Non-Operative Management of Total Mesorectal Excision Surgery

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Despite it being the optimal curative approach, elderly and frail rectal cancer patients may not be able to undergo a total mesorectal excision. Recent advancements in non-operative treatment modalities have enhanced the toolbox of alternative treatment strategies in patients unable to undergo surgery. Therefore, a proposed strategy is to aim for the maximal non-operative treatment, in an effort to avoid the onset of debilitating symptoms, improve quality of life, and prolong survival. The complexity of treating elderly and frail patients requires a patient-centred approach to personalise treatment. The main challenge is to optimise the balance between local control of disease, patient preferences, and the burden of treatment. A comprehensive geriatric assessment is a crucial element within the multidisciplinary dialogue.

rectal cancer non operative management elderly patients

1. Introduction

Although total mesorectal excision (TME) surgery is the optimal approach for curation, elderly and frail rectal cancer patients may not always be able to undergo a surgical procedure [1][2][3]. In these patients, decision making is challenging, and no standardised treatment regimen or guideline is available [4][5][6]. Frequently, patients receive no treatment at all and doctors and patients wait out the natural course of the disease [1][7][8]. This often results in tumour progression and the onset of debilitating symptoms that impair quality of life. Palliative treatment may then be offered to alleviate symptoms, if possible [7][9].

However, improvements in chemotherapeutic and radiotherapeutic treatment modalities provide alternative non-operative treatment strategies for patients who are unable to undergo TME surgery [10][11]. These strategies may provide long-term local control of the primary tumour and avoid the early-onset of debilitating symptoms, improve quality of life, and prolong survival. In some patients, curation might even be possible.

Various evidence-based and expert-based recommendations exist on how elderly and frail rectal cancer patients should be treated surgically. However, the optimal treatment approach for patients who are unable to undergo TME surgery is still unknown. The patient complexity, as well as the risk for undertreatment or overtreatment require a patient-centred approach to propose the most optimal treatment strategy, considering the patient's level of frailty, personal preferences, and treatment goals.

2. Non-Operative Treatment Options

The non-operative management of rectal cancer in elderly and frail patients unable to undergo TME surgery should not be considered the same as palliative treatment. In palliative treatment, the natural course of the disease is often awaited and symptoms are treated when they arise, whereas the non-operative management is a more active approach with clear treatment goals to obtain local control of the primary tumour and prevent the onset of symptoms.

The advancements in chemotherapeutic and radiotherapeutic treatment modalities over the recent years have improved tumour responses [10][11][12][13]. Radiotherapy-based treatment strategies may result in adequate local control of the primary tumour. In fact, some patients can even be cured without the need for surgery. This has been supported by data from the International Watch and Wait Database. They reported 5-year overall and cancer-specific survival rates of 85% and 94%, respectively, among 880 patients with a clinical complete response [14]. A recent study by Haak et al. investigated the effectiveness of a watch-and-wait strategy among 43 elderly patients [15]. After a minimal follow-up of 2 years, the complete response was sustained in 88%, while the 3-year overall survival was 97% [15].

The beneficial outcomes have led to increased interest in the non-operative management of rectal cancer patients, which is especially relevant for elderly and frail patients who are not able to undergo TME surgery [5][6]. While curation would be the best possible outcome, the treatment of these patients mostly aims at achieving local control of the primary tumour. Improved tumour responses can be obtained by increased radiotherapeutic doses, which can be delivered endoluminally [5][10][13][16]. The addition of systemic chemotherapy may also improve tumour response, while local excision can be performed to treat small residual disease [17][18][19]. Multiple studies have explored the advantages and disadvantages of non-operative treatment modalities in selected groups of patients. Most of the performed studies reported on complete or near-complete response rates, rather than on local control. Nevertheless, the complete or near-complete response rates associated with a non-operative treatment modality may indicate its effect on the tumour response and the probability to obtain local control.

It has become clear that each modality may benefit each patient differently, supporting the need for a personalised treatment strategy [20]. Despite separate modalities as well as certain combinations having been explored, the optimal allocation in the elderly and frail is unknown. Centralisation of care to a dedicated centre with expertise on all non-operative treatment modalities in the elderly and frail seems warranted.

