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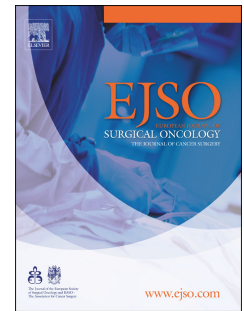
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Neoadjuvant chemoradiotherapy with capecitabine followed by laparoscopic resection in locally advanced tumors of middle and low rectum – toxicity and complications of the treatment.

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Abstract**Aims:**

The aim of this prospective study is to elucidate feasibility of protocol of neoadjuvant concomitant radio chemotherapy with capecitabine and long course radiotherapy with subsequent laparoscopic rectal resection. We assessed treatment toxicity, downstaging rate, pathological response to the neoadjuvant treatment, surgery complications, rate of conversions and sphincter-preserving surgical procedures, and intraoperative and early postoperative complications too.

Methods:

We acquired data of 78 patients from 1 January 2005 to 31 December 2007 with a locally advanced rectal cancer in our study. All patients were indicated for the neoadjuvant concomitant chemoradiotherapy due to locally advanced tumor (T3 or T4) or lymph nodes involvement suspicion (N+). Both radiotherapy (to pelvic region) and chemotherapy (capecitabine) were administered. Rectal tumors were localized within 12cm from the anocutaneous verge. The average follow-up time was 23.9 months.

Results:

All patients completed their treatment according to the planned regimen and dose. The surgery was performed laparoscopically within 4-8 weeks following the concomitant chemoradiotherapy – in 17% cases was converted into conventional surgery. Downstaging was achieved in 69% of patients, pathological complete response in 10 %, histologically negative lymph nodes were documented in 58% of patients. Grade 3 toxicity of the concomitant chemoradiotherapy was present in 3%; grade 2 in 29% of patients, particularly skin and gastrointestinal form. Intraoperative and early postoperative complications of the surgery were 18%. Reoperation was needed in 5% cases.

Conclusions:

We demonstrated safety and low toxicity of the concomitant chemoradiotherapy with capecitabine.

Key words

Rectal cancer – Laparoscopy – Neoadjuvant concomitant chemoradiotherapy – Capecitabine
– Treatment toxicity

Introduction

Curative radical surgery is essential treatment of the localized rectal tumors. In the locally advanced tumors (T3, T4 or N+) the surgery is combined with preoperative radiotherapy (RT), which leads to better local control of the disease and to improved survival compared with surgery alone (1,2). Randomized trials have demonstrated, that the outcomes of concomitant chemoradiotherapy (CHT/RT) are superior to the radiotherapy alone (3). The EORTC phase III trial compared radiotherapy alone with radiotherapy combined with chemotherapy (CHT) consisting of administration of 5-fluorouracil and leucovorine (FUFA) as a bolus in weeks 1 and 5. In the CHT arm was the rate of pathological complete response significantly higher; it is very important for the prognosis of the patient (4).

The primary endpoint of the neoadjuvant concomitant chemoradiotherapy is overall survival improvement but an important secondary aim is to reduce the size of the tumor (downstaging) but to improve the local disease control too. Highly discussed benefit of this treatment is the increasing of sphincter-preserving surgeries in more distally located tumors too. In some trials this benefit was statistically significant; in other trials it was not confirmed. Major German trial (CAO/ARO/AIO-94) compared the use of concomitant CHT/RT before the surgery and after the surgery (5). Sphincter-preserving surgery following preoperative administration was successfully performed in 39% vs. 19% in after CHT/RT surgery group, late stenosis of the anastomosis occurred in 3% vs. 9%, local recurrence occurred in 7% vs. 11%. Grade 3 and 4 acute toxicity was lower in neoadjuvant concomitant CHT/RT group (27% vs. 40%), late toxicity too (14% vs. 24%). However, distant dissemination was comparable in both arms (34% vs. 36%) as well as overall survival (76% vs. 74%).

