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Prognostic Factors of Local Recurrence and Survival after Curative Rectal Cancer Surgery: A Single Institution Experience

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A B S T R A C T

The aim of our study is to evaluate the importance of prognostic factors, both tumor-related and therapy related, and their impact on local recurrence rate of rectal carcinoma. It is also important to evaluate impact of chemoradiotherapy (CRT) on local recurrence rate and survival. We used the data of 514 patients with rectal carcinoma treated at Clinic of surgery at University Hospital Centre in Osijek, during the period from 2000 to 2007. Routine follow-up was carried out until March of 2012 or death. Median life expectancy for all patients who underwent surgery was 98 months. 47% of patients with resection without residual tumor (R0) did not develop local recurrence after median of observation of 90 months. 5-year survival rate for patients with R0 resection was 76.4%. The patients who had preoperative serum levels of carcinoembryonic antigen (CEA) within the normal range (<5 μg/mL) had a significantly better prognosis with 5-year survival of 75.8%, than patients with elevated levels who had 5-year survival of 46.5%. Tumor stage had great influence on survival and was defined by UICC TNM (International Union against Cancer, Tumor Node Metastases) classification, 7th edition. 5-year survival rate was (93.5% for stage I, 87.4% for stage II, 58.2% for stage III, 8.1% for stage IV). Patients with low grade differentiation tumors had 5-year survival rate of 73.5%, and those with high-grade had 38.2%. We have found that preoperative CRT significantly reduces the rate of local recurrence (5.3% vs. *14.1%), but patients who were treated with preoperative CRT did not appear to benefit significantly in terms of their long-term prognosis, because there was no difference in overall survival between the patients who received preoperative radiochemotherapy and those who did not receive it (66.2%* vs. *67.8%). It was found that the R-classification, anatomical extent of tumor described by the TNM classification of the UICC, tumor grade, and preoperative CEA serum level were prognostic factors that influenced survival.*

***Key words**: rectal carcinoma, local recurrence, survival, risk factors, surgery*

Introduction

With approximately 1600 new cases in Croatia and an estimated 80,000 new cases in EU countries per year, rectal carcinoma is one of the most prevalent tumor types. Incidence of rectal carcinoma is strongly connected with age because ninety percent of cases are diagnosed over the age of 50. It is known that as many as 30 to 50% of individuals older than 50 harbor one or more adenomatous polyps. The risk of developing rectal carcinoma continues to increase with age. Incidence in Croatia is slightly lower than in EU countries (34/100,000 with men, and 27,8/100,000 with women)[1–3]. Several features make the successful management of rectal cancer clinically challenging. The absence of a serosal barrier permits early tumor extension into the perirectal tissues. The rectum

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also lays close to vital, and sometimes unresectable, pelvic structures (e.g., the bladder, ureters, iliac vessels, and the sacrum). The compact nature of the mesorectum within the confines of the pelvis complicates the adequate removal of all mesenteric nodes at risk for metastatic disease. Due to these specific characteristics of rectal cancer, surgery alone has been associated historically with local recurrence in up to one in four patients. Local control and survival following surgical treatment of rectal cancer have been improved by the introduction of total mesorectal excision (TME)[4]. The rate of local recurrence has been proven to have an influence on the survival rate of afflicted patients and apart from distant metastases loco-regional recurrence is the most important factor determining prognosis and survival. Isolated loco-regional recurrence of rectal carcinoma have been reported from 5% to 33% with a median of 15%[4,5]. Increasing recurrence is also associated with increased UICC TNM stage. The most common location is anastomotic, perianastomotic and in the presacral region. Preoperative chemoradiotherapy has been shown to significantly decrease the local recurrence rate and because of the potential benefits associated with preoperative therapy, interest has evolved in adopting this approach in rectal cancer patients[6].

Many randomized trials compared preoperative *vs*. postoperative radiochemotherapy (German rectal cancer trial, CAO/ARO/AIO-94 and The National Surgical Adjuvant Breast and Bowel Project R0-3, NSABP R0-3). Studies showed that preoperative radiochemotherapy resulted with fewer local recurrences, but with no significant difference in overall survival[6–8]. During the data collection period there were some changes to the therapeutic approach; the percentage of patients treated with radiochemotherapy increased from 3 to 22%; the rate of intersphinteric resection for carcinomas in the lower third of the rectum increased from 1% to 8%[9,10]. These changes in therapeutic strategy, together with the increase in sphinteric-preserving operations has brought quality of life to the forefront. Due to fact that prognostic factors are of special interest to estimate prognosis of the individual patient, we analyzed the known factors that have influence on developing of the local recurrence and survival.

