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CHEMORADIATION THERAPY FOR LOCALIZED COLORECTAL CANCER: A VIEW FROM THE OUTSIDE

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Abstract

Background. Colorectal cancer is among the most lethal and prevalent malignances in the world. The management of localized colorectal cancer is highly debated. Surgical resection of the rectum, such as total mesenteric excision (TME) is usually associated with significant morbidity and mortality. The integration of various chemotherapy options into the standard treatment of localized rectal cancer could potentially enhance the tumor control with a subsequent reduction in the frequency of recurrence, thus improving overall and disease-free survival. Moreover, there are categories of patients for whom surgical treatment is contraindicated and chemotherapy will be more useful for them. Although rectal cancer is predominantly a disease of older patients, current guidelines do not incorporate optimal treatment recommendations for elderly patients with comorbidities; therefore this issue remains a matter of debate. **Aim.** We aimed to consider alternative approaches to the treatment of localized rectal cancer and the management of selected patients with this diagnosis. **Material and Methods.** We searched for publications in the Pubmed, eLibrary databases and up-to-date information on the basis of world cancer associations. **Conclusions.** Comparison of surgery with concurrent chemoradiotherapy for localized rectal cancer showed that in some cases neoadjuvant therapy can be useful and successful, acting as an ideal alternative. However, this approach may be suitable for selected patients who meet certain criteria. In addition, a follow-up care after treatment should include a specific range of diagnostic imaging tests.

Key words: localized rectal cancer, chemoradiotherapy, nonsurgical approach, fragile patients.

ХИМИОЛУЧЕВАЯ ТЕРАПИЯ ЛОКАЛИЗОВАННОГО КОЛОРЕКТАЛЬНОГО РАКА: ВЗГЛЯД СО СТОРОНЫ

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Аннотация

Введение. Колоректальный рак занимает лидирующие позиции по заболеваемости и смертности от злокачественных опухолей. Выбор вектора терапии локализованного колоректального рака вызывает много дискуссий. Хирургическая резекция прямой кишки, такая как ТМЭ, обычно связана с высоким уровнем послеоперационных осложнений и летальностью. Потенциально интеграция различных вариантов химиотерапии в стандартное лечение локализованного рака прямой кишки может усилить контроль над опухолью с последующим снижением частоты рецидивов и, следовательно, повысить общую и безрецидивную выживаемость. Более того, есть категории пациентов, которым противопоказано оперативное лечение, и для них будет полезнее химиотерапевтический подход. Определенный режим лечения для пациентов пожилого возраста, имеющих отягощенный анамнез, с этим видом рака еще не сформирован, несмотря на то, что средний возраст установления диагноза колоректального рака составляет около 70 лет. Оптимальные рекомендации по лечению этой группы пациентов еще не консолидированы, поэтому этот вопрос остается предметом дискуссий. **Цель исследования.** Мы рассмотрели альтернативные подходы к терапии локализованного рака прямой кишки и ведению особых групп пациентов с этим диагнозом. **Материал и методы.** Проведен поиск публикаций в базах данных Pubmed, eLibrary, а также поиск актуальной информации на базе мировых онкологических ассоциаций. **Выводы.** Сравнивая хирургический подход и химиолучевую терапию у пациентов с локализованным раком прямой кишки, отмечено, что в некоторых случаях неоадъювантная терапия может быть полезной, выступая в качестве идеальной альтернативы. Однако такой подход может подойти только для определенных групп пациентов. Кроме того, наблюдение после лечения также должно включать строгий перечень диагностических процедур.

Ключевые слова: локализованный рак прямой кишки, химиолучевая терапия, консервативный подход, пожилые и соматически осложненные пациенты.

Introduction

Colorectal cancer is among the most lethal and prevalent malignances worldwide [1, 2]. According to Americal Cancer Society, (Colorectal Cancer Facts & Figures 2017–2019), only 39 % of patients are diagnosed with localized rectal cancer [1, 2]. The definition of localized rectal cancer and the management of patients with this cancer differ from one medical community to another. American, European and Asian cancer societies have diverse views of this issue. Therapy for localized rectal cancer raises many controversial issues and is highly debated. Current guidelines do not incorporate optimal treatment recommendations for elderly, fragile patients at high surgical risk [3]. Surgical resection of the rectum, such as TME, is usually associated with significant morbidity and mortality [4]. However, it is unknown how useful these recommendations are. That is why clinical trials are aimed at finding the optimal treatment that combines effectiveness and minimal complications for each patient. This review aims to analyze the publications regarding therapy for local rectal cancer, including controversies in surgical and non-surgical treatments, and to search for information on optimal treatment strategies from national and international clinical guidelines and articles.