2.1. Systemic Chemotherapy

Adding systemic chemotherapy before or after (chemo)radiotherapy seems to improve local tumour response and may increase local control. Over recent years, the addition of systemic chemotherapy has been explored increasingly in studies on total neoadjuvant treatment [11][21]. Although some studies only reported small effects, promising response rates have been described in several randomised trials and cohort studies [22][23][24][25][26]. Calvo et al. reported significantly higher rates of tumour downstaging after adding systemic chemotherapy, which was also observed in a phase II study by Markovina et al. [27][28]. Meta-analyses by Petrelli et al. and Kasi et al. reported a pooled complete response rate of 22.4–29.9% in patients with locally advanced rectal cancer in whom

systemic chemotherapy was added to (chemo)radiotherapy [18][29]. In patients with lower stages of rectal cancer, the complete response rates seem even higher. A study by Cercek et al. reported a complete response in 53.5% of patients with stage II disease [23]. However, the benefits of the addition of systemic chemotherapy for achieving local control and survival are unclear, especially in the elderly and frail.

Systemic chemotherapy may induce toxicity, resulting in morbidity and decreased physical reserve capacity, particularly in the elderly and frail. The performed studies showed high compliance rates of 80–100% and similar toxicity rates when compared to chemoradiotherapy, but these studies were mostly conducted in relatively young and fit patients with a median age between 57 and 69 years [18][29]. Many studies investigated oxaliplatin-based chemotherapy, which is, particularly in the elderly, known for its adverse effects [30]. Studies exploring the effectiveness, the toxicity, and compliance of adding systemic chemotherapy in the elderly and frail are lacking. While it may be beneficial in relatively fit patients who refuse surgery, the absence of data and the potential toxicity probably limits its use in the non-operative management of the elderly and frail.

2.2. External Beam Radiotherapy (EBRT)

EBRT is most commonly administered in two different schedules: long-course chemoradiotherapy (45–50.4 Gy in fractions of 1.8–2.0 Gy with concomitant capecitabine) or short-course radiotherapy (SCRT) (25 Gy in fractions of 5 Gy).

Both schedules are associated with beneficial tumour response rates and form a viable basis for combinations in the non-operative management of rectal cancer. When compared to chemoradiotherapy, SCRT seems to result in slightly lower response rates. After chemoradiotherapy, a complete response is reported in 15–27% of patients with cT3–T4 rectal cancer [31][32]. Two population-based studies on data from the NCR showed that SCRT combined with a waiting interval of 4–5 weeks resulted in fewer complete (6.4–9.3% vs. 16.2–17.5%) and good (yT0–1) (11.0–17.5% vs. 20.6–22.6%) responses than chemoradiotherapy [33][34]. The Stockholm III trial reported significantly increased tumour regression rates in patients with a delayed interval (median 6.4 weeks) until surgery after SCRT, with a complete response in 11.4% of patients [35]. Response evaluation at 4–5 weeks after SCRT may be too early to evaluate the tumour response adequately. Furthermore, tumour response rates seem correlated with the initial tumour stage. In a pooled analyses by Maas et al. that included 3105 patients who underwent chemoradiotherapy, complete responses were observed in 58% of cT1, 28% of cT2, and 16% of cT3 tumours [32]. Most studies were performed in locally advanced rectal cancer and the response rates of chemoradiotherapy and SCRT in early stage tumours (cT1–3bN0) are relatively unexplored. The currently ongoing STAR-TREC phase II/III study (NCT02945566) is investigating the effects of chemoradiotherapy and SCRT on early stage rectal cancer and may provide valuable insights on the non-operative management of rectal cancer patients [36].

Earlier studies have shown that elderly patients treated with chemoradiotherapy achieved comparable response rates, disease-free survival, and tolerability in relation to their younger counterparts [6]. Data from the ACCORD12/PRODIGE2 phase 3 trial by François et al. reported that elderly patients treated with chemoradiotherapy had increased rates of grade 3 and 4 toxicity (25.6% vs. 15.8%) when compared to younger

patients [37]. Still, 95.8% of the elderly successfully completed chemoradiotherapy [37]. While literature is controversial, SCRT seems associated with reduced toxicity. The preliminary results of the randomised NACRE study (NCT02551237) showed that all patients above 75 years old completed SCRT, while 14% did not complete chemoradiotherapy [38]. The number of serious adverse events (13 vs. 7 events) was also higher in patients treated with chemoradiotherapy [38]. A randomised trial by Bujko et al. reported less acute toxicity in patients treated with SCRT when compared to chemoradiotherapy (3.2% vs. 18.2%), while late toxicity was comparable (7.1% vs. 10.1%) [39]. Similar results were observed in a later meta-analysis [40].

