Original article

Neoadjuvant chemoradiotherapy plus adjuvant chemotherapy versus adjuvant chemoradiotherapy in the treatment of patients with resectable rectal adenocarcinoma: a single-center 6-year study

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SUMMARY

The last 20 years have seen significant advances in the use of radiation and chemotherapy in the treatment of rectal cancer patients. Studies comparing preoperative chemoradiotherapy to postoperative chemoradiotherapy in Greek patients with resectable rectal adenocarcinoma are rare. Patients and Methods: We conducted a retrospective cohort study of 74 patients (48 men, 26 women, mean age 63,8 years) with resectable rectal stage II or III cancer. Eighteen patients received preoperative chemoradiotherapy and postoperative chemotherapy (group A). Fifty-six patients received postoperative chemoradiotherapy (group B). Chemotherapy consisted of Capecitabine alone or in combination with Oxaliplatin and 5-FU. Radiotherapy consisted of 25Gy (in 5 fractions in group A) or 45Gy (in 28 fractions in group B). Results: Overall 5-year survival was 69,7% (95% CI 50,3 - 89,1%). Median overall survival (OS) was 24,5 months. There was no statistically significant difference in survival curves and recurrence free survival (RFS) between the two treatment groups. Twelve patients (16,2%, 95% CI: 9,0 – 27,0%) developed recurrence. Total RFS was 22,5 months, 20,0 months in group A and 25,0 months in group B (N.S). Adverse effects of therapies were the same in both groups. Conclusions: Preoperative chemoradiotherapy did not enhance OS and RFS in stage II and III rectal carcinoma patients who received adjuvant chemotherapy.

Keywords: rectal adenocarcinoma, overall survival, recurrence free survival, therapy evaluation

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INTRODUCTION

The last 20 years have seen significant advances in the use of chemotherapy in the treatment of colorectal cancer patients. Increased understanding of the pharmacology of 5-fluorouracil (5-FU) and the discovery of modulators of its activity, e.g. leucovorin, resulted in some initial improvements in treatment. Systemic chemotherapy now has a clear role as an adjunct to surgery to improve survival in stage III and certain 'high-risk' stage II colorectal cancer patients.[1,2]

Better preoperative imaging, innovations in surgical technique, more accurate histopathologic reporting and clearer indications for radiotherapy, more accurate planning techniques and greater precision of its delivery have improved the treatment of rectal cancer. However, preoperative radiotherapy remains a controversial issue. Radiotherapy has many aims: to reduce the risk of local recurrence, to improve the likelihood of achieving a curative surgery with a pathologically complete resection margin as defined by a clear circumferential margin greater than

1mm, to facilitate sphincter-sparing procedures, as a definitive treatment in the elderly and frail and finally as a means of palliation.[3]

Radiation therapy to the pelvis is recommended for patients with rectal cancer because it reduces by 20–25% the probability of regional recurrences following complete surgical resection of stage II or III tumors, especially if they have penetrated through the serosa. This alarmingly high rate of local disease recurrence is believed to be due to the fact that the contained anatomic space within the pelvis limits the extent of the resection and because the rich lymphatic network of the pelvic side wall immediately adjacent to the rectum facilitates the early spread of malignant cells into surgically inaccessible tissue. Radiation therapy, either pre- or postoperatively, reduces the likelihood of pelvic recurrences but does not appear to prolong survival. Preoperative radiotherapy is indicated for patients with large, potentially unresectable rectal cancers; such lesions may shrink enough to permit subsequent surgical removal. Radiation therapy is not effective in the primary treatment of colon cancer.[3-6]

However, to our knowledge, studies in Northern Greek populations which compare preoperative chemoradiotherapy-postoperative chemotherapy to postoperative chemoradiotherapy in patients with stage II or III rectal cancer who undergo surgical resection are lacking. Moreover, in many studies[7-9] full doses of chemotherapy were not given because of toxic effect. Chemotherapy targets the micrometastatic disease.

We conducted a retrospective, progressively censored, cohort study. The primary aim was to evaluate the impact of full doses of adjuvant chemoradiotherapy or the combination of preoperative chemoradiotherapy and adjuvant chemotherapy to overall survival in patients with resectable stage II and III rectal adenocarcinoma. We further studied the impact of these different therapies to the recurrence free survival and the toxicity of therapies.