According to European guidelines, very early (T1sm1) and early (T1sm2–3) local rectal cancers have not grown beyond the inner lining of the rectum (cT1N0, with low grade) or have grown into deeper layers of the rectal wall but have not spread outside the rectum itself (cT1–cT2; cT3a/ b if middle or high, N0 (or also cN1 if high) without involvement of mesorectal fascia (MRF) and extramural venous invasion (EMVI)) [5–8]. American society includes stage 0 – Tis and stage 1 – T1–2N0 into localized colorectal cancer [2, 7, 9, 10]. Meanwhile, Japanese Society for Cancer of the Colon and Rectum (JSCCR) involves Tis and T1 in definition of localized rectal cancer [11]. Currently, most international guidelines emphasize that surgery is the main treatment of localized rectal cancer. Surgical resection is the primary treatment modality of early rectal cancer [1, 11–15].

European Society for medical oncology confirms the following scheme. Very early cT1sm1N0 should be treated using local excisional procedures, as a single modality for early cancers [12, 15]. Guidelines notice that early rectal cancer, like cT1–cT2, cT3a/b if middle or high, N0 (or also cN1 if high), is not suitable for local excision. More advanced tumors up to and including cT2c/T3a/b should be treated by radical TME. The total mesorectal excision aims to achieve meticulously removal, implying that primary tumor and all of the mesorectal fat, including all lymph nodes, should be excised [12, 13, 15–17]. TME is used during low anterior resection, when tumors are located in the middle and lower rectum, where it is necessary to remove the rectum together with the mesorectum to the level of the levators [16]. In this case, TME is indicated as a gold standard for adenocarcinoma of the middle and lower rectum [12, 14, 15, 18, 19].

Regardless of the fact that TME is a surgical standard, the morbidity and different dysfunctions associated with this method force to apply alternative surgical approaches for very early cancer. Local excision is an appropriate alternative to TME [12, 19–21]. Alternative approaches to management of early rectal cancer include local excision (LE) via transanal excision (TAE) or transanal endoscopic microsurgery (TEM) and transanal minimally in-

vasive surgery (TAMIS) [12, 13, 16, 17, 21–23]. A comparative analysis of the guidelines for colorectal cancer in Japan, the USA and Europe indicated that each of the guidelines proposed local treatment for Tis or T1 tumors, such as endoscopic approach or transanal excision for lower rectal cancer [23, 24]. Meanwhile, recommendations have some differences in surgical access and approach: Japan society adheres to endoscopic treatment through endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), meaning that endoscopic en bloc resection is possible [24]. Moreover, tumors with unfavorable histological features should be additionally resected with lymph node dissection. Guidelines emphasizes that correct treatment of T1 stage requires accurate endoscopic evaluation of the invasion depth based on the morphological findings by magnified endoscopy or Kudo's pit pattern classification [24]. After transanal exsicion that is recommended for T1 stage by NCCN and JSCCR, obligatoriness of complementary resection with lymph node dissection is determined by a histopathological assessment of the surgical specimens (excisional biopsy) [11, 24].

Unfortunately, surgical resection of the rectum, such as TME, may be associated with significant morbidity and mortality [4, 15, 25, 26]. The morbidity reaches 30 to 68 % and mortality approaches 7 % [22]. Hence, radical surgery may not lead to expected, increased overall and disease-free survival in these patients [27]. Moreover, TME, as radical surgery, has a high risk of significant complications, involving anastomotic leakage, sepsis, permanent or temporary stoma, perineal wound complications, and urinary, sexual and bowel dysfunction [22, 25, 28, 29].Thus, radical surgery can impair quality of life, regardless of its practical curability. The low anterior resection syndrome (LARS) is one of the postoperative complications. It is a complex of symptoms, such as fecal incontinence, emptying difficulties, urgencies and fragmented bowel movements, which is a recognized entity and is seen in as much as 90 % of patients who undergo an anterior resection [20].

Local excision, which is considered an alternative to radical surgery, also has a significant rate of post-surgical complications [23, 26]. After transanal excision (TAE), patients experience minimal pain, but fever is not uncommon [17, 26, 30]. Postoperative complications include rectal bleeding, rectal stenosis, urinary retention, fecal incontinence, and rectovaginal fistula [17, 26, 30]. Moreover, a major disadvantage for TAE is the poorer surgical outcomes compared to TME [26, 30].

Transanal endoscopic microsurgery (TEM) has following complications among operated patients: hemorrhage (27 %), urinary tract infection (21 %), and suture line dehiscence (14 %) [23, 31–33]. Bleeding and perforation can influence the quality of life, especially in elderly patients, claiming reoperations and extending recovery period in hospital [17, 32, 33]. Oppositely, the incidence of fecal incontinence is generally temporary and is 1 % [31].

However, at the same time, rectal cancer (T3-T4) treated with chemoradiation therapy recommended by most of the guidelines, demonstrates promising outcomes. It should be noted that the therapeutic strategies for local rectal cancer have been changing, particularly from surgery alone to multimodal approaches [3].

