzed the interval time between neoadjuvant treatment and surgery failed to show advantages in relation to survival and only in two of them did the delay translate into a higher rate of pCR.[1,42,60,129,196]

A meta-analysis including 4 of these randomized clinical trials and 22 non-randomized studies concluded that a wait greater than 8 weeks is associated with greater downstaging and probability of achieving pCR.[195] However, this did not translate into a greater number of resections R0 or sphincter preservation. Furthermore, this higher probability of pCR was associated with a lower number of metastatic relapses, but not fewer local relapses, or improvement in survival.

A trial conducted in France, Lyon 90-01, had already shown that a longer interval between RT and surgery increases the rate of pCR. This study compared an interval of 6 vs. 2 weeks after RT without ChT and obtained a pCR of 14 vs. 7%, respectively, although with p=0.17. However, there was a statistically significant decrease in the stage (26 vs. 10%, p = 0.007).[61] More recent studies have also shown that a longer waiting time between RT and surgery seems to be related to a higher incidence of pCR.[81,83,227] Thus, Habr-Gama´s group has proposed prolonging the wait to no less than 12 weeks and has increased the dose of RT to 5400 cGy, and even added ChT during the waiting period.[31] García Aguilar compared 66 patients operated 6 weeks after the completion of CRT, with 70 patients with a good response at 4 weeks in whom surgery was postponed for another 5 weeks while ChT was continued with a variant of the FOLFOX regimen. There was an increase in pCR rate (18 vs. 25%, respectively) without increasing complications.[67]

Specifically, current guidelines, both European (ESMO) and American (NCCN), recommend a very wide margin of waiting time after the end of CRT, ranging from 4 to 12 weeks for the first and 5 to 12 weeks for the latter. l. Therefore, it is universally accepted that after neoadjuvant treatment, when surgical intervention is planned, it is performed after a period of no less than 4 to 6 weeks.

Timing for surgery with the short-course RT regimens

Although in the US and particularly in Argentina the short-course RT strategy has not been widely accepted, the small number of fractions makes this regimen less expensive and perhaps more convenient in terms of toxicity than CRT. Although, the total dose is lower due to its administration in such a short period, the daily dose is more than double that of the long-course regimen (500 vs. 180 cGy). This higher intensity allows a comparable effect, however, CRT has shown some oncological advantages compared to RT as the only treatment. As already mentioned, to the reduction of the risk of local recurrence is added the benefit of reducing the size of the tumor, which can even reach a pCR.

Recently, it has been suggested that preoperative short-course RT with a longer time interval before surgery could be a valuable option for unresectable cancer patients who are not suitable for ChT.[89,184]

In a Swedish series, 112 patients treated with this mo-

dality for comorbidities that contraindicated ChT, achieved 8% pCR, in addition to significant tumor regression in 74% of cases, according to the evaluation carried out by HR-MRI.[177]

The indication for initial ChT and short-course RT (5 × 5 Gy) with delayed surgery has also been described in patients with distant metastases and locally advanced tumors who underwent simultaneous resection of the primary tumor and metastatic lesions.[206]

A recent randomized study compared 46 patients treated with neoadjuvant CRT with 37 patients treated with short-course RT (5x5 Gy), all operated at 6 weeks. Although there was significantly greater downsizing and downstaging in the CRT group, there were no differences in sphincter preservation, number of complications, or rate of R0 resections.[128]

Although it is traditionally accepted to wait one week after the end of short-course RT, based on these experiences, the optimal time for surgical intervention has been the subject of debate, as it was with long-term CRT. The Dutch TME Trial, extended this period to 21 days. Waiting between 4 and 8 weeks has also been considered in order to achieve a pCR rate similar to that observed with the long-course regimen, or the downstaging observed with the latter when treating bulky tumors. On the other hand, it has been considered that a wait of less than 7 days could prevent the leukopenic response to treatment and thus avoid complications.

The Stockholm III study attempted to answer this question by comparing 3 groups of patients: short-couse RT with surgery at 7 days, short-course RT with surgery after 4 to 8 weeks, and long-course RT with surgery at 4 to 8 weeks. Although it showed a better response and fewer complications with the long wait, this study has some shortcomings.[177] Recruitment was very slow, no concurrent ChT was used in the long-course RT arm, and very few patients in the 3 groups received adjuvant ChT.

