Biology- and Location-Oriented Precision Treatment of Rectal Cancer: Present and Future

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Keywords

Rectal cancer · Multimodal therapy · Chemoradiation

Abstract

Background: The surgical approach in rectal cancer treatment has evolved in the last decades and a standardized surgical technique for tumor resection – total mesorectal excision – has been established. **Summary:** In a multidisciplinary effort with the use of total mesorectal excision in combination with adjuvant and neoadjuvant treatments to complement surgery disease management can achieve excellent long-term local control and improved patient survival. Further improvements in imaging techniques and the ability to identify prognostic factors such as tumor regression, extramural venous invasion, and threatened margins have introduced the concept of decision-making based on preoperative staging information. **Key Message:** Therefore, in the modern era treatment algorithms are based on high-resolution imaging to plan neoadjuvant therapy and precision surgery followed by pathological and molecular analysis to stratify patients for the need of adjuvant chemotherapy. Despite excellent results with guideline structured treatment pathways, there is still a need to improve long-term results especially for individuals with locally advanced or metastatic tumors.

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on a broad variety of clinical and radiologic parameters and those can be supplemented with the detection of cancer-specific gene mutations and other molecular characteristics. Therefore, tailor-made or personalized therapies can result from the precision medicine strategy. The ultimate goal is to apply a treatment plan for the best possible short- and long-term results for each individual patient with the lowest possible risk for over- and undertreatment. In the future it can be expected that the accessibility to tumor genome sequencing technologies increases and genome-driven cancer treatment will support standardized treatment protocols that are applied nowadays [1, 2]. Colorectal cancer in its early stages can be controlled with appropriate long-term survival results. However, the overall prognosis of patients with advanced/metastatic colorectal cancer remains poor and needs to be improved. With regard to cancer treatments, precision medicine approaches are currently being applied with molecular targeted and immune-based therapeutics across a variety of malignancies with convincing results, although in (colo)rectal cancer the development of biomarker-driven therapeutic success has fallen behind compared to those developed for other malignancies. In depth analyses of multiple gene panels and liquid biopsies settled well-designed prospective trials are necessary to move the treatment of metastatic rectal cancer forward.

Introduction

Precision medicine is a strategy designed to treat individual patients with the most suitable therapy at the most appropriate time based on the patient's biologic and molecular features. The process of decision making is based

Rectal Cancer Staging

In addition to a broad variety of clinical parameters, precise pretherapeutic diagnostic imaging including high-resolution pelvic magnetic resonance imaging

Table 1. UICC TNM staging classification of rectal cancer

<i>T – primary tumor</i>	
TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ: invasion of the lamina propria
T1	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the subserosa or nonperitonealised pericolic or perirectal tissues
T4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum
T4a	Tumor perforates visceral peritoneum
T4b	Tumor directly invades other organs or structures
<i>N – regional lymph nodes</i>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s), i.e., satellites, in the subserosa or in nonperitonealised pericolic or perirectal soft tissue without regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
<i>M – distant metastasis</i>	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ (liver, lung, ovary, nonregional lymph node[s]) without peritoneal metastases
M1b	Metastasis in more than one organ
M1c	Metastasis to the peritoneum with or without other organ involvement

Table 2. Stage grouping of rectal cancer

Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II	T3, T4	N0	M0
Stage II A	T3	N0	M0
Stage II B	T4a	N0	M0
Stage II C	T4b	N0	M0
Stage III	Any T	N1, N2	M0
Stage III A	T1, T2	N1	M0
	T1	N2a	M0
Stage III B	T1, T2	N2b	M0
	T2, T3	N2a	M0
	T3, T4a	N1	M0
Stage III C	T3, T4a	N2b	M0
	T4a	N2a	M0
	T4b	N1, N2	M0
Stage IV	Any T	Any N	M1
Stage IV A	Any T	Any N	M1a
Stage IV B	Any T	Any N	M1b
Stage IV C	Any T	Any N	M1c

(MRI) should be applied to accurately define a locoregional clinical tumor stage (Tables 1, 2). By detecting extramural vascular invasion (EMVI), and determining the T substage and the distance to the circumferential resection margin (CRM), MRI can also predict the risks of local recurrence and synchronous/metachronous distant metastases, and it should be carried out to select patients for the respective preoperative management and to define the extent of surgery. Endoscopy and pelvic MRI can also precisely determine the tumor location with respect to the surrounding anatomical structures and therefore allow ideal planning of the surgical strategy. Widely used surgical options following precise staging include transanal local resection and total mesorectal excision (TME) (Fig. 1).