Nowadays more trials aim to explore non-surgical kinds of treatment. Scientists try to find alternative methods for treating localized rectal cancer. In accordance with many studies, multidisciplinary approach, including radiotherapy and chemotherapy, is an alternative to classical surgery. Each of them has controversial outcomes, requiring detailed comparison.

One of the recent clinical trials [34] was aimed at evaluating the effectiveness of external beam radiation therapy in treating early-stage distal rectal cancer and clinical factors that predicted clinical outcome. The study included 231 patients with stage cT1–2N0M0 rectal adenocarcinoma (tumors located <7 cm from the anal verge), who refused or were ineligible for surgery. All patients received radiotherapy, and 120 of them got additional concurrent chemotherapy. Treatment outcomes were as follows: of 231patients, 135 (58.4 %) achieved cCR, 84 achieved partial response (PR) and 12 showed no response. Clinical T stage, concurrent chemotherapy and radiation dose were found to be independent predictors of complete clinical response (cCR). The 3- and 5-year overall survival (OS) rates were 93.90 % and 86.19 %, respectively. Thirty-five patients had tumor progression: local progression occurred in 10 patients, distant failure in 19 patients and both local and distant failure in 6 patients. Thirty-one patients developed distant failure: 12 patients developed only liver metastases and 10 patients had only lung metastases. Three patients developed both liver and lung metastasis. Bone metastases were observed in 4 patients and paraaortic lymph node metastases in 2 patients. When comparing treatment outcomes in patients with T1 and T2 rectal cancers, it was found that in patients with T1N0, the rates of complete response (CR), PR and SD (stable disease) were 76.1 %, 23.9 % and 0 %, respectively. However, in patients with T2N0, only 51.2 % of them achieved CR, with PR in 41.5 % and SD in 7.3 %. The most common acute toxicity types were diarrhea, neutropenia and radiodermatitis. In conclusion, researchers resumed that definitive radiotherapy or chemoradiotherapy is feasible for early-stage distal rectal cancer [34].

Australian investigation included 48 patients with various stages of rectal cancer, who received definitive long course radiotherapy with or without 5-fluorouracil, but did not undergo surgery [35]. Out of these patients, 32 were with T3 disease, 13 had T2 and three had T1. All patients were divided into 2 groups: 24 patients, who were medically inoperable, and another 24 patients, who refused recommended surgery. The majority of patients had several factors that

increased surgical risk. The treatment plan involved long-course radiotherapy (RT) with 5-fluorouracil chemotherapy in 36 patients and long-course RT alone in 12 patients. Twenty-seven patients demonstrated a complete clinical response, whereas 14 patients had a partial response. It should be noted that most of the patients with complete response (16 patients) had T1/2 stages. Moreover, the progression-free survival (PFS) rate was much higher in these patients of the T1/2 group, with a median PFS of 64 months. Patients, who refused surgery, had an increased median overall survival compared with those who underwent surgery (64 months). Thus, the investigation revealed that in spite of uncertainty of initial staging, concurrent chemoradiation or radiotherapy alone is a suitable and safe alternative to operating approaches, being able to show high treatment completion rates. Scientists suggest that in most patients at high risk of operative mortality, local control can be achieved with chemoradiotherapy. After 30 months, 50 % of patients who demonstrated disease progression did not show it during treatment. The study did not show clear plateau to the progression – free survival curves for the patients with a complete response to treatment, with patients continuing to relapse at three years and beyond. It means that other patients have a risk of progression with continued follow-up [35].

Thus, the results obtained in relation to 3- and 5-year survival rates for these patients, treated only by therapy strategies, look encouraging. How do these results compare with those after conventional surgical treatment, recommended by the national guidelines for this group of patients? Recent data reveals that 5-year survival in this group of patients is 90 % [1]. Certainly, those results seem highly hopeful, but there are categories of patients for whom surgical treatment is contraindicated and a chemotherapy approach will be more useful for them.

The average age at the time of diagnosis of colorectal cancer is 70 years [2, 36, 37]. Additionally, half of these patients also suffer from cardiovascular disease [38–42]. Approximately 70 % of cases are diagnosed in patients aged over 65 years and 40 % in patients aged over 75 years [2, 36, 37]. These facts make one think about an appropriate approach in the treatment of elderly and fragile patients that should be treated less aggressively [41, 43]. However, most guidelines have not yet consolidated optimal treatment recommendations for older adults, resulting lack of a specific standard of care for this group of patients [44, 45]. Increasing age, comorbidity and reduced functional reserves are associated with negative consequences, such as higher early postoperative mortality, which is so common in older patients [5, 36, 38, 40]. The predictive factors associated with mortality include: age 80+ years, chronic obstructive pulmonary disease and palliative surgery. Such patients would have a 23.5 % risk of death within 30 days of the intervention [46]. Thus, formal geriatric assessment or at least screening tools for frailty are so considerable before any treating strategy, especially for patients over 70 years [5, 40, 41, 46].