Although the question about the ideal waiting period until surgery after short-course RT was not satisfactorily answered with scientific evidence, at present the ESMO guidelines accept both immediate surgery, before 10 days, and deferred surgery, between 4 to 12 weeks, after completing the short-course RT regimen.

pCR vs. cCR

Various studies, including one published by our group, have shown that the presence of a cCR is not synonymous with pCR.130 Hiotis et al. from the MSKCC,40 reported that only 25% of cCRs were confirmed by histopathology.

At the FICARE (Acronym in Spanish for International Forum of Rectal Cancer) meeting, held in São Paulo in 2009, Bujko showed unpublished data from the Polish Rectal Trial, in which a series of 137 patients with T3 tumors were treated with neoadjuvant CRT. There were 21 (15%) patients with cCR, in 10 (48%) of whom a remnant tumor was found in the surgical specimen, including 2 cases of ypT3 and another 2 with mesorectal LN+. On the other hand, several studies, including that of our Co-Recto group, show that pCR may exist even in cases with persistent macroscopic lesion.

In other words, on the one hand, a cCR may not imply a pCR and on the other, there may be a pCR even without cCR, either due to a stenosis or a tumor scar visible in the HR-MRI but without neoplastic cells.

These two facts acquire fundamental importance in light of the strategy proposed by Habr-Gama, based on the high proportion of patients who achieve pCR; since, although receiving a histopathological report without tumor cells could be taken as good news, removing a rectum devoid of tumor is undesirable.[82] It is also obvious that no one would want to be exposed to the risk of having a tumor considered by mistake as fully sterilized.

In this sense, it is relevant to deepen the evaluation of diagnostic imaging methods that allow ratifying or refuting the clinical suspicion of pCR and validating the safety of a NOT strategy, something that we will deal with later.

Usefulness of biopsy

A biopsy of the anterior tumor site is also unreliable. In this regard, Mareto's experience is interesting: in 22 tumors biopsied after 5 weeks of CRT, he obtained 17 negative biopsies, while he found residual tumor in 65% of the rectal resection specimens.[139] The San Pablo group also studied this aspect and confirmed that in patients with a response <30%, clinically and endoscopically evaluated, the negative predictive value of the post-CRT biopsy is 21%. In another study of 178 patients, 79 underwent a biopsy of the primary lesion after neoadjuvant therapy, and the sensitivity and specificity were 12.9% and 94.1%, respectively, compared to the findings of resective surgery.[253]

In addition, the group from Poland analyzed the presence of distant intramural spread in patients undergoing neoadjuvant treatment. Although they confirmed that it can exist both after short-course RT and long-course CRT, with the latter strategy, spread can be discontinuous in 57% of cases compared to 16% with RT as the only treatment.[36]

The risk of disease persistence in the mesorectum

Another interesting fact is the existence of a non-negligible number of cases in which the treatment achieved the eradication of the tumor in the rectal wall, but viable tumor cells, detected with conventional techniques, persisted in the lymph nodes of the mesorectum (ypT0N1). This finding was reported by several authors with a variable incidence, which in the series by Kim et al. was only 2.2%.[114,167] Zmora and Wexner found tumor foci in mesorectum nodes in 12% of T0 tumors, although included one case in which was not possible to identify whether the tumor deposits were a lymph node.[83] Hughes et al.[101] and Onaitis et al.[166] found incidences of 17 and 21%, respectively. In our series, it was 18.7%.[130] This implies that neither a negative biopsy nor a local resection of the rectal wall in the area where the tumor was located could rule out the persistence of the disease, if it were located in the mesorectum. Habr-Gama no encontró recaídas pélvicas en sus pacientes incluidas en el protocolo W&W, lo que llevó a algunos seguidores de esta estrategia a postular que estas células tumorales en los ganglios linfáticos podrían ser inviables o que en un período de espera más largo podrían desaparecer debido a la efecto continuo de la radioterapia. However, cases of mesorectal lymph node recurrence have been described two years after the decision to postpone surgery, so one must be very careful when stating the null clinical importance of this finding.

The place of images

This topic has already been developed in another chapter, but it is worth reiterating here that, as in pretreatment staging, HR-MRI is the best imaging method to assess post-neoadjuvant response. To this purpose, the aforementioned degree of tumor regression was described by HR-MRI (mrTRG).[170] This score has been validated as a predictor of survival and a multicenter clinical trial known as the TRIGGER Trial, currently underway, assesses its value to define the post-neoadjuvant therapeutic strategy.[7,171]

In conclusion, it should not only be taken into account that cCR does not imply pCR, but the latter can occur in cases where there appears to be residual tumor, both clinically and on imaging. Biopsies are not helpful and the possibility of mesorectal disease should not be overlooked. Confirming the existence of a pCR remains one of the IDT's biggest challenges.