PATIENTS AND METHODS

We evaluated the medical records of 79 consecutive Caucasian patients from northern Greece. All patients were referred to the department of Gastroenterology, G. Papanikolaou General Hospital, Thessaloniki, Greece, after initial histologically confirmed diagnosis of rectal adenocarcinoma (beginning within 12cm of the anal verge, as determined by endoscopy), from August 2002 to November 2008. All patients underwent surgical resection of their tumor.

Inclusion criteria were: age > 18 years, high-risk stage II (T_3-T_4 N_0 M_0 patients with one of the following: age <50 years old, first degree relative with colorectal cancer, infiltration of lymph vessels or nerves and difficult surgical resection) or stage III patients, ECOG performance status 0-2, adherence to therapy and follow-up, absence of other oncologic therapy or malignancy prior to surgical resection or during therapy and informed consent. Exclusion criteria were: absence of adequate chemo - or radio - therapy cycles, absence of close follow-up, presence of other malignancy, pregnant or lactating women and ECOG performance status > 2. Laboratory criteria in the initial evaluation included: neutrophil count $\geq$1500/mm^3, platelets $\geq$100000/mm^3, serum creatinine < 1,5mg/dL, AST/ALT <3 x normal value and ALP < 3 x normal value. Staging studies included chest X-ray, abdominal – pelvic computed tomography scan, colonoscopy, blood cell count, biochemistry profile, tumor serum markers CEA and Ca 19-9.

Patients in group A received surgical treatment 7 to 10 days after the end of chemoradiotherapy, which consisted of 2 or 3 chemotherapy cycles and 25Gy, equally divided in 5 fractions; Four to six weeks after surgical resection they started receiving chemotherapy. Patients in group B received surgical treatment followed, four to six weeks later, by chemoradiotherapy; radiation therapy consisted of 45Gy to the whole pelvis, equally divided in 28 fractions. Postoperative 45Gy radiotherapy is considered to have the same biologic effect as 25Gy delivered preoperatively.[6]

Rectal radiotherapy took place in Papageorgiou General Hospital, Thessaloniki, Greece. Radiation was delivered with linear accelerators (energy range 6-18MV), 5 days per week. The patients were treated in a prone position with distended bladder. Customised blocks were used to exclude normal tissues from the treatment field. The postoperative clinical target volume included the tumor bed, 5cm below the anastomosis or the pelvic floor down to the level of the ischiac tuberosity (after an abdominoperineal excision), the pre-sacral and internal iliac nodes and the dorsal wall of the pelvic organs. The upper limit of the field was the top of the sacrum.

Seventy nine patients met the inclusion criteria. All patients received chemotherapy (3 to 8 cycles) with capecitabine (Xeloda) or capecitabine plus oxaliplatin (Xelox) or 5-FU/LV.[7] For clinical purposes we considered patients who received capecitabine or 5-FU/LV as one group because they are considered to have equal effects on overall survival and recurrence free survival[11] and patients who received Xelox as another.

Medical data from 74 patients were finally analyzed. Five of the original 79 patients were excluded from the study. One of them passed away because of a car accident, another died of a documented not-related to cancer cause

and the rest were lost to follow-up. Eighteen patients were enrolled in group A and 56 in group B.

All patients received supportive care. Antiemetic drugs were chosen in accordance with the conventional antiemetic protocol of our centre. In case of diarrhea, the patients underwent supportive care as well as intensive treatment with loperamide and were hospitalized if necessary. Blood laboratory tests and imaging studies were done at regular intervals during therapy and follow-up (every 3 months for the first 3 years and every 6 months for the next 2 years) and adverse effects (AE) of therapies were recorded.

We evaluated the baseline characteristics of the patients in the two treatment groups (table 1). We compared the overall survival (OS) and recurrence free survival (RFS) as well as the adverse effects of therapies in groups A and B.

Statistical Analysis: We set statistical significant level for type I error as a = 0,05. All analyses were two-sided and performed according to the per-protocol principle. Normal distribution of continuous data was estimated with Kolmogorov–Smirnov test. We used t-test (parametrical data) or Man–Whitney U-test (non-parametrical data) to compare continuous variables. Parametrical data were expressed as mean (M) and standard deviation (SD), while non-parametrical as median and maximum/minimum values. Categorical data were compared with chi-square or Fisher's exact test. Proportions were expressed with 95% confidence intervals (CI) with continuity correction. Kaplan-Meier estimates of the time-to-event end points were calculated because the number of patients in the study was relatively small.[12] Cox proportional-hazards regression analysis[13] was used to estimate p values with 95% confidence intervals to account for comparisons of different clinically significant factors in the primary or secondary end-points of the study. The study was powered 0,306 (or 0,213 with continuity correction) to detect 20% difference in 5-year survival between the two study groups. Statistical packages WinSTAT (R. Fitch Software, Vers. 2007.1), Primer of Biostatistics (Glantz, Statistical software program version 6.0, McGraw Hill 2005) and VassarStats (http://faculty.vassar.edu/lowry/VassarStats.html) were used.

