

Defining Preoperative Treatment Strategies in T3 Rectal Cancer

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For a long time, surgery alone was considered the cornerstone of curative treatment for rectal cancer. It was sufficient, however, only for stage I disease (5-year overall survival [OS] ~90%). For tumors extending beyond the muscularis propria (stage II) and for those involving the draining nodes (stage III), 5-year OS rates range from 50% to 60% and 30% to 40%, respectively.¹

In the early 1990s, three major advances emerged: randomized clinical trials established postoperative chemoradiotherapy (CRT) or preoperative moderate-dose radiotherapy (RT) as standard treatments for resected stages II-III or for resectable cT3 tumors, respectively; and total mesorectal excision (TME) was adopted as optimal surgical resection.²⁻⁴

These changes raised the following issues: the role of preoperative RT in the field of TME; whether CRT should be administered preoperatively or postoperatively; and the role of adjuvant chemotherapy (CT). The Dutch Colorectal Cancer Group questioned the value of preoperative RT (short course) in patients with resectable disease undergoing TME. The 5-year local recurrence rate decreased significantly from 11.4% with surgery to 5.8% with preoperative RT. Subgroup analysis showed that preoperative RT was ineffective in patients with tumors in the low rectum submitted to abdominoperineal resection (APR) and in those having a circumferential resection margin (CRM) ≤ 1 mm (~20% of the resected patients).^{5,6} Preoperative RT had no effect on OS. The German Rectal Cancer Study Group trial compared preoperative CRT vs. postoperative CRT in cT3-4 or N+ disease. TME was recommended. Five-year local recurrence rates were 6%

and 13% in the preoperative and postoperative groups, respectively. Acute and late side effects were significantly lower in the preoperative group.⁷ The European Organisation for Research and Treatment of Cancer (EORTC) 22921 study questioned the value of preoperative CRT vs. preoperative RT and that of postoperative CT vs. nil in cT3-resectable cT4 disease. Five-year local failure rates decreased significantly from 17% without CT to 8% with CT. Adjuvant CT, compliance with which was < 50%, had no effect on OS, except in the patient subgroup whose tumors were downstaged with preoperative treatment (ypT0-2N0).^{8,9}

From the above, the following conclusions can be drawn: Preoperative RT (short course) or preoperative CRT (long course) are two valuable treatment options for improving local control of T3 rectal cancer, but neither preoperative treatment nor adjuvant CT has a significant effect on OS.

In order to progress, we need to define those patients who may or may not benefit from preoperative RT or preoperative CRT, and to develop new treatment strategies to improve OS.¹⁰

The extent of extramural spread (EMS) has long been identified as a powerful predictive factor for local recurrence, distant metastasis, and OS.¹¹ In patients undergoing surgery alone, those with pT3 stage and EMS < 5 mm (pT3a) had significantly better 5-year cancer-related survival than those with pT3 and EMS > 5 mm (pT3b) (survival, 85% and 54%, respectively). Local recurrence rates of 5.5% in pT3aN0, 15% in pT3bN0, 17% in pT3aN1-2, and 34% in pT3N1-2 have been reported.¹²

Thus, the identification of tumor extension outside the rectal wall and nodal involvement may be helpful in preoperative decision-making. High spatial resolution magnetic resonance imaging (MRI) results are in agreement with histology to identify clear surgical margins in 95% of patients, and the amount of extramural spread in 87%. For lymph node staging, agreement is inferior (50% to 80%), but specific contrast agents (eg, paramagnetic iron oxide particles) appear promising.¹³

When a standard TME will be performed, different treatment strategies must be explored for patients with T3 disease, as follows:

- First group: EMS > 5 mm, CRM > 1 mm, or N2 or any T3 requiring APRs: Up-front CT followed by long-course chemoradiotherapy should be explored.
- Second group: CRM < 1 mm or T4 rectal fascia: same scheme as above. Higher radiotherapy dose to be explored.
- Third group: T3aN0 in the mid rectum: TME alone or preoperative short-course RT.

It is now time to tailor preoperative treatments according to recognized predictive/prognostic factors.

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