Matherials and Metods

The data of 514 patients (Table 1) treated with the following inclusion criteria were analyzed:

- Solitary invasive carcinoma of the rectum, 16 cm or less from the anal verge as measured with a rectosigmoidoscope.
- No other previous or synchronous malignant tumor.
- Tumor resection at the Clinic of surgery in the University Hospital Centre in Osijek between 2000 and 2007.

Rectal carcinoma was defined as tumor 16cm or less from the anal verge as measured with a rigid rectosigmoidoscope, and was classified in three groups according to the distance from the distal margin of the tumor to the anal verge: 12–16 cm, upper third; 7,5 to <12 cm, middle third; <7.5 cm, lower third.

Tumor staging (clinical and histopathological examination) was recorded according to current 7th edition of the tumor node metastasis (TNM) classification by UICC.

R classification was used to determine the presence of residual tumor in specimen by pathologist and was divided in three groups:

R0 – No residual tumor

R1 – Microscopic residual tumor, tumor directly at the resection margin

R2 – Macroscopic residual tumor

Total mesorectal excision (TME), according to the procedure described by Heald et al., and was carried out routinely during the study interval.

Several operating methods were used (local excision, anterior resection, abdomino-perineal excision) and the choice was influenced by the biology, anatomical extent of tumor and the tumor site in the rectum.

Radiochemotherapy was used for neoadjuvant or adjuvant therapy. Neoadjuvant radiochemotherapy was used for patients with tumor in lower third of rectum and in stages II and III by TNM classification.

Data was collected prospectively. Preoperative findings and data on treatment and patohistological examination were collected by a standardized system. All patients were followed until March of 2012 or death. Routine follow-up was carried out at 3-month intervals for two years, and during that period patients had colonoscopies after every year, abdominal ultrasound every 3 months, and tumor marker CEA serum level control every 3 months. After first two years patients had controls every 6 months for minimally total of 5 years. If suspicion of local recurrence occurred we did CT scan, or MRI of pelvis and in some cases PET/CT. After completion of regular follow-up, patients or their family doctors were contacted by mail or telephone every year until death or end of study in March of 2012. Locoregional and distant recurrences were documented by medical imaging and pathological examination.

Loco-regional recurrence was defined as recurrence of the tumor in the pelvis. Patients with recurrent cancer are a heterogeneous group. To establish LR or pelvic disease after definitive resection of rectal cancer, we have accepted at least one of the following major criteria: (1) Histological confirmation; (2) Palpable or evident disease with subsequent clinical progress; (3) Clear evidence of bone destruction; and (4) Positive positron meission tomography examination, and at least one of the minor criteria: (1) Progressive enlargement of soft tissue mass on repeated computed tomography (CT) or magnetic resonance (MRI) examination; (2) invasion of adjacent organs; (3) subsequent rise in tumor markers; and (4) typical appearance in endoscopic ultrasound, CT or MRI imaging.

TABLE 1
PATIENTS AND TUMOR CHARACTERISTICS

Characteristic	N	Percentage
Gender		
Male	321	62.45
Female	193	37.55
Age(years); median, range	63, 24–89	
Follow-up(months); median, range	64, 0–120	
Tumor site		
Upper third	94	18.3
Middle third	234	45.5
Lower third	186	36.2
Surgical therapy		
Local excision	16	3.1
Anterior resection	309	60.2
Hartmann's procedure	21	4.0
Intersphinteric resection	56	10.9
Abdomino-perineal excision	112	21.8
Radiochemotherapy		
No	227	44.16
Neoadjuvant	38	7.3
Adjuvant	249	48.44
Stage(UICC)		
Stage y0	5	1.0
Stage I	60	11.7
Stage II	169	32.9
Stage III	198	38.5
Stage IV	82	15.9
R clasification		
R0	430	83.7
R1	15	3.0
R2	67	13.0
RX	2	0.3

Cancer-related death was defined as an event, i.e. death due to recurred locoregional carcinoma and/or distant metastases. Patients who died with metachronous rectal carcinoma or other malignant tumors were excluded.