Continual administration of 5-fluorouracil is more favorable over the bolus administration as for the toxicity, but the handicap is a need of hospitalization and central venous catheter insertion, both with negative influence on the quality of life of the oncological patients (6).

Capecitabine (Xeloda; Hoffmann–LaRoche, Inc., Nutley, NJ) imitates the continual administration of 5–FU. According to phase I study the recommended capecitabine dose 825 mg/m² administering twice daily was determined for concomitant administration with radiotherapy (7). Phase II studies have confirmed good tolerance and efficacy in patients with locally advanced rectal cancer (8). Convenient safety profile of capecitabine has been recently demonstrated in randomized phase III trials in comparison with bolus FUFA; the preference of oral form of chemotherapy by patients too (9)

Diarrhea, local skin reactions and hand-foot syndrome are the most common side effects of concomitant chemoradiotherapy with capecitabine.

Continual administration of 5-fluoruracil or oral administration of capecitabine during all the time of radiotherapy are standard concomitant neoadjuvant CHT/RT treatment in local advanced rectal cancer now.

Laparoscopic surgery is alternative to the open surgical procedure which comply all criteria for oncological radicality (10, 11).

Material and methods

All patients were completely examined and underwent all staging procedures, including CT, transrectal sonography and MRI. Blood analysis, including tumor marker analysis was performed as a standard part of the examination. Tumors were histologically verified before the treatment in all cases. We discussed the indication for neoadjuvant chemoradiotherapy case to case in everyone patient at the multidisciplinary hospital committee, consisting of surgeons, gastroenterologists, imaging specialists, radiotherapists and clinical oncologists.

The neoadjuvant chemoradiotherapy was indicated to patients in good general status (ECOG – Eastern Cooperative Oncology Group – performance status ≤ 2) with histologically verified adenocarcinoma. According to the initial transrectal ultrasound examination and pelvic CT scan respectively, tumors were classified as T3 or T4 or N+ (TNM classification) (12).

Patients who had lower or middle rectal tumors within 12cm from anocutaneous verge, were prospectively enrolled into our study.

Radiotherapy (RT) was performed by a linear accelerator to the pelvic region in the dose of 45.0–50.4 Gy in 25–28 fractions given within 5–5.5 weeks. 3- or 4-field method with multileaf collimator was used (three-dimensional – 3D conform RT). Simultaneously with the radiotherapy, capecitabine in the dose of 825 mg/m² twice daily was given all time long (5 weeks). All patients completed the scheduled treatment. Toxicity of the neoadjuvant chemoradiotherapy was assessed according to the EORTC/RTOG criteria.

Within 4 to 8 weeks from the completion of the neoadjuvant chemoradiotherapy the patients underwent the surgery. The surgery was carried out in a single hospital by a single team. Follow-up CT and TRUS were performed close before the surgery. The procedure was initiated in laparoscopic way in all cases. Both total mesorectal excision (TME) and abdominoperineal amputation (APR) were carried out by “nerves sparing surgery” method. We performed colonic lienal flexure deliberation in most patients with low anterior resection (LAR). All events leading to surgical tactic modification and iatrogenic lesion treatment outside the planned resection extent were assessed as intraoperative complications. All surgical and non-surgical complications reported until day 30 after surgery we considered as early postoperative complications.

Statistics

We used the Fischer exact test to test the difference between groups according to gender. The Mann–Whitney U test was used to compare the age, surgery duration, postoperative hospital stay, distance between the tumor and anocutaneous verge and number of lymph nodes assessed. The analysis was performed by software SPSS (SPSS Inc, Chicago IL) and SAS

(SAS Institute, Cary NC). Significance level below 0.05 was considered statistically significant.

Results

Patients

From January 2005 to December 2007 we treated 78 patients, 62 men and 16 women. Average follow-up was 23.9 months, median 24 (7–39). Average age was 62 years, median 62.8 years (27 – 84). Most of patients had tumor assessed as T3 (72 %). All tumors were located within 12cm from the anocutaneous verge; median distance was 6cm. Stratification of patients according to the TMN classification is in Table 1.