Sphincter preservation post-neoadjuvant therapy

A point of contention is whether neoadjuvant therapy plays a role in the possibility of preserving the anal sphincter. That is, it is debated whether the decision about the surgical approach (anterior resection or APR) should be made before or after neoadjuvant treatment. Although there is no firm evidence, some phase II studies and individual experiences show that in many cases in which APR had been considered, the sphincter was preserved after neoadjuvant treatment.[115,150,232,245]

A study carried out in China in 277 patients with tumors of the lower rectum, showed that CRT significantly increased the probability of preserving the sphincter in tumors located 3-4 cm from the anal margin, but the same did not occur in tumors located closer or further away from the anal margin.[5] Other authors have reported a low number of local relapses and excellent survival with this change in management adopted after neoadjuvant CRT.[136] Furthermore, considering that the long-term prognosis is determined by the response to neoadjuvant treatments, it seems more than reasonable that some decisions are made based on the magnitude of the response.[84] HR-MRI has proven to be very useful in defining this change in management.[121] With this premise, Bujko and the Polish group conducted a study in which patients were randomized to short-course RT vs. CRT to determine whether the long-course regimen increases the possibility of preserving the sphincter. The decision was made on the basis of re-staging after neoadjuvant treatment, but there were no significant differences in favor of the regimen that postponed surgery for 4 to 6 weeks. In fact, the sphincter was preserved in 61% of the patients who received short-course RT vs. 58% of those treated with CRT ($p = 0.57$).[22]

However, a systematic review published by Bujko, which included 10 randomized clinical trials and 4596 patients, could not demonstrate that preoperative treatments increase the chance of preserving the sphincter.[19] The German trial was the only study in this analysis that confirmed a higher incidence of anterior resections in the neoadjuvant group, however, this was a secondary endpoint and the number of patients with low tumors, candidates for APR, was significantly lower than in the control group (postoperative RT).[198]

Although there is no definitive evidence, in specific cases properly studied with quality images, a change in surgical strategy may be considered according the response to neoadjuvant therapy.

TAE after neoadjuvant treatment

TAE, in any of its forms, is an accepted strategy for its oncological safety only in the cT1 stages. Its indication in

cT2 stages carries the risk of metastatic or micrometastatic disease in the mesorectal nodes, as well as the risk of residual tumor in the surgical site.

The theory that the tumor tends to shrink and then be replaced by fibrosis could justify not only the strategy of preserving the sphincter, but also that of preserving the rectum through TAE, or that of avoiding resection of any viscera previously invaded (e. g., vagina), and even not to operate, as promoted by Habr-Gama group and currently considered by many surgical groups.

Thus, preservation of the rectum through TAE, whether conventional or minimally invasive (TEM or TAMIS) is presented as an alternative for cT1/2 and incipient cT3 tumors of the lower third after CRT, with the aim of avoiding APR or resection with coloanal anastomosis and its morbidities.

The proposed option consists of performing a TAE as excisional biopsy to evaluate the response to neoadjuvant treatment in cT1-3 N0 tumors and define subsequent management based on the pathological report. The probability of recurrence for stage ypT0 is around 4%, but increases to more than 20% when there is residual tumor.[86] It is even estimated that an identical percentage of patients with ypT1-2 tumors could have metastases in the mesorectal nodes.[211]

Oncological safety

Oncological safety was proven in several studies, including two prospective randomized trials:

- In the CARTS study, 55 patients with T1-3N0 rectal cancer underwent long-course neoadjuvant ChT. After clinical re-assessment at 6 to 8 weeks, those with a significant clinical response (reduction in tumor size) underwent minimally invasive TAE.[243] Thirty of 55 (55%) patients had ypT0-1 and did not require additional surgery. After a mean follow-up of 17 months, only 1 patient of these 30 patients developed a local recurrence and underwent salvage radical resection. At five years, 64% of these 55 patients achieved rectal preservation. The 5-year OS and DFS were 81.6 and 82.8%, respectively.[213] Despite favorable oncological results, 50% of the patients who preserved the rectum had significant symptoms, similar to those of the low anterior resection syndrome. Furthermore, one third of the patients could have avoided neoadjuvant RT as they eventually underwent TME. Two patients died from side effects of neoadjuvant treatment.
- In another study, 89 patients with T1-3N0 rectal cancer were treated with short-course CRT or RT followed by TAE. Perhaps due to poor adherence to RT, the study reported a local recurrence rate of 10% at two years in those with pT0-1 tumors.[21]
- In another study, 53 patients with early rectal cancer underwent neoadjuvant therapy followed by TAE.[175]Although 36 patients had high-risk pathologic features, none underwent another surgery. At two years, 12 (33%) patients developed local recurrence. Of these 12 patients, only 8 were candidates for salvage surgery and a negative CRM was achieved in only one of them. At three years, 4 patients developed local recurrence. The 2-year local recurrence-free survival was 77% and re-recurrence-free survival 60%.
- An Italian study randomized 100 patients with post-CRT T2N0 distal tumors to TEM or TME.131 In both arms R0 resection rate was 100%. No patient in the TEM group required radical resection, and this group had a significantly shorter operative time and less blood loss. However, postoperative complications did not differ significantly in both groups. After almost 10 years, there were no differences in the number of local or distant relapse.
- GRECCAR 2, a phase 3 trial conducted in 15 centers in France, randomized patients with cT2/3 N0-1 tumors, smaller than 4 cm in diameter, located less than 8 cm from the anal margin, with a good response to neoadjuvant treatment (residual tumor < 2 cm on HR-MRI), at TAE vs. TME. Of the 186 patients included, 148 (80%) showed a good response and 145 were randomized.[91,92] In the TAE group, TME was indicated if the excisional biopsy was reported as ypT2-3 or R1, which occured in 35% of cases (26/74). The variables studied were death, recurrence, rate of grade 3-4 surgical complications and severe adverse events at 2 years, such as incontinence, sexual impotence, or the need for a definitive colostomy. One or more of these events were observed after 2 years in 41/73 (56%) patients in the TAE group and in 33/69 (48%) patients in the TME group (p = 0.43). There were also no significant differences in local or distant relapse, OS or DFS at 5 years. Patients who refused new surgery suffered high rates of local recurrence and poor survival. The conclusion of the study is that the role of local resection after neoadjuvant treatment is not clear enough.
- In a systematic review and meta-analysis of 20 studies (14 cohorts, 5 comparative cohorts, and 1 randomized trial), more than 1000 patients with early rectal cancer (23, 46, and 31% of patients with T1, T2 and T3 tumors, respectively) were treated with neoadjuvant therapy followed by TAE.[86] The cCR rate was 46% and the pCR rate was 44%. After a mean follow-up of 54 months, ypT0, ypT1, ypT2, and ypT3 tumors had accumulated local recurrence rates of 4, 12, 24, and 60% respectively. Based on these data, the authors concluded that TAE after neoadjuvant therapy should only

be considered curative if pCR (ypT0) has been achieved, while radical surgery should be offered to any patient with an incomplete response to avoid the high risk of local recurrence.

In summary, TAE as the only surgical treatment for rectal cancer ≥T2N0 is still under investigation, due to the risk of mesorectal micrometastases and residual disease at the excision site. Furthermore, neoadjuvant treatment for patients with stage cT1-T2N0 is not standard practice and may not be necessary if these patients are initially treated with TME. It should always be remembered that ChT and/or pelvic RT can cause morbidity or functional impairment comparable to that associated with radical surgery. Therefore, it remains highly doubtful that TAE after neoadjuvant treatment is equivalent to radical surgery for the treatment of cT1-3N0 rectal cancer.

More trials are currently underway to compare the three potential approaches for this: TME without neoadjuvant therapy, neoadjuvant therapy followed by TAE and neoadjuvant therapy followed by NOT (for those who achieve cCR).

TAE complications after neoadjuvant treatment

Beyond oncological safety, other issues also need to be considered:

- First, the complications of TAE are much greater when performed on an irradiated rectal wall. Dehiscence is extremely common and healing is significantly delayed.
- On the other hand, if the pathological findings are unfavorable and reveal that this treatment was not sufficient, the local conditions to perform TME worsen significantly, making this operation very difficult, reducing the chances of preserving the sphincter, or when possible, causing much greater defecatory disturbances. In this context, radical surgery is associated with higher rates of morbidity and definitive colostomies than when TME is initially indicated, and in addition, in the latter case, the oncological results of these early tumors are obviously optimal.