Statistical analysis

The Kaplan-Meier method was used to calculate rates of loco-regional recurrence, distant metastasis and survival. For comparison of the rates of loco-regional recurrences and survival we used the log-rank test. To identify independent prognostic factors, we performed a Cox regression analysis. For analysis of disease free survival in patients who had a R0 (curative resection), recurrent disease or death from any cause was defined as an event. χ^2 test and Fisher's exact test were used to compare frequencies, and the Mann-Whitney U-test was also used. P value of less than <0.050 was considered to be significant. Statistical analysis was carried out using SPSS® for Windows® version 17.0 (SPSS, Chicago, Illinois, USA).

TABLE 2
TUMOR RELATED SURVIVAL RATES IN CURATIVELY RESECTED PATIENTS WITH NO DISTANT METASTASES, POSTOPERATIVE MORTALITY EXCLUDED

Tumor-related factors	N	5-Year Survival (%)	95% CI%	p
All	408	80.3	77.4–83.3	
Upper third	73	76.4	68.6–84.1	
Middle third	139	81.6	76.8–86.4	0.3718
Lower third	196	80.8	76.5–85.0	0.4302
ypT0	2	100.0		
pT1	37	98.6	95.8–100	0.7789
pT2	124	92.0	88.3–95.8	0.0015
pT3	224	73.7	69.4–78.1	<0.0001
pT4	21	46.1	29.5–62.8	<0.0001
pN0	235	93.1	90.6–95.6	
pN1	98	71.6	64.7–78.5	<0.0001
pN2	75	48.6	39.7–57.4	<0.0001
Low grade	327	83.8	80.8–86.8	
High grade	81	56.7	46.8–66.7	<0.0001

Results

A total of 514 patients who were treated for rectal cancer during the study period were identified. Of these 514 patients 309 underwent anterior resection, 112 underwent abdomino-perineal excision, and only 16 local excisions were done. Median follow-up for all patients was 64 months. Median age for all patients was 63 years, and the majority of patients were male (62.45%). On pre-operative evaluation the majority of patients had stage II or III disease. 7.4% of patients received preoperative chemoradiotherapy, and 48.44% of patients received postoperative chemotherapy (Table 1). Patients who underwent surgery after preoperative chemoradiotherapy and tumor resection or had adjuvant chemoradiotherapy had a median life expectancy of 98 months. Postoperative mortality is included. Patients who had a palliative tumor resection (R1 or R2) without evidence of primary distant metastases had a median life expectancy of 31 months. The percentage of patients who had a primary, resectable R0 rectal carcinoma was 83.7% (Table 2). 47% of this group of patients did not develop distant metastases or local recurrence with a survival rate of 81% after a median observation period of 64 months.

Tumor-related factors and prognosis

The parameter that has the greatest influence on the survival of patients with rectal carcinoma is residual tu-

TABLE 3
THERAPY RELATED SURVIVAL RATES IN CURATIVELY RESECTED PATIENTS WITH NO DISTANT METASTASES, POSTOPERATIVE MORTALITY EXCLUDED

Therapy related factors	N	5-Year survival (%)	95% CI(%)	p
Anterior resection	296	80.6	77.1–84.1	
Intersphinteric resection	31	82.0	70.5–93.5	0.9786
Abdominoperineal resection	81	79.1	72.9–85.3	0.7683
No RCT	313	81.6	78.2–84.9	
Neoadjuvant RCT	38	83.8	75.4–92.3	0.4952
Adjuvant RCT	249	71.2	62.2–80.1	0.0212
Loco-regional recurrence, no	359	86.1	83.4–88.9	
Loco-regional recurrence, yes	66	44.1	34.2–54.0	<0.0001