Anatomy and Tumor Location as a Basis for Precision Treatment

TME is a standard surgical technique for treatment of rectal cancer. It is a fine dissection of the mesorectal envelope containing the tumor together with all of the surrounding fatty tissue that contains lymph nodes and blood vessels. Dissection is along the avascular plane be-

Fig. 1. Simplified therapeutic algorithm for rectal cancer. cCR, complete clinical response.

tween the presacral and mesorectal fascia and thus preserves the sacral vessels and hypogastric nerves.

Understanding the rectal and pelvic anatomy is complex, yet it is the basis for successful (surgical) treatment of rectal cancer. The transition from the sigmoid to the rectum is marked by the coalescence of taenia coli, the loss of appendices epiploicae, and fusion of the surgical mesocolon approximately at the level of the sacral promontory, or 15 cm from the anal verge [3, 4]. Somatometric differences make the formulation of the rectal borders by metrics or anatomical landmarks rather difficult. The definition of the distal end of the rectum is equally vague and therefore it is suggested to include the tumor location with respect to the puborectalis sling, the dentate line, and the anal verge as preoperative diagnostic parameters to plan the surgical approach [3]. The rectum exhibits a unique pattern regarding its peritoneal cover in which its upper third is usually covered anteriorly and at its sides, the middle only anteriorly, while the lower part is subperitoneal [5]. The rectum is surrounded by the mesorectum in which vessels, nerves, and locoregional lymph nodes are embedded. The mesorectal fascia covers the rectum almost universally, except from the lower posterior aspect below the rectosacral fascia, where is difficult to divide it from the rectal wall [6]. Most posterior to the mesorectum lies the presacral fascia, which covers the sacral bone and its venous plexus and extends to the pelvic floor to cover the proctococcygeus muscle [7, 8]. Ventrally to the presacral fascia lies the dual-lamella parietal pelvic fascia surrounding the hypogastric and pelvic splanchnic nerves [9]. At the level of the levator ani muscle it fuses with the presacral fascia. The rectosacral fascia (Waldeyer's fascia) is found on the posteroinferior side of the rectum and it is a thickening of the presacral fascia that descends to meet the mesorectal fascia about 3–5 cm from the anorectal junction [9, 10] and represents the anchorage of the rectum with the sacral bone to allow motil-

ity [6, 11]. On the ventral side is the rectoprostatic fascia (Denonvillier fascia) [12]. Inside this fascia, nerve fibers from the hypogastric nerve and small vessels leading to the prostate and male genital organs are located.

Knowledge of the pelvic anatomy and preoperative analysis of the high-resolution pelvic MRI are inevitable for the surgical approach. It is necessary to have a precise understanding of the proximal border of the rectum and the relationship between the tumor location and the anterior peritoneal reflection. Anterior rectal tumors located at or above the anterior peritoneal reflection and invading the peritoneum are at a great risk of intraperitoneal spread [13]. In the MERCURY study it was shown that involvement of the anterior peritoneal reflection or the serosa of the intraperitoneal rectum by the tumor is a risk factor for a poor prognosis [3]. The posterior dissection line should separate the mesorectum from the parietal fascia. On the ventral side dissection is close to the Denonvillier fascia or the rectogenital septum with a threat to small nerve fibers and the vessels that are sheathed in it.

Surgical Strategies in the Treatment of Rectal Cancers

The goal of surgery for rectal cancer is to achieve optimal survival and a low risk of local recurrence while maintaining defecation and urogenital function. This can be achieved by either a radical surgical approach or an organ-sparing approach, depending on many factors including preoperative staging of the tumor.

Radical Surgical Approach

In this approach complete excision of the tumor and the surrounding mesorectum (TME) is conducted with a tumor-free margin. This surgical strategy is the greatest

effect on recurrence and overall survival [14]. TME in which the primary tumor is resected along the embryological fascial planes with all of the associated lymphatics remains the gold standard for curative resection [15]. In a subset of patients with tumor invasion of the anal sphincter complex, an abdominoperineal resection needs to be applied. To achieve low anterior rectal resection with TME, open, laparoscopic, hand-assisted, robotic, and transanal approaches are feasible. As long as TME is performed, low local recurrence rates can be achieved in both open and minimally invasive approaches [16–20]. Oncologic long-term analysis found no statistically significant differences between laparotomy and laparoscopy [21, 22]. Application of robotics-assisted low anterior rectal resection with TME results in oncologic outcomes comparable to those of other approaches [23].