All these data do not favor TAE in the context of neoadjuvant treatment, since, with the available studies, it is extremely difficult to establish with certainty the level of involvement of the rectal wall and the mesorectum. At the moment, TAE can only be recommended when there is a contraindication to major abdominal surgery or in the context of a clinical trial. Patients with rectal cancer ≥ T2N0 should continue to undergo radical surgery for optimal cancer outcomes.

NOT

Neoadjuvant treatment arises as a consequence of adjuvant RT, which aimed to reduce local relapses, although at the cost of adding complications due to the impact of radiation in a recently anastomosed area. The search for an alternative that would maintain the benefit of RT without this risk culminated in the German Trial, which definitively changed the paradigm of rectal cancer treatment and opened a new perspective. One of the most striking derivations was the complete disappearance of some tumors, evidenced both in clinical and pathology, and even without coincidence between the two. But even before this publication, the TNO strategy emerged in the late 1990s, promoted globally by Habr-Gama. Although widely accepted today, almost 30 years later this strategy remains controversial. The fact that no residual tumor was found in some patients undergoing APR motivated this strategy, initially used in patients considered inoperable due to their comorbidities or who refused surgery after neoadjuvant treatment because they were completely asymptomatic and with no certainty of residual tumor. On the other hand, even patients who initially undergo surgery to try to preserve the sphincter are at risk of being left with a definitive ostomy due to anastomotic complications. Furthermore, even after an uncomplicated anastomosis, functional results are often suboptimal due to urinary and sexual complications, which can also be increased by surgery.

We'll review the evidence supporting TNO's strategy below:

- Habr-Gama, in 2004 published a study comparing 194 patients operated on for persistent disease after neoadjuvant treatment and 71 patients observed after obtaining a cCR. The regimen consisted of 5040 cGy, administered with a linear accelerator in daily doses of 180 cGy, 5 days per week for 6 consecutive weeks. At the same time, the patients received intravenous 5-FU (425 mg / m2 / d) and folinic acid (20 mg / m2 / d) during the first 3 and last 3 days of radiation. In the group of operated patients, there were 8.3% with pCR (ypT0N0), of whom 41% had a definitive ostomy. In the observed group there were only 2 intraluminal recurrences, both rescued without the need for APR and with excellent oncological outcome. There were no pelvic recurrence and 3 distant relapses. The 5-year DFS and OS were 88 and 83%, respectively, in the resection group and 100 and 92%, respectively, in the observation group.[82] This study shows that patients with pCR have a very low probability of local recurrence, although they may have distant recurrence. Other studies show that patients with a significant response to

neoadjuvant treatment represent a population with an excellent oncological outcome, better than that of patients who do not have the same response.

- A study published by the MSKCC group in 2006, compared 60 pCR patients with 140 nonresponders, excluding those with partial response in the analysis. DFS and OS were, respectively, 96 and 90% in the pCR group and 54 and 60% in the non-response group. Both differences were highly significant.[216]
- A meta-analysis compared 1,263 patients treated with neoadjuvant CRT and pCR with 2,100 patients with incomplete or no response. In the pCR group, there were 0.7% local recurrence and 8.7% distant recurrence. The risk of recurrence was significantly lower and the OS and DFS were significantly higher in this group.[145]

Despite the lack of randomized trials, NOT is becoming an acceptable alternative for those patients who experience cCR to neoadjuvant treatment and lately to TNT. This policy is based on the inevitable risks that surgery still entails today, with a perioperative mortality of no less than 2%, 11% of anastomotic dehiscence, 5% of reoperation, a variable risk of sexual and urinary dysfunction, and the impact on the quality of life derived from an ostomy, whether temporary or, even more, definitive. In reality, there are still no definitive data to ensure that survival of NOT after neoadjuvant treatment is equivalent to that of surgery, and this is particularly important given the natural history of rectal cancer and its late recurrence rates at 5 and 10 years after resection. However, the NCCN 2020 guidelines establish that NOT can be considered by the IDT for patients who achieve a cCR, and without evidence of residual tumor neither in DRE, nor in endoscopy, nor in HR-MRI. In contrast, ASCRS guidelines still state that patients with apparent cCR to neoadjuvant therapy should be offered radical resection and that NOT can only be considered in highly selected patients in the context of a protocolized setting and after careful discussion with the patient about risk tolerance.