However, when assessing the patient's condition, treatment approaches may still differ [40, 41, 46, 47]. European Society for Medical Oncology (ESMO) supports that the local excision can be a variant in patients with cT1 tumor or in elderly or fragile patients. They conclude that TEM is the procedure of choice [5, 44].

The study by H.H. Peng et al. observed 231 patients, who had refused surgery or were medically inoperable due to various reasons [34]. In another study, 50 % of patients were medically inoperable, and 50 % had refused recommended surgery [35]. The most frequent medical reasons that increased surgical risk were advanced patient age and diverse somatic comorbidity, such as cardiovascular, respiratory, coagulopathies, neurologic or cognitive impairment. Every patient has one or a complex of these factors [35, 47]. So, individual reasons in patients who refused surgery were the following: the desire to avoid a permanent stoma or the fear of operative morbidity or mortality [35]. Notably, most of them were elderly patients. Another study highlighted the most common diseases in fragile patients: diabetes (16.3 %) and chronic obstructive pulmonary disease (12.5 %), accounting for 16.3 % and 12.5 %, respectively [37]. Researches also noted a lower proportion of the elderly population with diabetes mellitus treated surgically in 2005–2007 than in 2011–2012 (6.0 % versus 15.9 %) [37]. I. Montroni et al. reported that elderly patients were less likely to undergo surgery due to a high rate of comorbidity [39]. Moreover, the authors indicated that frailty played a more significant role than age. Thus, if the patient is elderly, but has no comorbidity, surgery may be considered [39]. F.M. Smith et al. discussed about the most common criteria to identify patients eligible and ineligible for surgical treatment. The study compared three patient groups: 60-year-old men with mild comorbidities, 80-year-old men with mild comorbidities, and 80-year-old men with significant comorbidities. This comparison assigned watch-and-wait approach versus surgery after neoadjuvant treatment. Results obtained found that the 1-year survival rate in 80-year-old patients was significantly higher in the watch-and-wait group than in surgery group [48]. Estimation of the effectiveness of CRT by positron emission tomography (PET) with computed tomography (CT) imaging may provide complementary information about tumor response, metabolic activity in the tumors and choose patients, who can avoid radical resection [49, 50].

Conclusion

Comparing surgical approach and chemoradiotherapy for patients with localized rectal cancer, it was decided that neoadjuvant therapy could be useful and successful in some cases, acting as an alternative.

However, this approach may be suitable for certain patients who should have necessary conditions:

1) Rectal cancer should be located in the distal rectum (<7 cm from the anal verge) [34]. According to another similar study, tumor location also should be in the lower rectum (<8 cm from anal verge) and the mid rectum (8–12 cm from anal verge) [35]. Sigmoidoscopy or colonoscopy measures this distance from the tumor to the anal verge [8, 34, 51]. Tumor should have a clinical stage of cT1–2N0M0 [35]. Endorectal ultrasound can accurately determine the T stage [34].

2) Patients should undergo definitive radiotherapy or chemoradiotherapy [34, 35].

3) Patients must not have distant metastases during the treatment, as assessed by chest radiography, abdominal ultrasound and CT. In addition, patients should also be referred for pelvic CT or magnetic resonance imaging (MRI) to detect possible lymph node metastasis in the pelvis [34, 35]. The use of PET/CT is an additional tool for identifying patients, who can avoid radical surgery [50, 51].

4) No concurrent malignancy or prior history of radiotherapy to the pelvis [34, 35].

5) Refusal of surgery or medically unfit for surgery [34, 35]

Clinical observations after treatment should include:

1) The first evaluation 3 months after the completion of radiotherapy. The observation should be carried out every 2 months (digital rectal and endoscopic exams) for the first 2 years and every 6 months (cross-sectional imaging) thereafter. Evaluations includes complete blood count, biochemical routine, carcinoembryonic antigen (CEA) and physical examination (digital rectal and endoscopic exams) during each visit. Chest radiography, CT or MRI scanning of the abdomen and pelvis and colonoscopy should be conducted every 6 months. The short-term response evaluates at 3 months after the completion of definitive radiotherapy. cCR should define as no gross tumor on digital rectal examination, endoscopy or pelvic MRI [27, 34, 51, 52].

2) Most of studies note that a biopsy is not routinely performed after radiotherapy [35, 51]. Predictive factors have influence on tumor response and following quality of patient's life. According to H.H. Peng et. al. radiation dose, CEA and concurrent chemotherapy significantly impact on recurrence-free survival (RFS) [34].

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