Patients were informed and consented for their therapy plan, which was approved by the oncology committee of G. Papanikolaou Hospital. No further approval by the ethics committee for the purpose of the study was needed.

RESULTS

There was no statistically significant difference between the two treatment groups regarding age, sex and stage of the disease (table 1). Table 2 shows the number of cycles, the type of chemotherapy and the percentage of adverse effects in the two treatment groups. The median chemotherapy cycles in group A was 8 and in group B 6 (p = 0,001). Seventeen patients (94,4%) in group A received Capecitabine or 5-FU/LV whereas 41 patients (73,2%) in group B received the same regimen. One patient (5,6%) in group A received Capecitabine plus Oxaliplatin (Xelox) whereas 15 patients (26,8%) in group B received Xelox. There was a statistically significant difference in the frequency of the type of chemotherapy regimens between the two groups (p = 0,049). Overall, 58 patients (78,4%) received Capecitabine or 5-FU/LV and 16 patients (21,6%) received Xelox.

Median overall survival in group A was 20,0 months (Max:72, Min:10) and 26,0 months (Max:84, Min:9) in group B (p = 0,071). Total median OS in both groups was 24,5 months. Twelve patients overall (16,2%, 95% CI: 9,0 – 27,0%) developed recurrence during follow-up. Recurrence free survival was 20,0 months in group A (Max:72,

Table 1. Baseline characteristics of the study patients.

Variable	group A (n_1 = 18)	group B (n_2 = 56)	Total (N =74)	p
Age M ± SD (years)	61,8 ± 9,3	64,5 ± 9,3	63,8 ± 9,3	0,285
Sex (%)				0,750
Men	11 (61)	37 (66)	48 (65)	
Women	7 (39)	19 (34)	26 (35)	
Stage (%)				0,052
II	12 (67)	23 (41)	35 (47)	
III	6 (33)	33 (39)	39 (53)	

M: mean, SD: standard deviation, CHT: chemotherapy, Max: maximum, Min: minimum

Table 2. Number of cycles, type of chemotherapy and percentages of adverse effects in the two treatment groups.

Variable	group A (n_1 = 18)	group B (n_2 = 56)	Total (N =74)	p
CHT cycles				
Median	8	6	6	0,001
Max - Min	5-8	3-8	3-8	
CHT type – No (%)				0,049
Capecitabine or 5-FU/LV	17 (94,4)	41 (73,2)	58 (78,4)	
Capecitabine plus Oxaliplatin	1 (5,6)	15 (26,8)	16 (21,6)	
Adverse effects (%)	11 (61)	28 (50)	39 (53)	0,433

CHT: chemotherapy, Max: maximum, Min: minimum, 5-FU: 5-flouoracil

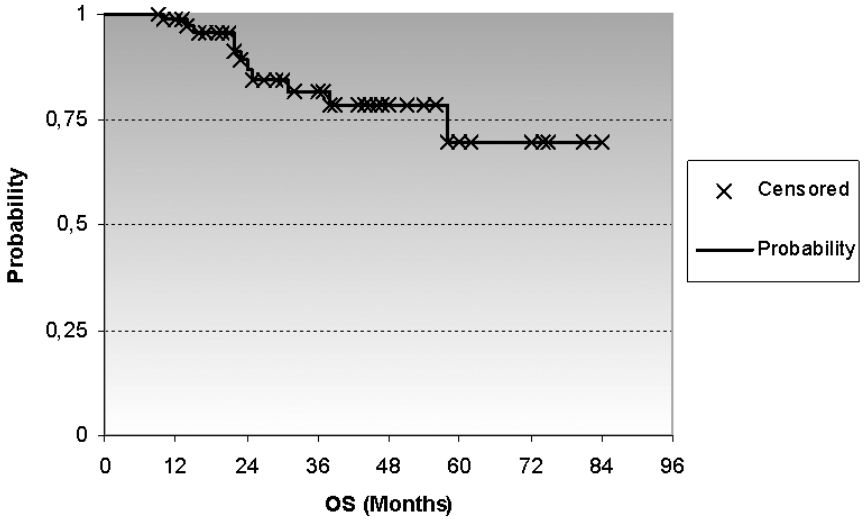

Figure 1. Kaplan-Meyer curve of overall survival (OS) in total study patients.