TABLE 4
CANCER RELATED SURVIVAL RETES OF ALL PATIENTS WITH TUMOR RESECTION

Factor	N	Univariate Analysis		p	Multivariateanalysis		p
		5-Year survival (%)	95% CI%		Relative risk	95% CI%	
All	514	68.1	64.0–72.1				
Upper third	96	60.4	52.2–68.6		1.0		
Middle third	183	67.9	60.0–75.8	0.0312	0.8	0.4–1.2	0.423
Lower third	235	70.2	67.1–73.3	0.3435	1.0	0.7–1.3	0.756
CEA normal	291	75.8	67.4–84.2		1.0		
CEA abnormal	223	46.5	42.8–50.2	<0.0001	1.5	1.1–1.9	0.012
Local excision	16	94.2	91.1–97.3		1.4	0.4–5.2	0.637
Anterior resection	309	67.6	59.8–74.8	0.0012	1.0		
Abdomino-perineal excision	112	65.9	61.1–70.7	0.5537	1.3	0.8–1.7	0.312
No RCT	227	67.8	63.2–72.4		1.0		
Neoadjuvant RCT	38	66.2	63.5–68.9	0.8521	0.9	0.5–1.3	0.593
Adjuvant RCT	249	68.3	63.1–73.5	0.3618	0.8	0.4–1.2	0.152
R0	430	76.4	69.4–83.4		1.0		
R1	15	25.3	18.9–31.7	<0.0001	4.1	2.1–8.4	<0.001
ctlparR2	67	2.9	0.0–6.0	0.0182	3.2	2.3–4.7	<0.001
Stage Y0	5	100.0					
Stage I	60	93.5	91.0–96.1	0.5753	1.0		
Stage II	169	87.4	83.5–91.3	0.0131	1.8	1.1–3.2	0.032
Stage III	198	58.2	50.8–65.6	<0.0001	5.3	3.2–9.1	<0.001
Stage IV	82	8.1	4.9–11.3	<0.0001	12.9	6.5–22.7	<0.001
Low grade	409	73.5	67.1–79.9		1.0		
High grade	105	38.2	35.0–41.4	<0.0001	2.2	1.6–2.8	<0.001

mor or R classification. 83.7% of patients had R0 resection, 3% of patients had R1 resection, and 13% of patients had R2 resection. Patients who had undergone a resection without residual tumor R0, had a cancer-related 5-year survival rate of 76.4%, and only 3% of patients with grossly residual tumor R2, survived for 5 years (Table 4). Patients with R1 resection had 5-year cancer related survival of 25.3%.

The tumor site in the rectum (lower, middle, upper third) did not have an influence on the likelihood of 5-year survival (70.2%, 67.9%, 68.1%) for patients who did not have distant metastases and who had undergone R0 resection. The patients who had preoperative serum levels of CEA within the normal range (<5 μg/mL) had a significantly better prognosis with 5-year survival of 75.8% than patients with elevated levels with 46.5% of survival (Table 4).

The next important prognostic parameter that has influence on the survival is anatomical extent of the tumor due to UICC TNM classification. UICC stage I is associated with a 5-year survival rate of 93.5%; pT1 carcinomas have a significantly better prognosis 98.6% than pT2 carcinomas 92.0%.The prognosis is even significantly worse when lymphogenus metastases is present. In stage III, the cancer-related 5-year survival rates drops to 73.7%, and the involvement of more than three regional lymph nodes (pN2) reduces survival to 48.6%, which is significantly lower than the prognosis for pN1 involvement 71.6% (Table 4).

Therapy-related factors and prognosis

No significant differences in terms of long-term survival rates have been shown among the available options for surgical treatment of rectal carcinoma such as anterior resection, abdomino-perineal resection, low intersphinteric resection (80.6%; 82.0%; 79.1%; Table 2). The choice of operation is limited and influenced surely by tumor location,and the extent of the tumor at the time of the diagnosis.

In our clinic, radiochemotherapy is used for neoadjuvant (preoperative) chemoradiotherapy or adjuvant radiation therapy. The majority of patients did not receive preoperative CRT because it was not available at the time. All 38 patients who were treated with neoadjuvant radiochemotherapy (short-term RT 5 x 5 Gy + 5FU in one week) and then delayed surgery (eight to ten weeks after CRT) were patients with stage II or III of disease and the tumor site was in middle or lower rectum. 5-year local recurrence rate was 5.3% in this group. 48.44% of patients received postoperative chemotherapy with 5--year local recurrence rate of 12.5%. 44.16% of patients did not receive CRT and they had 14% of local recurrence after 5 years. Although there was difference between local recurrence rates of these groups of patients there was no difference in overall survival (pre-op CRT-66.2%; postoperative CRT-68.3%, no adjuvant therapy-67.8%; Table 4).

Discussion and Conclusion

Rectal carcinoma has been subject of many clinical studies over the last 20 years, due to fact that this type of tumor allows differentiation among, patient-related, tumor-related and therapy related factors. As a result of advances in surgical resection technique (TME) and multimodal treatment, survival rates have improved and locoregional recurrence rates have decreased[1–4,6,9,11]. This aim of this study was to evaluate factors associated with local recurrence outcomes and long-term survival of patients with rectal carcinoma.