When tolerated, chemoradiotherapy seems to be the most effective treatment for achieving local control in patients unable to undergo TME surgery [4][6]. SCRT has a shorter treatment duration and seems to result in lower toxicity, which may be preferable in frail or comorbid patients unfit for chemoradiotherapy or for whom treatment compliance might be a potential issue.

Outcomes of other EBRT schedules (e.g., 13 × 3 Gy) on local control rates are scarce and unexplored. In the Lyon R90-01 trial, 29% of patients with cT2–T3 rectal cancer who were treated with 13 × 3 Gy EBRT achieved a complete or near-complete response after a waiting interval of 6–8 weeks [41]. These alternative schedules are currently under investigation, mostly in combination with dose escalating endoluminal radiotherapeutic boosts [42][43].

2.3. Dose Escalation of Radiotherapy

Radiotherapeutic dose-response analyses have showed that tumour responses can be improved by increasing the radiotherapy dose [13]. An earlier analysis by Appelt et al. showed that 72 Gy was needed to achieve a major tumour response in 50% of cT3–T4 rectal tumours [13]. Increased radiotherapy doses can be delivered by endoluminal radiotherapeutic modalities, such as contact X-ray brachytherapy (CXB) or high-dose rate endorectal brachytherapy (HDR-BT). Endoluminal radiotherapy has the ability to deliver high doses of radiotherapy directly to the tumour with a rapid dose fall-off, thus sparing normal surrounding tissue. If technically eligible, definitive dose escalations of radiotherapy are an attractive modality in elderly and frail patients unable to undergo TME surgery to maximise local control. These endoluminal interventions are only available in selected centres and should be surveilled by dedicated multidisciplinary teams.

2.3.1. Contact X-ray Brachytherapy

The use of CXB is mainly described as a beneficial dose-escalating modality in patients unable to undergo surgery. Sun Myint et al. and Gérard et al. have described the use of CXB in rectal cancer patients as monotherapy (in early and small tumours), as an additional boost to EBRT, or as adjuvant treatment after local excision [16][44][45][46].

CXB as an additional boost to EBRT has been explored in multiple studies. In the Lyon R96-02 trial, a significant improvement in clinical complete response rates (24% vs. 2%) and pathological complete and near-complete response rates (57% vs. 34%) were observed in patients treated with an additional CXB boost after EBRT (13 × 3 Gy) when compared to EBRT (13 × 3 Gy) alone [43]. A multicentre phase II study by Gérard et al. showed that

EBRT combined with a CXB boost resulted in complete and near-complete response rates of 95% in cT2–T3 rectal cancer [47]. Another study by the same group described complete and near-complete response rates after CXB and EBRT of 33–88% [48]. In a cohort described by Sun Myint et al., patients unsuitable for or refusing surgery achieved a complete response in 64–72%, of which 86–87% were sustained after a median follow-up of 2.5–2.7 years [44][49]. An additional 21–23% of patients with a clinical incomplete response had pathological complete responses after resection [44][49]. A recent study by Custers et al. reported on local control rates in older and inoperable rectal cancer patients who were treated with CXB after different schedules of radiotherapy (79%) or local excision (21%) [50]. The research showed that local control was achieved in 13 out of 19 (68.4%) patients, while 9 out of 19 (47.4%) patients had a clinical complete response [50]. The 1-year local progression-free survival was 78%, while the overall 1-year survival was 100% [50]. The quality of life was only slightly impaired and successfully returned to baseline after 6 months [50]. These results suggest that, if technically possible, CXB is an effective option in the elderly and frail to improve local control. Most studies were not randomised and did not include locally advanced tumours. The currently ongoing randomised OPERA trial (NCT02505750) and the OPAXX study will likely give more insights in the value of CXB in more advanced rectal tumours [51].

The reported toxicity rates of CXB are relatively low [44][49][52]. In the Lyon R96-02 trial, early and late grade III toxicity involved 9% and 11% of patients, respectively [47]. According to other studies, toxicity mostly included rectal bleeding. Grade I-III rectal bleeding occurred in 24–40% of patients, while grade III bleeding was described in <5% [46][49]. Rectal ulceration was described in 30% of patients, which was most often asymptomatic and usually healed within 3–6 months [46][49]. Functional outcomes after CXB are reported to be relatively good, with 65% of patients having no LARS complaints [47][53].