Min:7) and 25,0 months in group B (Max:84, Min:5) (p = 0,158). Total median RFS in both groups was 22,5 months. Figure 1 shows total OS and figure 2 OS in groups A and B. Figure 3 shows total RFS and figure 4 RFS in groups A and B. There was no statistically significant difference in OS (p = 0,323) and RFS (p = 0,683) between groups A and B.

Table 3 presents the adverse effects (AE) of chemotherapy and radiotherapy in the two groups. The proportions of the total AE in the two groups did not differ significantly (p = 0,433).

Figure 5 presents OS according to the stage of the disease. There was no statistically significant difference between stage II and III of the disease (p = 0,147). Figure 6 presents RFS according to the stage of the disease. There was no statistically significant difference between stage II and III of the disease (p = 0,242).

Group A showed a higher hazard ratio (HR) for death (1,92) as well as recurrence (1,32) compared to group B. Likewise, for patients in stage III of the disease HR for death was 2,56 higher than for those in stage II.

Overall 5-year survival was 69,7% (95% CI 50,3 - 89,1%). Five-year survival in group A was 55,7% (95% CI 15,1 – 96,3%) and in group B 73,0% (95% CI 51,4 – 94,6%) (p = 0,454). Five-year survival in stage II was 84,8% (95% CI 68,7 – 100%) and in stage III 60,2% (95% CI 47,3 – 73,1%) (p = 0,562).

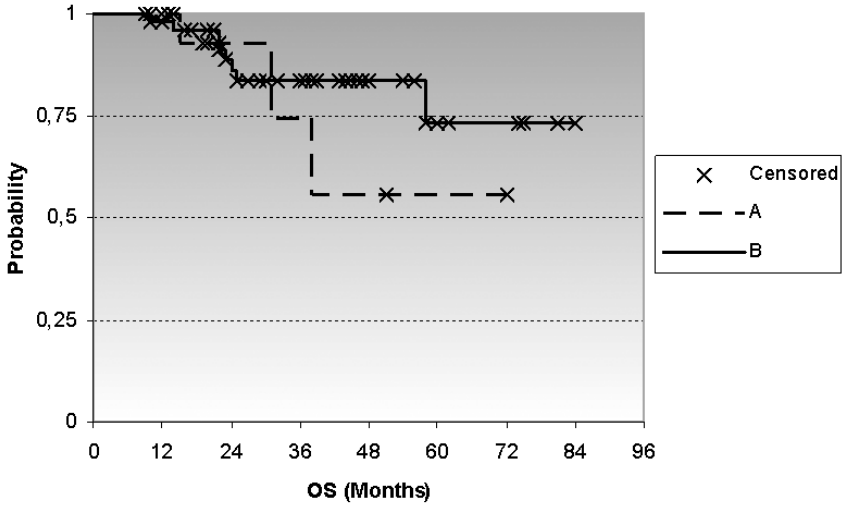

Figure 2. Kaplan-Meyer curves of overall survival (OS) in patients of group A and B (p = 0,323).

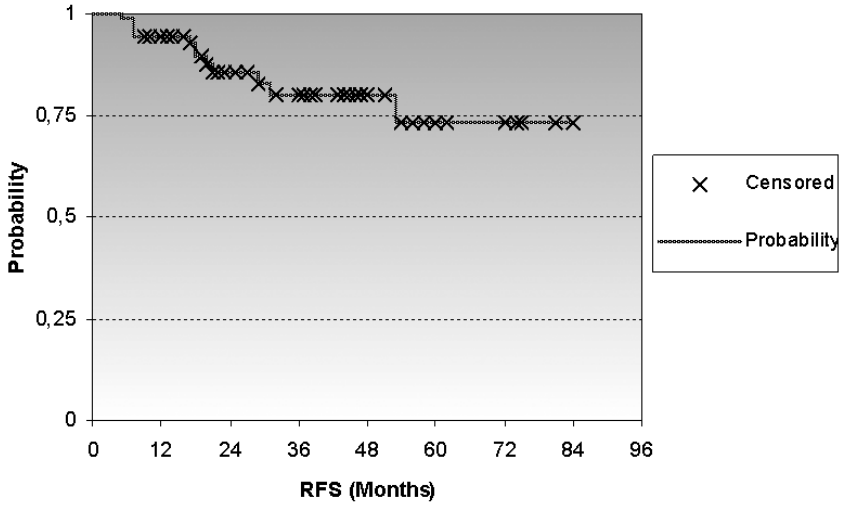

Figure 3. Kaplan-Meyer curve of total recurrence free survival (RFS).