There are no randomized clinical trials comparing NOT with TME in patients with cCR. However, some retrospective studies that evaluated important populations subjected to this strategy will be analyzed.

- The first is a systematic review of 23 studies (all prospective or retrospective cohorts, no randomized trials) with 867 patients.[47] Local regrowth rate, assessed in 10 studies, was 15.7%. Of these patients, 95.4% were surgically rescued and 49.4% of them were able to preserve the anal sphincter. In the 8 studies that compared patients who underwent NOT with those with cCR who underwent radical surgery or whose biopsy was reported as pCR, there was no significant difference in distant relapses or OS, but there was a lower DFS at the expense of endoluminal regrowth. The regrowth rate in patients who underwent NOT was higher than in patients who underwent surgery despite having reached cCR, whether or not pCR had been found. The regrowth rate in patients undergoing NOT compared to those undergoing surgery after cCR with pCR was analyzed in 5 studies and ranged between 4.8-21% and 0-7.7%, respectively. Regrowth in patients with NOT and in those undergoing surgery after cCR without pCR was analyzed in 3 studies and in this case ranged between 3.3-30.4% and 0-2.2%, respectively.
- The second study corresponds to the W&W database (IWWD), the most important international multicenter registry.[235]Between 2015 and 2017, of the 1009 patients in neoadjuvant treatment registered, 880 achieved cCR. With a mean follow-up of 3.3 years, the cumulative incidence of local regrowth at 2 years was 24% and 88% were diag% in the different centers, which may be due to the greater or lesser propensity to indicate NOT. Ninety-seven percent were located in the rectal wall and only 3% relapsed exclusively in the lymph nodes. Seventy-eight percent of the patients who were rescued required TME. There were 71 patients (8%) who developed distant metastases during follow-up, ranging from 4 to 14%. This risk was higher in patients with local regrowth (38 of 213, 18%). The 5-year DFS for the entire group was 94% and OS was 85%.
- Another interesting study compared 113 patients who entered a W&W protocol with 136 patients operated on with pCR, which is somewhat close to what would be expected from a clinical trial comparing NOT and surgery in a population with cCR.[208]
- There were 22 cases (20%) of regrowth after NOT and none after surgery. All 22 were detected on routine surveillance and all could be rescued with surgery. The sphincter complex was preserved in 93 of the 113 patients. However, these patients had a higher rate of distant metastasis than those who did not relapse (36 vs. 1%). Furthermore, the DFS was lower in the W&W group compared to the surgically treated patients (90 vs. 98%).
- Finally, a US population study published in 2020, evaluated in 22,561 patients with stage II-III rectal cancer and a mean follow-up of 37.5 months, the rate of use of NOT from 2010 to 2015 and its influence in survival in patients older and younger than 55 years. The rate of NOT use increased from 10.7% in 2010 to 15.2% in 2015. Older patients were more likely to

receive this treatment, although the rates also increased among young people (7.1 to 10.6%). NOT negatively influenced OS and this effect was more evident in young patients. Among them, 3-year OS with and without surgery was 92.1 vs. 73.4%. On the other hand, in older patients, these values were 85.5 vs. 63%, respectively.

Taken together, all these data suggest that careful endoscopic, clinical, and imaging evaluation after initial treatment could identify cCR patients who have a good chance of local tumor control and therefore do not require surgery. However, none of these data come from trials that randomized patients with cCR to surgery or NOT and thus have significant limitations.

In the case of adopting the strategy promoted by Habr-Gama, it should not be forgotten that cCR does not imply pCR. Similarly, it must be assumed that pCR may exist even in cases where clinical examination and even imaging suggest persistence of the tumor. Therefore, with the diagnostic methods available to date, it is inevitable that in several operated patients no tumor cells are found in the especimen. Likewise, it is known that the pCR, although it is much more frequent, is not an absolute patrimony of early tumors and it also occurs in locally advanced ones.

In light of current evidence, the strategy of W&W is not standard, although it should be considered for patients with cCR and it must be accepted that, after being duly informed, they decide to be included in these protocols. In fact, its indication is already considered in international guides. However, it must be possible to comply with a strict follow-up protocol with absolute certainty and it must also be clear that this is a decision to postpone surgery indefinitely, which will last only as long as the studies continue to show an absence of tumor recurrence.