NEOADJUVANT CHEMORADIOTHERAPY FOR PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER. A RETROSPECTIVE STUDY ON PATIENTS TREATED AT THE CLINICAL COUNTY HOSPITAL OF SIBIU, BETWEEN 2011-2015

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Abstract: *48 patients with local advanced or low-lying rectal cancer were treated with radiotherapy and concurrent chemotherapy in our institution, from January 2011 to December 2015. 77% were cT3 and the rest of them, 23 %, were cT4. The localisation of the tumour related to the anal verge was below 5 cm in 33 % of the cases, while 67 % of the patients had middle and upper rectal tumours. Histopathologically, 87% were moderately differentiated adenocarcinoma. Methods: all patients underwent pelvic radiotherapy with 45 Gy/1,8 Gy/fraction x 5 days/week, 25 fractions. Chemotherapy was given concomitantly and consisted of oral Capecitabine 1600 mg/mp bid Monday-Friday, during radiotherapy. Seven patients could not finish the concurrent treatment due to sever toxicities or non-compliance. 41 patients subsequent surgery 6 to 8 weeks after concurrent chemoradiotherapy. Results: the most common acute toxicity was grade 1 to 2 diarrhea and tenesmus during radiation. Only 5 of the 48 patients experienced symptomatic grade 3 acute toxicity. The sphincter was preserved in only 4 out of the 16 patients in whom the tumour was located within 5 cm above the anal verge, because the patients could not afford radical standard surgery (total mesorectal excision - TME) at an Oncological Surgery Department. The 2-year overall survival rate was 81% and the disease-free survival was 73 %. Our findings indicate that preoperative concurrent chemoradiotherapy allows low-lying rectal tumours to be resected while preserving sphincter function at Oncological Surgery Department and also results in good local control and acceptable toxicity. Conclusion: concurrent chemoradiotherapy is the standard strategy for locally advanced rectal cancer. Neoadjuvant chemoradiotherapy reduces the pelvic recurrence and improves the quality of the surgery. The management of rectal cancer must be a multi-modal approach performed by an experienced multi-disciplinary expert team.*

INTRODUCTION

The neoadjuvant concurrent chemoradiotherapy has improved cancer care dramatically. Three clinical rationales support the use of chemoradiotherapy: concomitant chemoradiotherapy can be used with organ-preserving intent, resulting in improved cosmesis and function, chemotherapy can act as a radiosensitizer, improving the probability of local control and, in some cases, survival, by aiding the destruction of radioresistant clones and chemotherapy given as part of concurrent chemoradiation may act systemically and potentially eradicate distant micrometastases.(1)

Preoperative chemoradiotherapy for locally advanced rectal cancer decreases the risk of local and distance failure. Neoadjuvant radiotherapy has the effect of inducing an objective tumor skrinkage, chemotherapy is radiosensitizing with potential benefits in terms of resecability and/or salvage for the anal sphincter (2,3). The chemoradiation has become the standard of care for patients cT3 or cT4, or enlarged regional lymphnodes. This should be followed by radical surgery 6-8 weeks later.(4,5)

In the past, local pelvic recurrence after radical surgery for rectal cancer, was high rated. The rectum has no serosa and lies below the peritoneal reflection so that tumour growth extends deeply into perirectal fat. Neoadjuvant chemoradiotherapy reduces the pelvic reccurence and improves the quality of the surgery.(6) The standard of care today in rectal cancer surgery is TME implying that all of the mesorectal fat, including all lymph nodes, should be excised.(5)

Several recent studies have shown that concurrent treatment led to a superior locoregional control and lower toxicity than postoperative radiotherapy.

MATERIALS AND METHODS

From January 2011 to December 2015, 48 patients with local advanced or low-lying rectal cancer were treated with radiotherapy and concurrent chemotherapy at Clinical County Hospital Sibiu /Oncology Department and Polisano Hospital /Radiotherapy Department.

RESULTS

Patients' characteristics are presented in table no. 1. 77% were cT3 and the rest of them, 23 %, were cT4. The localisation of the tumour related to the anal verge was below 5 cm in 33 % of the cases while 67 % of the patients had middle and upper rectal tumours. The performance status (ECOG) was 1 for 41 patients (86%) and only 7 patients were asympthomatic or had minor signs or symptoms of disease. Histopathologically, 87% were moderately differentiated adenocarcinoma.