DISCUSSION

The primary aim of the study was to evaluate OS and RFS in patients who received either preoperative chemoradiotherapy and adjuvant chemotherapy or adjuvant chemoradiotherapy. Although patients who received adjuvant chemoradiotherapy had a better OS and RFS, the difference between the two groups did not reach statistical significance. This lack of statistical difference persisted even though we controlled for age and stage of the disease.

These results can be interpreted in three ways: (a) there is no actual difference in OS and RFS between the two groups and survival probability for the observed curves was the result of chance alone or (b) patients who receive only adjuvant chemoradiotherapy may have better OS and RFS, but our study did not have enough power to detect the difference or (c) patients who receive preoperative chemoradiotherapy and adjuvant chemotherapy have better OS and RFS, but our study did not have enough power to detect the difference.

Hazard ratios showed that patients who received preoperative chemoradiotherapy had almost twice the risk of death than those who received postoperative chemoradiotherapy. However, hazard ratios must be cautiously interpreted because of the statistical assumption that the risk of death or recurrence is the same throughout the period of the study. This assumption may not always be true in cohorts of cancer patients.

Previous studies have shown overall 5-year survival 60% to 85% for stage II patients and 27% to 60% for stage

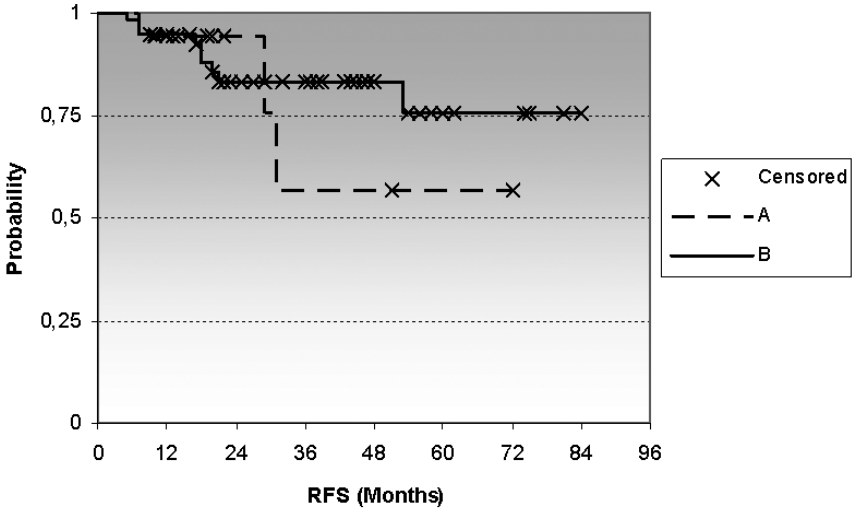

Figure 4. Kaplan-Meyer curve of total recurrence free survival (RFS) in group A and B (p = 0,683).

Table 3. Adverse effects (AE) of chemotherapy and radiotherapy in the study patients.

AE	group A (n_1 = 18)	group B (n_2 = 56)	Total (N =74)	p
Diarrhea (G)				0,779
2	3	8	11	
3	2	10	12	
Stomatitis (G2)	0	1	1	
Hand-Foot syndrome (G2)	0	3	3	
Nausea-Vomiting (G2)	0	2	2	
Neutropenia (G)				1,000
1	1	0	1	
2	1	4	5	
3	0	2	2	
Thrombopenia (G)				0,675
2	0	3	3	
3	1	3	4	
Neuropathy	0	1	1	
Transaminemia	1	0	1	
Radiation colitis	1	0	1	
Radiation toxicity (G)				
1	3	0	3	
2	2	0	2	
Sexual dysfunction	1	0	1	
Others	0	2	2	
Total number of patients (%)	11 (61)	28 (50)	39 (53)	0,433

G: grade.