Toxicity of the neoadjuvant therapy

The toxicity of the neoadjuvant chemoradiotherapy was assessed according to the EORTC/ROG criteria. No patient had grade 4 toxicity, grade 3 toxicity occurred in 2 patients only – both were hematological (neutropenia). Grade 2 toxicity had 23 patients – 10 had gastrointestinal, 9 had dermatologic and 2 genitourinary symptoms. Hand foot syndrome did not occur in any patient.

Type of surgical procedure

Sphincter-preserving surgery was possible to carry out in 47 % of cases only, but patients with abdominoperineal amputation (APR) had significantly more caudally located tumor (5cm vs. 7cm, $p=0,01$). Patients with abdominoperineal amputation were significantly older too ($p=0,01$). Groups were comparable according to hospital stay, time of surgery and number of assessed lymph nodes (Table 2).

We had to carry out conversion of laparoscopy into open surgery in 13 cases. It was caused by tumor size in 9 of them.

Surgical complications

Intraoperative complications we had in 4 patients. The urethral lesion required conversion of laparoscopic resection to an open surgery. All other intraoperative complications (small rectal lesion, small urinary bladder lesion and stapler failure) were solved by laparoscopic approach and no further complications were recorded in time of the postoperative period.

Average hospital stay was 10 days. No patients died due to treatment complications. Surgical postoperative complications (until day 30) occurred in 7 cases. Anastomotic leak we had in 4 cases from 37 patients after low anterior resection of rectum, but in 2 patients re-operation was needed only. 4 patients had to undergo re-operation during the early postoperative period. Non surgical complications we had in 3 cases – 1 pneumonia, 1 urinary retention and 1 paresis of brachial nerve.

Response to the treatment

Downstaging was achieved in 54 patients (Table 1). 58% patients with advanced rectal carcinoma had pathologically negative lymph nodes after neoadjuvant CHT/RT. From all patients in the group almost 25% were initially as T4 stage according to the transrectal sonography (TRUS) and CT, only in 2 patients the subsequent pathological classification was ypT4. Pathological complete response was reported in 8 patients. All patients underwent radical surgery.

Discussion

Neoadjuvant concomitant chemoradiotherapy

Neoadjuvant concomitant chemoradiotherapy is standard part of the treatment of patients with the locally advanced rectal cancer in effort to downstaging achievement, improved tumor operability, improved local disease control and the most important - overall survival. Downstaging was achieved in our work in 69% patients. Pathological complete response we

achieved in 10%. These data are comparable to other cohorts in the literature. Outcomes of the phase II trials of concomitant chemoradiotherapy with capecitabine are in Table 3 (13–21).

Slovenian study reported pathological complete response in 9 % in cohort of 57 patients; downstaging they achieved in 49% (16). Toxicity and efficacy was assessed in the Greek study in group of 30 patients (17). In their work downstaging was in 75% patients, pathological complete response was high – in 23% of them. In comparison to our cohort, 17% patients with T4 tumor were enrolled into this trial, while almost 25% patients in T4 stage were enrolled into our cohort, but only in 2 cases the disease was subsequently classified as ypT4. Grade 3 toxicity was seen in 10% of patients (leucopenia), in our cohort it is 3% only. Intraoperative and early postoperative complications were similar – 20%.

Side effects

Capecitabine is radiosensitizer with different toxicity profile than continual or bolus administration of 5-fluorouracil. Administration of capecitabine can lead into side effects – hematologic (leucopenia, thrombocytopenia, anemia) or non-hematologic (fatigue, stomatitis, nausea, vomiting, diarrhea, dermatitis, hand-foot syndrome). The most common complication of simultaneous administration of capecitabine and radiotherapy is acute gastrointestinal toxicity. It is 12 - 34% in grade 2 and 3 toxicity (18). It is similar to our results.

Low presence of hand-foot syndrom is, in our opinion, caused by relatively short time of administration of capecitabine. Most studies, where this syndrome is recorded, are carried out in patients with metastatic disease when the time of administration is longer.