Table no. 1. Patients' characteristics

Total	**48**	**%**
Median age, years	**59 (42-73)**	
Male	31	64
Female	17	36
ECOG		
0	7	14
1	41	86
Clinical T stage		
cT3	37	77
cT4	11	23
Clinical N stage		

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cNo	27	56
cN1	17	35
Unknown	4	9
Distance from anal verge,		
<5 cm	16	33
>5 cm	32	67
Grade		
Well differentiated	2	4
Moderately differentiated	42	87
Poorly differentiated	3	6
Unknown	1	3

Pre-treatment evaluation

All patients underwent complete history and physical examination, complete blood count, liver and renal function tests, carcinoembryonic antigen, digital rectal examination, chest X-ray, abdomen and pelvic computed tomography (CT) scan or magnetic resonance imaging (MRI), and flexible endoscopy. Clinical stage was based on CT or MRI scan. Endoscopies were done by the gastroenterologists at the Clinical County Hospital of Sibiu and Polisano Hospital. Biopsies and operative pathologic specimens were reviewed by pathologists at Clinical County Hospital of Sibiu or Radusan of Cluj Napoca.

Treatment

All underwent pelvic radiotherapy with 45 Gy/1,8 Gy/fraction x 5 days/week, 25 fractions. Chemotherapy was given concomitantly and consisted of oral Capecitabine 1600 mg/mp bid Monday-Friday, during radiotherapy.

Treatment related adverse events

The most common acute toxicity was grade 1 to 2 diarrhea and tenesmus during radiation. Only five of the 48 patients experienced symptomatic grade 3 acute toxicity (table no. 2). 7 patients could not finish the concurrent treatment, 5 patients due to sever toxicities and 2 patients due to non-compliance.

Response

41 patients underwent subsequent surgery 6 to 8 weeks after concurrent chemoradiotherapy. Pathological examination disclosed complete tumour regression in 4 patients and microscopic residual disease in 6 patients after preoperative chemoradiation. Of the 41 patients who completed the intended treatments, only 2 had local recurrence. The sphincter was preserved in only 4 out of the 16 patients in whom the tumour was located within 5 cm above the anal verge, because the patients could not afford radical standard surgery (total mesorectal excision, TME) at an Oncological Surgery Department. The 2-year overall survival rate was 81% and the disease-free survival was 73%. Our findings indicate that preoperative concurrent chemoradiotherapy allows low-lying rectal tumours to be resected while preserving sphincter function at Oncological Surgery Department and also results in good local control and acceptable toxicity (table no. 3).

Follow-up

Patients were scheduled for follow-up visits every 3 to 4 months for the first 2 years, and every 6 months thereafter. Follow-up examinations included physical examination at each visit, and abdominopelvic CT scans and chest X-rays every 6 months for the first 2 years and every year thereafter.

Table no. 2. Toxicity

Toxicities	Grade	Patients	%
Diarrhea and tenesmus	1-2	43	90
	3	5	10
Hand-foot syndrome	1-2	13	27

Table no. 3. Response

Response	Patients	%
Surgery	41	85
Pathological Complete regression	4	10
Microscopic residual disease	6	14
2-years overall survival rate	39	81
Disease-free survival	35	73

DISCUSSIONS

Loco-regionally advanced rectal cancer has a poor prognostic. Preoperative long-term radiotherapy should always be combined with fluoropyrimidine chemotherapy. Standard preoperative CRT means a dose of 45 Gy, together with 5-FU given preferably as prolonged continuous infusion (likely better than bolus) or oral 5-FU prodrugs [capecitabine or uracil–tegafur (UFT)]. Role of capecitabine versus i.v. 5-FU: The NSABP R-04 trial and an Arbeitsgemeinschaft Internistische Onkologie-(AIO) trial showed that 5-FU and capecitabine are equivalent (proven non-inferiority).(7)

Preoperative treatment is preferred because it is more effective and less toxic than postoperative treatment and provides a sphincter saving surgery by downsizing and improves functional outcome in low located tumours. The most frequent gastrointestinal toxicities were grade 1-2.

CONCLUSIONS

1. Concurrent chemoradiotherapy is the standard strategy for locally advanced rectal cancer.
2. 85% patients were appropriate for surgery after neoadjuvant treatment.
3. Only 4 out of 16 patients with lower rectal tumours had the sphincter preserved. The major problem of sphincter preservation was the lack of a surgical oncologist with versatility for a total mesorectal excision.
4. 2-year overall survival rate was 81%.
5. Disease-free survival was 73%.
6. Only two out of 41 patients who completed the intended neoadjuvant treatment had local recurrence.
7. The management of rectal cancer must be a multi-modal approach performed by an experienced multi-disciplinary expert team (Oncologist, Radiotherapist, Surgeon, Pathologist, Radiologist).

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