In populations in whom there has been a focus on the important components of rectal cancer management, 5-year survival is better in rectal cancer than in colon cancer, which was not the case in the past. Total mesorectal excision (TME) is one of many important components of current management.

Drs. Cellini and Valentini describe the developments in the management of rectal cancers over the past decades, the results of major trials, and the conclusions members of the medical community have reached concerning these developments and results, which have led to both areas of agreement and controversies. Better imaging, improved surgical techniques, and the integration of radiotherapy alone or with chemotherapy have resulted in marked improvements in loco-regional control but not in survival. Still, in populations in whom there has been a focus on the important components of rectal cancer management, 5-year survival is better in rectal cancer than in colon cancer, which was not the case in the past.[1,2] Dissection outside the embryologic plane surrounding the mesorectum—total mesorectal excision (TME)—is one of many important components of current management.

In order to discuss agreement and controversies, we must agree on what is to be discussed. In recent decades, there has been a substantial increase in what is considered locally advanced rectal cancer; this increase has paralleled the improvements in results. Everyone likely agrees that some rectal cancers can be managed by surgery alone, either TME or a local procedure, with low risk of local failure and good survival. In another group, with slightly more advanced disease, TME will result in an R0 resection but there will be too many local recurrences. In this group, radiotherapy decreases the risk of local recurrence by 50% to 70%, and preoperative therapy is more dose-efficient and less toxic than postoperative therapy.[3] The additional therapy increases morbidity, but treatment is warranted if the risk of local failure is sufficiently high, considering the severity of such failures. In this group, in patients in whom no downsizing or down-staging of the primary tumor is needed, the effects and toxicity of the short-course Swedish 5 × 5 Gy schedule are well documented; however, long-course chemoradiotherapy (CRT) is used by many clinicians.[4] The additional chemotherapy improves local control but not survival, as has been shown in two large randomized trials.[5,6] A pooled analysis of five trials, including the two randomized trials, has indicated that survival is improved,[7] but the pooling of trials with different designs may introduce bias. In even more advanced tumors, TME will not result in an R0 resection and extended surgery is required. These tumors were previously often described as nonresectable, even if technically they were not. Even if an R0 resection was achieved, local failures were common. In these patients, preoperative CRT to effect down-staging or to at least kill peripherally located tumor cells left behind after surgery is likely unanimously considered standard therapy. The addition of fluorouracil (5-FU)/leucovorin to 50 Gy significantly improves local control (R0 + no local failure) and disease-free and cancer-specific survival, but not overall survival.[8] In patients who cannot tolerate CRT, a 5 × 5 Gy schedule with delayed surgery is an effective, low-toxicity alternative, based on recent retrospective studies.[9-11] What should these three groups be called, and where is the disagreement? The first rectal cancer group, for which surgery alone is sufficient, is usually denoted by the term “early,” and the second is referred to by most as “locally advanced”—but what about the third group, which requires an entirely different strategy? “Most locally advanced”? In the Second European Rectal Cancer Consensus Conference, EURECA-CC2, for which Professor Valentini served as chairman,[4,12] the terms “early” (or “good”), “intermediate” (or “bad”) and “locally advanced” (or “ugly”) were used. Cellini and Valentini use these terms once; otherwise, they use “locally advanced” to refer to the intermediate group. Most phase II/III trials performed over the past decades have chiefly included patients from the intermediate group. Patients with locally advanced (ugly) disease, which constitutes 10% to 15% of primary rectal cancers, are usually excluded, since they would tend to worsen the results of a study. If we cannot agree on what tumors are included, it is meaningless to discuss agreement and
controversies. I believe there is less disagreement than may seem to be the case concerning treatment of rectal cancers if we agree on what is discussed.

In the early group (30% to 40% of tumors), surgery alone is standard therapy for most patients. Which T1 substages can be treated with local surgery is a question open to discussion. Radiotherapy alone (contact therapy or brachytherapy) is used as an alternative[13] but has not gained wide acceptance. Whether a partial mesorectal excision is sufficient in tumors in the upper rectum is debated. Organ preservation may be a consideration for some patients,[14,15] but the morbidity of surgery alone (for some, abdominoperineal resection [APR], and for others, sphincter-preserving surgery) must be weighed against the morbidity of CRT in about 30% of patients, and against the morbidity of both CRT and major surgery in the rest. Most patients included in organ preservation studies belong to this early group.[14,15]

All tumors in the early and intermediate groups benefit from preoperative radiotherapy, which is associated with a relative reduction in local failure rates of 50% to 70%.[3,16] Depending on the absolute risk of recurrence, the number needed to treat to prevent one local recurrence must be balanced against the morbidity that radiotherapy adds to the surgery for all treated. The absolute risk of recurrence is dependent on many factors: tumor height and location, clinical T-stage, N-stage, tumor differentiation, signs of extramural vascular invasion, and the skill of the surgeon. A major disagreement concerning patients in the intermediate group relates to the radiotherapy schedule: short-course radiotherapy with immediate surgery or long-course CRT with 5-FU. Cellini and Valentini give the pros and cons for both approaches. However, it is incorrect to state that long-course CRT increases sphincter preservation; this was a seemingly well-founded hypothesis espoused by many, but it failed in trials.[17] It does not become truer by being repeated.

In the locally advanced (ugly) group, CRT with a fluoropyrimidine is standard treatment—about which there is basically no disagreement. A 5 × 5 Gy schedule with a delay is an option in patients unfit for CRT. Combinations with other drugs, including targeted drugs, are experimental. Despite apparently favorable results in multiple phase II studies of combinations of drugs (due to the inflation in what is considered locally advanced disease), the phase III trials have failed to show superiority of a combination (such as oxaliplatin and a fluoropyrimidine) over a fluoropyrimidine alone, only more toxicity.[18-20] Organ preservation is not relevant in these tumors.[21]

Large randomized trials have provided a solid evidence base that can be used to determine the appropriate treatment for many patients. However, the trials have not determined conclusively which therapy is the best in all clinical situations—which is why we have to extrapolate. Consensus statements or international surveys have been used to overcome lack of knowledge from trials.[4,22]

There is a high risk, however, that such statements and surveys may arrive at inappropriate recommendations, since reimbursement (as Cellini and Valentini also mentioned) plays an important role in many treatment decisions, sometimes overriding scientific evidence.

The loco-regional problem in rectal cancer has been more or less resolved in most cases, except for the most locally advanced rectal cancers with extensive lateral growth or growth into the sacral nerves or proximal sacral bone. Fortunately, these constitute only 1% to 2% of newly diagnosed rectal cancers (about 10% of ugly tumors). Integrated boosts should be explored in these cases.[23]

In order to improve overall survival, however, other strategies must be explored. The high cell-kill effect of the 5 × 5 Gy schedule, its brevity and low toxicity, and the possibility it affords of rapidly starting effective combination chemotherapy, also make it at present the optimal regimen for improving survival. This is explored in the phase III RAPIDO trial (Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation; [www.clinicaltrials.gov-NCT01558921](http://www.clinicaltrials.gov-NCT01558921)) in patients at high risk of local or systemic failure (basically those with ugly disease [cT4, cT3mrf+] and some with bad tumors [EMVI+, N2]). The control group receives CRT, surgery, and adjuvant combination chemotherapy. Rationally designed trials such as the RAPIDO trial may resolve some of the remaining controversies.

**Financial Disclosure:** The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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