Hematological toxicity of grade 3 and 4 is low too, in comparison to bolus or continual administration of fluorouracil (9).

Low presence of grade 3 adverse effects, similar to our results, was reported in a paper of Dutch authors, the same percentage - 3% only in 60 cured patients (21). Pathological complete response was reported in 13%. Another Slovenian study reported pathological complete response in 9% in 57 patients; downstaging they achieved in 49% (16).

Neoadjuvant concomitant chemoradiotherapy was well tolerated in our patients and there was no reason to interrupt the treatment. Pathological response is a proven factor influencing overall survival; therefore there are efforts to achieve the highest response rate possible without an unacceptable toxicity increase (22).

Pathological N stage

The pathological N stage is very important prognostic factor for overall survival too. In our paper almost 60% of patients had negative lymph nodes, in the Craven's study the figure was similar (19). Lymph nodes were originally assessed positive in 49 patients (63 %). But we have to realize, that an exact method for determining preoperative positivity of lymph nodes does not exist.

Radical lymphonodectomy belongs to criteria of oncological radicality too. Quantity of lymph nodes removed is determined by several factors. The first factor is the patient alone, according to his anatomic circumstances what determines the quantity of lymph nodes in the resected region. The second factor is the surgeon alone, who can by the surgical method, technique, experience and the extent of resection significantly influence the quantity of lymph nodes. The third factor is the pathologist by his way of specimen processing and by the precision of the assessment determines pN component of the TMN classification of the colorectal cancer. The number of examined lymph nodes is usually lower following the neoadjuvant therapy (23), in our cohort it was 14-18 lymph nodes in average. This finding we can confirm in our

cohort of patients operated without the neoadjuvant therapy by the same team of surgeons, where the average number of examined lymph nodes was 24.9 (24).

Anastomotic leak

One of the most severe surgical complications is the anastomotic leak following the lower rectal resection with total mesorectal excision, which is reported from 1% to 24%. The anastomotic leak was seen in 11% of cases in our cohort of patients operated by the sphincter-preserving approach following the pre-surgical chemoradiotherapy. It was necessary to treat the symptomatic dehiscence of the anastomosis by re-operation in 5% only. Sauer et al. from the German Rectal Cancer Study Group report in their multicentre randomized study postoperative complication in 36% patients following the preoperative chemoradiotherapy compared to 34% of postoperative complications in a cohort of patients operated primarily with the intention of postoperative chemoradiotherapy ($p = 0.68$). They report the leak of anastomosis in 12% of patients following the preoperative chemoradiotherapy compared to 11% patients treated by primary surgery ($p = 0.77$). In the group of preoperative chemoradiotherapy the mortality was 0.7% vs. 1.3 % in the other group ($p = 0.41$) (25). The mortality was 0% in our cohort.

In the randomized multicentre trial published by Swedish authors RECTODES (REctal Cancer Trial On DEfunctioning Stoma) the outcomes of patients with rectal cancer within ≤ 15 cm from the anal verge with or without primarily established protective ileostomy were reviewed. The presence of the symptomatic leak was reported in 19 % of cases, in patients with protective ileostomy in 10%, without the primarily established ileostomy in 28%. Urgent re-operation was necessary in 9% of patients with stoma and in 25% of patients operated without protective ileostomy (26).

The trials with preoperative concomitant chemoradiotherapy with 5-fluorouracil (5-FU) led into local disease control improvement, to the tumor downstaging, but with no difference in disease dissemination and overall survival. This is the argument for searching of new cytostatic agents or their new combinations. Capecitabine is one of them. The low toxicity and achieved pathological responses raises the question, whether the combination with other cytostatic agents could improve the rate of pathological complete response and thus also overall survival in the group of patients with locally advanced disease. Several phase I and II trials have been published, especially the combinations of capecitabine with irinotecane and oxaliplatin. The pathological complete response is usually more than 20% (27–30), but the toxicity of the treatment is higher.