Robotics-assisted surgery has been developed to overcome the limitations of laparoscopic surgery while maintaining the advantages of a minimally invasive approach. A newly established technique – i.e., transanal TME (TaTME) combines minimally invasive abdominal TME with a transanal endoscopic resection [24]. Studies are necessary and ongoing to evaluate this approach in a broad setting.

Organ-Sparing Approach

Local transanal excision might be an option for highly selected patients with small (<3 cm), low (within 8 cm of the anal verge), and well-to-moderately differentiated rectal tumors that are limited to <30% of the lumen and have no evidence of nodal involvement [25]. Due to the missing TME no lymphadenectomy is performed, resulting in a reduced surgical morbidity but an increased risk of positive resection margins, locoregional recurrence, and lower overall survival compared to abdominal resection with TME [26]. Based on this information, the current recommendations for local excision apply to patients with early (T1) rectal lesions. The field of organ-sparing surgical treatment of rectal cancer is continuously evolving. A multicenter study of 62 patients with clinical T1–2N0 rectal cancer who received short-course radiotherapy followed by transanal endoscopic microsurgery was effective in the majority of patients considered high risk or who refused TME surgery [27]. In addition, initial results from trials using conventional neoadjuvant chemoradiotherapy followed by local excision reported good overall oncological and survival outcomes [28]. However, long-term follow-up using neoadjuvant chemoradiotherapy and local excision for clinically staged T2N0 rectal cancers resulted in decreased 3-year disease-free survival [29]. For patients with T2 and T3 staged cancers and a good clinical response to neoadjuvant chemotherapy, the GRECCAR 2 trial failed to show superiority of local excision over TME, with many patients in the local excision group undergoing a completion TME [30]. Therefore, lo-

cal excision can only be suggested for selected patients having a small T2/T3 rectal cancer with an excellent clinical response after chemoradiotherapy.

Complete Clinical Response and Watch-and-Wait Strategy

Neoadjuvant chemoradiation can lead to a complete clinical and pathological response of rectal cancers. Therefore, the question arises of whether any surgery is necessary in this subset of patients or a “watch-and-wait strategy” can be beneficial [31]. This strategy applied to patients with a complete clinical response to neoadjuvant therapy can result in similar oncologic outcomes compared to patients receiving radical surgery [32–35]. It is worth noting that patients with initial an apparent complete clinical response develop local recurrence in nearly 25% of cases [33, 35]. Most of these recurrences are endoluminal and usually amenable to salvage surgery with no apparent oncological compromise from delayed definitive surgical resection [36]. Besides the mostly applied “accidental watch-and-wait strategy,” discussion and evaluation of the “intentional watch-and-wait strategy” are ongoing where patients with early-stage rectal cancer undergo neoadjuvant chemoradiotherapy for the purpose of avoiding radical surgery and entering the organ-preservation pathway [31, 37]. Organ-preserving strategies are feasible and optional for patients with rectal cancer with a complete clinical response after neoadjuvant chemoradiotherapy; however, additional prospective trials, tracking of long-term outcomes, and standardized protocols are all required before such a strategy can be widely implemented [38].

Neoadjuvant Chemoradiation for Locally Advanced Rectal Cancer

Neoadjuvant therapy based on radiotherapy can be applied via 3 different approaches, i.e., long-course chemoradiotherapy, induction chemotherapy followed by long-course chemoradiotherapy, and short-course radiotherapy. An observed trend in the multimodal treatment of rectal cancer is that all chemotherapy is delivered before surgery [39, 40]. In long-course chemoradiotherapy 50–54 Gy in 28–30 fractions are applied concomitantly with fluoropyrimidine chemotherapy followed by rectal resection 6–8 weeks later. In short-course radiotherapy 25 Gy in 5 days are applied followed by surgery about 1 week after completion. Both strategies show similar oncologic results [41]. After short-course radiotherapy a longer interval to surgery can be applied with higher rates of pathological complete response, downstaging, and postoperative complications [42, 43]. However, compared to long-course chemoradiotherapy it results in reduced disease-free survival of the patients.

Neoadjuvant Chemotherapy (Alone) for Locally Advanced Rectal Cancer

The idea to use chemotherapy alone in the neoadjuvant setting is based on excellent local control rates in combination with TME. Significant downstaging can be achieved with chemotherapy alone and at the same time it is more likely to eradicate micrometastatic disease. In phase II studies neoadjuvant chemotherapy alone using FOLFOX resulted in a pathological complete response rate of 6–12%, with substantial differences when comparing several studies [44, 45]. However, regarding the disease-free survival in these studies, the strategy for neoadjuvant treatment did not result in any changes. Especially in patients with a prior history of pelvic radiotherapy, this approach may be applied in a suitable fashion. In patients with low rectal tumors with an increased risk of local recurrence, radiotherapy should not be omitted.

