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Conditional Survival in Patients with a Complete Clinical Response to Neoadjuvant Chemoradiotherapy Managed with Watch & Wait. Retrospective, International and Multicenter Study

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INTRODUCTION

The Watch & Wait strategy for selected patients with clinical complete response (cCR) to neoadjuvant therapy is currently at the forefront of rectal cancer treatment. However, this strategy carries a potential risk for local regrowth in 1 out of 4 patients who achieve a complete clinical response. This is particularly relevant during the first years of follow-up. For these reasons, we usually keep these patients on a very strict surveillance program for LIFE!.

In the paper published in December 2020 at The Lancet Oncology,[1] we attempted to answer how intensive should be the follow-up and for how long.

To this end, we used a specific statistical strategy: conditional survival. Usually, we are used to estimate patient survival once for each patient, at the end of treatment for the next 3, 5 and 7 years. The difference is that conditional survival estimates survival considering that the patient has already survived /remained disease free for a certain number of years. For each new disease-free year, the probability for subsequent years is calculated again. Condition: each additional year without a recurrence. So, if a patient survived the first year without recurrence, the probability of remaining disease-free for the following year will be better than it was at the beginning.

We performed this analysis in 793 patients with rectal cancer and cCR managed with W&W from the international IWWD database (International Watch & Wait Database). The median follow-up was 55.2 (36.0-75.6) months. Local regrowth free survival for the entire cohort of patients was 83.8% (95% CI 81.2-86.4) at 1 year, 74.3% (71.1-77.4) at 3 years and 72.1% (68.8-75.4) at 5 years. However, applying conditional survival, the probability of remaining free from local regrowth for an additional 2 years if a patient achieved and sustained a complete clinical response for 1 year was 88.1% (95% CI 85.8-90.9), for 3 years was 97.3% (95.2-98.6), and for 5 years was 98.6% (97.6-100.0).

Similar results were observed for distant metastasis free survival. Even though the risk of metastasis in this group of patients is low, the probability after 3 years from the W&W decision is almost 10%. However, 2 years conditional distant metastasis free survival in patients who were distant metastasis.free from the decision to commence W&W for 1 year was 93.8% (95% CI 92.3-95.9), for 3 years was 97.8 % (96.6-99.3) and for 5 years was 96.6% (94.4-98.9). These results suggest that, for patients that survived the first year without recurrence, the risk for local regrowth and distant metastasis for the subsequent 2 additional years is considerably low obviating the need for intensive surveillance after 3 years.

Finally, analyzing the known risk factors for local regrowth (baseline cT stage and final radiation dose), we observed that after an initial clinical complete response to neoadjuvant chemoradiotherapy, these risk factors appear to be less relevant after 1 year of a sustained clinical complete response. These results suggest that performing any additional treatment in patients with cCR for the purpose of minimizing the risk of local regrowth may be unnecessary.

In conclusion, in this group of patients, maintaining cCR during the first year after the W&W decision is the most relevant protective (risk) factor for the development of further recurrences and provides an excellent prognosis. These results may have relevant clinical implication and should be taken into account for the design of future follow-up protocols and alternative treatment strategies.

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