Heald et al. suggested total mesorectal excision (TME) as a surgical technique of choice in treatment of rectal carcinoma in 1998, when they achieved a very low 10--year actuarial local recurrence rate of 4% in 200 consecutive patients undergoing curative anterior resection[4]. Before the introduction of TME, surgery alone was associated with local failure rates of up to 30–50%. In our study TME was carried out for all patients and 5-year local recurrence rate for patients who did not receive either pre-operative or post-operative CRT was 14.4%. Overall 5-year survival for this group of patients was 67.8% (Table 4).

For patients who are candidates for curative resection, important prognostic factor is tumor-related anatomical extent, as described by the UICC TNM 7-th classification[1,16,19]. The higher the classification stage, the greater is the risk of developing loco-regional recurrence. There was only one patient with local recurrence with stage I of disease. The incidence of local recurrence reaches 15.15 % with stage III, and even 26% with stage IV of disease compared to 8.2% with stage II of the disease (Table 4).

We have also showed that tumor related factor R-classification is very important factor for developing local recurrence, and only those patients who undergo an R0 resection can, potentially be cured. In our study 83.7% of patients were curatively resected R0 with 5-year survival rate of 76.4% (Table 2).Comparison with survival rate of 25.3% for R1 resected patients, or only 2.9% 5-year survival rate is showing significance of R-classification. The survival rate for patients with R0 resection can also be influenced by the choice of therapy, due to use of neoadjuvant radiochemotherapy which can increase, for example, survival rate for R0 resections in treatment of T4 rectal carcinomas[19–22].

The most investigated biological tumor marker is CEA, and it's preoperative serum values can predict prognosis for operated patients, and patients with high serum levels of CEA preoperatively have worse prognosis and significantly lower 5-year survival[10,11,22].

The use of neoadjuvant or adjuvant chemoradiotherapy and strategies to improve outcomes following rectal resection have been explored throughout the world. Swedish Rectal Cancer Trial which compared surgery alone with surgery following short-term pelvic RT (5 x 5 Gy) before the TME introduction showed decreasing local recurrence rate and improvement in overall survival. The German trial CAO/ARO/AIO as well as The National Surgical Adjuvant Breast and Bowel Project R0-3 (NSABP R0-3) compared preoperative use of CRT vs postoperative use of CRT, and revealed that use of preoperative CRT has many advantages like decreasing of local recurrence rate (11% *vs*. 7%), increasing disease free survival (44% *vs*. 34%), and increasing overall survival rate (85% *vs*. 78%)[6–8].

Two other European studies also evaluated the use of short-course preoperative RT with TME. Medical Research Council CR07, and a Dutch TME trial showed that there was significant difference in 5-year local recurrence rates between patients undergoing TME (10.6% CR07,and 10.9% Dutch TME trial),and patients undergoing preoperative RT (5.6% CR07, and 4.4% Dutch TME trial)[6–8,22–24].

In our study we showed that patients who were treated with neoadjuvant radiochemotherapy did not appear

to benefit significantly in terms of their long-term prognosis. 5-year survival rate was 67.8% for patients who did not receive CRT *vs*. 66.2% for patients with neoadjuvant CRT, and 68.3% for patients with adjuvant CRT (Table 4). This may be due to fact that the patients who receive this treatment are those who have advanced local tumors (stage II, or stage III). Receiving the neoadjuvant chemotherapy results in significantly better prognosis than adjuvant radiochemotherapy concerning local recurrence. 5-year local recurrence rate was 5.3% for patients who have received neoadjuvant CRT compared with 14.16% rate of patients who did not receive CRT.

After median of observation of 90 months we have analyzed several prognostic factors that have influence on developing of local recurrence and overall survival.

Our study showed that the pelvic recurrence rate is tumor stage dependent, so the more advanced the stage is, described by TNM classification, there is a higher chance of developing local recurrence. Also, inadequate removal of primary tumor described by residual tumor classification or R-classification seems to be very important tumor-related prognostic factor for developing of LR. Patients with macroscopically residual tumor (R2) had the worst prognosis with 5-year survival rates under 3%.

Because of the inadequate technical equipment at the time of this study only 38 patients were treated with neoadjuvant radiochemotherapy (short-term RT 5 x 5 Gy + 5FU in one week) and then delayed surgery (eight to ten weeks after CRT) and they had benefit from receiving it with 5-year local recurrence rate of 5.3% in this group.