Oxaliplatin-Based Neoadjuvant Chemo(Radio) Therapy

The prognosis of patients with rectal cancer highly depends on distant metastatic relapse [46]. To address this problem, the addition of oxaliplatin to fluoropyrimidine therapy resulted in a survival benefit for patients with stage 3 colon cancer [47]. Numerous studies applying oxaliplatin to the neoadjuvant chemoradiotherapy for rectal cancer have demonstrated similar rates of pathological complete response with high rates of grade 3/4 toxicity compared to fluoropyrimidine-based chemoradiotherapy [48–50]. No survival benefit has yet been observed.

Radiosensitization as a Future Strategy

The combination of systemic agents with radiotherapy aims to increase the therapeutic index. The primary goal is to sensitize the effects of radiation with maximal tumor cell death – resulting in a complete pathological response – while simultaneously reducing harmful destruction of the surrounding tissues. This concept of achieving a high therapeutic index is critical in the design of novel drug-radiation combinations. This can be accomplished by using 3 general principles, i.e., spatial cooperation, synergistic tumor cell killing, and normal tissue protection [51]. Spatial cooperation involves radiation to control local disease and systemic agents to control distant metastatic spread. Synergistic tumor cell killing supports tumoricidal effects of radiotherapy through additive or synergistic inclusion with another agent. Normal tissue protection is important for functionality after therapy and can be achieved by modulating the cellular response to radio-

therapy and reducing radiation injury to normal tissues. Hence, a higher cumulative radiation dose can be delivered. In current clinical practice only the principle of synergistic tumor cell killing is routinely used; however, spatial cooperation is included in study protocols for further evaluation [52–54]. The vast majority of radiosensitizers in clinical practice act as cell cycle modulators, signal transduction inhibitors, and DNA-damaging agents. For neoadjuvant treatment of rectal cancer 5-FU remains the backbone of chemoradiotherapy and should be administered continuously, resulting in S-phase arrest and a reduced DNA repair capacity of tumour cells [55–57].

The development of new agents with radiosensitizing properties is ongoing and includes hypoxia modification in tumor cells as well as the combination of immunotherapy with radiotherapy with local and abscopal effects [58, 59]. Immunotherapy in this setting can potentially be performed by the anti-programmed death receptor 1/programmed death receptor ligand 1 antibody, dual inhibition of PD-(L)1 and cytotoxic T-lymphocyte-associated protein 4, and the oncolytic virus (talimogene laherparepvec) [60–67]. In addition to these therapeutic strategies, agents for “targeted therapy” are being tested in combination with radiotherapy for rectal cancer. These targeted therapies include mitogen-activated protein extracellular signal-regulated kinase inhibition for interfering with the RAS-RAF-MAPK pathway, protein kinase C inhibition for KRAS-mutant rectal cancer, heat shock protein 90 inhibition for downregulation of epithelial-to-mesenchymal transition and invasion, epidermal and vascular endothelial growth factor inhibition to decrease angiogenesis, poly (adenosine diphosphate-ribose) polymerase inhibition to block DNA repair mechanisms, and ropidoxuridine to decrease the nucleotide pool needed for DNA synthesis.

Circulating Tumor DNA as a Future Biomarker

Biomarkers are needed to stratify clinical decision making for personalized medicine for the treatment of locally advanced rectal cancer. Circulating tumor DNA (ctDNA) as a “liquid biopsy” is a blood-based biomarker with potential as a strong predictor for the risk of recurrence or relapse. However, ctDNA can so far not be used as biomarker in decision making during the early treatment phases of rectal cancer. Sequencing of DNA from colorectal cancers has identified several genes that are recurrently somatically mutated. These tumor-specific DNA mutations can be detected in the cell-free component of peripheral blood as ctDNA in the majority of patients with metastatic disease, allowing for noninvasive molecular characterization of tumors and also assessing the early treatment response or micrometastatic residual

disease [68, 69]. To deeply analyze the clear potential of ctDNA as a biomarker during the different treatment phases of rectal cancer, ctDNA needs to be detected at several time points in order to allow longitudinal assessment of treatment responses (both medically and surgically) and its underlying tumor biology/aggressiveness.

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Conflict of Interest Statement

The author declares no conflict of interests.

Funding Sources

There are no funding sources for this work.

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