2.3.2. High-Dose Rate Endorectal Brachytherapy

An alternative endoluminal dose-escalating modality to improve local control is HDR-BT [54]. Vuong et al. showed that a preoperative HDR-BT boost resulted in improved tumour response rates [55]. The research reported pT0N0-1 rates of 32%, while an additional 38% of patients only had small microscopic residual disease [55]. The beneficial effects of HDR-BT on the tumour response has been investigated in multiple other studies. In the phase I HERBERT study, 38 patients (median age of 83 years) were treated with 13 × 3 Gy EBRT followed by HDR-BT (3 fractions of 5–8 Gy) [42]. A clinical tumour response was observed in 29 out of 33 patients (87.9%), of which 20 patients achieved a complete response (60.6%) [42]. The 1-year local progression-free survival was 64% and the 1-year overall survival was 82% [42]. Overall grade 3/4 toxicity were observed in 33% and 4%, while acute and late grade 2/3 proctitis were observed in 81.6% and 88% of patients [42]. The researchers concluded that HDR-BT provided good tumour responses, but had a considerable risk for toxicity in the elderly and frail. In a study by Garant et al., elderly patients (median age of 82 years) with mainly cT2–T3 tumours achieved a clinical complete response in 86.2% after 40 Gy of EBRT (in 16 fractions) followed by HDR-BT (3 fractions of 10 Gy) [56]. The 2-year local control rate was 71.5% [56]. In a randomised study by Jakobsen et al., cT3–T4 rectal cancer patients were treated with chemoradiotherapy followed by HDR-BT (2 fractions of 5 Gy), which resulted in a complete or near-complete response rate of 44% [57]. Toxicity mostly included diarrhea, skin problems and proctitis, but was comparable to those treated with chemoradiotherapy alone [57]. Appelt et al. described that 40 out of 51 (78.4%)

patients with cT1–3ab rectal cancer achieved a complete response after chemoradiotherapy followed by a 5 Gy boost of HDR-BT, with 2-year local control rates of 58% [58]. These patients had relatively good functional outcomes, as 69% of patients did not report faecal incontinence [58]. Based on these results, HDR-BT may be a useful modality to improve tumour response and optimise local control. Currently, the randomised HERBERT-II study (Netherlands Trial Register: NL7795) is investigating the additional effect of HDR-BT (3 × 7 Gy) after EBRT (13 × 3 Gy) in elderly and frail patients unable to undergo surgery.

2.4. Local Excision

Early rectal cancer can be treated with local excision with relatively low risks for morbidity and mortality, and relatively good functional outcomes [4][59]. Over the years, the indication for local excision has been broadened. However, long-term results reported local recurrence rates after a primary local excision of pT2 tumours up to 37% [60]. In the CARTS-study, patients with cT1-3N0 rectal cancer underwent chemoradiotherapy followed by local excision in case of residual ycT0-2N0 disease [17]. The research reported successful organ-preservation in 64% of patients with residual ycT0-2N0 disease, and in 55% of all patients that started with chemoradiotherapy [17]. A meta-analysis that investigated chemoradiotherapy followed by local excision in cT2–T3 rectal cancer showed adequate local control rates, with no recurrences in patients with a pathological complete response, while the recurrence rates were 2%, 7%, and 12% in patients with ypT1, ypT2, and ypT3 disease, respectively [61]. Additionally, several other studies reported comparable local control rates after local excision in patients after chemoradiotherapy [61][62][63]. However, local excision preceded by neoadjuvant treatment seems to result in an increased risk for wound infections, wound dehiscence and severe functional bowel complaints [62][64][65]. In the long-term follow-up of the CARTS-study, major LARS was observed in 50% of patients [64]. Local excision may be reasonable to treat small residual disease after chemoradiotherapy or SCRT in the elderly and frail unable to undergo completion TME surgery [66]. Nevertheless, selecting the patients that benefit most seems challenging. The outcomes in locally advanced rectal cancer are unknown. More insights will probably be gained by the currently ongoing OPAXX study, which randomises patients with more advanced rectal cancer and a near complete response between CXB and the extension of the waiting interval followed by a local excision [51].

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