Conclusion

The aim of the preoperative chemoradiotherapy is, but overall survival, to achieve downstaging of the tumor and to improve operability with eventually increased rate of the sphincter-preserving operations. However, this therapy should not be burdened by increased number of severe complications. We have demonstrated very good tolerability and efficacy of the concomitant chemoradiotherapy with capecitabine in our work, which can replace the continual administration of 5-fluorouracil in this indication. We have also demonstrated suitability and low rate of complication of the subsequent laparoscopic operation. The pathological complete response is by this approach according to the literature 9–20%, results probably could be improved by adding another cytostatic agent.

We did not register any direct relation between toxicity of capecitabine and laparoscopic surgery.

Proclamation:

All authors proclaim no financial and personal relationships with other people or organizations that could inappropriately influence their work.

ACCEPTED MANUSCRIPT

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Table 1

Stratification according to the TNM and ypTN classification

Clinical staging	Number	Rate	Pathological classification ypTN	Number	Rate
			ypT0	8	10 %
T1	0	0 %	ypT1	3	4 %
T2	3	4 %	ypT2	25	32 %
T3	56	72 %	ypT3	40	51 %
T4	19	24 %	ypT4	2	3 %
N0	24	31 %	pN0	45	58 %
N+	49	63 %	pN1,2	19+11	24+14 %
NX	5	6 %	pNX	3	4 %

Table 2

Comparison of the patient cohort according to the surgical procedure

	LAR	APR	P value
Number of patients	37	41	
Men	27	35	0.29
Women	10	6	
Age – median + SD range average	59±7 39 – 74 59	65±9 27 – 84 64	0.01
Distance T-ACV– median + SD range average	70±23 30 – 120 71	50±28 20 – 120 54	0.01
Hospital stay – median + SD range average	8±8 5 – 51 11	9±5 5 – 28 10	0.21
Duration of surgery – median + SD range average	240±56 110 – 360 240	230±59 70 – 380 232	0,42
Number LU – median + SD range average	12±9 0 – 38 14	16±12 3 – 45 19	0,06

Distance T-ACV = Distance between the lowest tumor edge and anocutaneous verge

Table 3

Results of trials with concomitant chemoradiotherapy with capecitabine

Chemotherapy	Radiotherapy (Gy)	Patients (Number) TN stages	Pathological CR	Reference
Capecitabine 875 mg/m ² BID	45 Gy, (1.8 Gy/fr.)	51 pts T3, T4, or N+	24 % + 12 % nCR	13
Capecitabine 875 mg/m ² BID	50.4 Gy (1.8 Gy/fr.)	18 T3, T4, or N+	12 % + 12 % nCR	14
Capecitabine 825 mg/m ² BID	52.5 (30 fr.)	51 T3 or T3N1	18 %	15
Capecitabine 825 mg/m ² BID	45 Gy in 25 fr. In 5 weeks	57 pts Resectable stage II/III	9 %	16
Capecitabine 825 mg/m ² BID	50,4 Gy in 28 fr. in 5,5 weeks	30 pts T3, T4, or N+	23 %	17
Capecitabine 1650 mg/m ² daily	46 Gy in 23 fr. (pelvis) + 4 Gy (2 fr.) boost on tumor	95 pts T3, T4, or N +	12 %	18
Capecitabine 900 mg/m ² in 5 days of RT	45 Gy in 25 fr. In 5 weeks	70 pts	9 % pN0 66%	19
Capecitabine 825 mg/m ² BID	45 Gy in 25 fr. in 5 weeks (pelvis) + 5,4 Gy (3 fr.) boost on tumor	55 pts T3, T4, or N+	17 %	20
Capecitabine 825 mg/m ² BID in days of RT	50 Gy in 25 fr. In 5 weeks	60 pts T3, T4, or N+	13 %	21
Capecitabine 825 mg/m² BID	45.0–50.4 Gy in 25–28 fr. in 5-5,5 weeks	78 pts T3, T4, or N+	10 % pN0 58 %	our study

BID – twice daily