Overall 5-year local recurrence rate for all patients included in this study was 12,8% and it matches major randomized trials in the last two decades which showed locoregional failure dropping from 30–40% to less than 15%.

Cancer-related 5-year survival rate for patients who were curatively resected was 80.3%, and overall 5-year survival for all operated patients was 68.1%.

We have found that preoperative CRT significantly reduces the rate of local recurrence, but patients who were treated with preoperative CRT did not appear to benefit significantly in terms of their long-term prognosis.

When we considered all patients in our study multivariate analysis showed that prognostic factors with greatest influence on local recurrence development were R-classification, tumor stage defined by TNM classification, preoperative serum CEA levels and use of neoadjuvant chemoradiotherapy.

There have been many improvements in surgery and the application of combined approaches in the management of rectal cancer in terms of reducing of local recurrence, and increasing of conservative surgery rates, as well as overall survival. Surgeons and pathologists have been extensively investigating anatomical and technical basis of tumor recurrence within the pelvis, and proved that the mainstay of treatment aimed at achieving locoregional control is still surgery, with of course multidisciplinary approach.

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ČIMBENICI RIZIKA ZA NASTANAK LOKALNOG RECIDIVA I PREŽIVLJENJE NAKON OPERATIVNOG LIJEČENJA KARCINOMA REKTUMA: REZULTATI JEDNE USTANOVE

S A Ž E T A K

Cilj naše studije je ocjena važnosti pojedinih čimbenika rizika, kako vezanih uz tumor, tako i onih vezanih uz terapiju, te njihova uloga u u nastajanju lokalnog recidiva karcinoma rektuma. Također je bitno u studiji evaluirati učinak kemoradioterapije na nastanak lokalnog recidiva kao i na preživljenje. Korišteni su podaci 514 operiranih bolesnika sa karcinomom rektuma, u periodu između 2000. i 2007. godine, na Klinici za kirurgiju, KBC Osijek. Rutinske kontrole i postoperativno praćenje bolesnika su učinjeni do ožujka 2012. godine ili do eventualne smrti bolesnika. Srednja očekivana postoperativna dob svih operiranih bolesnika bila je 98 mjeseci. 47% bolesnika sa učinjenom R0 resekcijom (resekcijom bez ostatnog tumora), nije razvilo lokalni recidiv nakon nakon srednje dužine postoperativnog praćenja od 90 mjeseci. 5-to godišnje preživljenje bolesnika kod kojih je učinjena R0 resekcija bilo je 76,4%. Bolesnici koji su imali preoperativnu serumsku razinu karcinoembrionskog antigena (CEA) unutar normalnog referentnog raspona (<5 μg/mL) imali su statistički značajno bolje 5-to godišnje preživljenje (75,8%), nego bolesnici sa preoperativno povišenom razinom CEA (46,5%). Tumorski stadij je imao velik utjecaj na preživljenje, a definiran je sa UICC TNM (International Union Against Cancer, Tumor Node Metastases) klasifikacijom, 7. izdanjem. 5-to godišnje preživljenje bilo je (93,5% za stadij I; 87,4% za stadij II; 58,2% za stadij III i 8,1% za stadij IV). 7,3% od ukupnog broja bolesnika koji su primili neoadjuvantnu kemoradioterapiju imali su značajno niži postotak lokalnog recidiva nakon 5 godina (5,3%), nego bolesnici koji neoadjuvantnu CRT nisu primili (14,1%). Iako je neoadjuvantna terapija imala utjecaja na nastajanje lokalnog recidiva, nije imala značajan utjecaj na ukupno 5-to godišnje preživljenje (66,2% *vs*. 67,8%). Bolesnici sa slabo diferenciranim tumorom imali su značajno lošije 5-to godišnje preživljenje nego bolesnici sa dobro diferenciranim tumorom (38.2% *vs*. 73.5%). Ova studija je pokazala da su R-klasiifikacija, stadij tumora prema TNM klasifikaciji, stupanj diferencijacije tumora, povišena serumska razina CEA prognostički čimbenici koji utječu na preživljenje, a upotreba neoadjuvantne kemoradioterapije smanjuje nastanak lokalnog recidiva, no ne utječe na ukupno 5-to godišnje preživljenje.