III.[14] The results of our study are in accordance with these findings. However, there was discordance in the proportion of patients in the study with local or distant recurrence which was relatively small and adverse effects of therapy, which were similar in the two treatment groups.

Our study had certain limitations. The external validity was limited because of the relatively small number of patients. We did not detect difference in OS or RFS, but the probability of making error type II was 78,7%. Moreover, the patients were Caucasians who lived in Greece and had access to a tertiary hospital. The internal validity of the study was limited because of its retrospective character, the lack of randomization and the presence of modifiers, such as the size of the rectal tumor, the social and family supportive opportunities for each patient and his/her socioeconomic level. It should also be noted that the two therapy groups differed in the number and type of chemotherapies.

Preoperative radiation therapy has many potential advantages, including tumor down-staging, an increase in resectability, possibly permitting the use of a sphincter-sparing procedure and a decrease in tumor viability, which may decrease the risk of local recurrence. Preoperative radiation therapy works better in well-oxygenated tissues prior to surgery. Postoperatively, tissues are relatively hypoxic as a result of surgery and may be more resistant to radiotherapy. If patients have postoperative complications, there may be delay in initiating adjuvant therapy. Preoperative radiation therapy also minimizes the radiation exposure of small bowel loops due to pelvic displacement and adhesions following surgery.[15] The disadvantages of preoperative radiation therapy include delay in definitive resection, possible loss of accurate pathologic staging, possible over-treatment of early-stage rectal cancer and increased postoperative complications, morbidity and mortality rates secondary to radiation injury. The advantages of postoperative radiation thera-

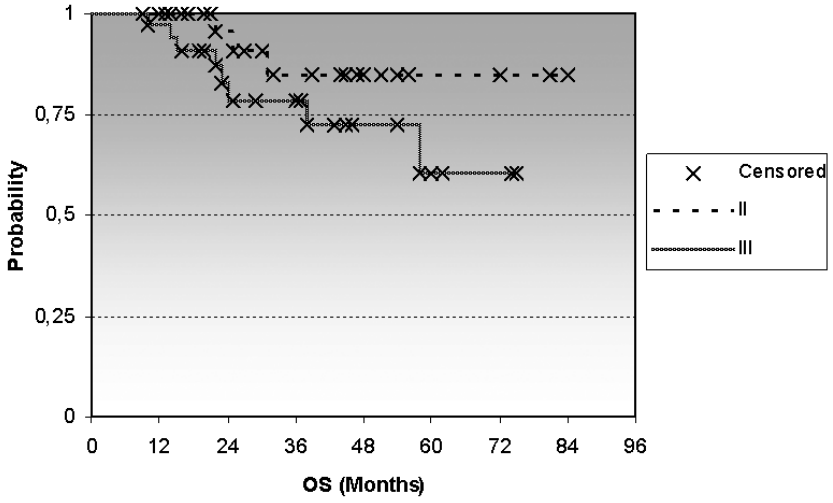

Figure 5. Kaplan-Meyer curves of overall survival (OS) in patients of stage II and III (p = 0,147).

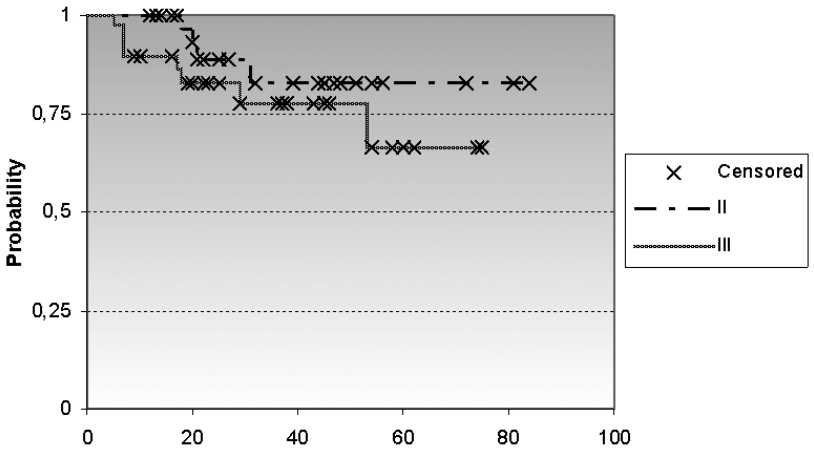

Figure 6. Kaplan-Meyer curves of recurrence free survival (RFS) in patients of stage II and III (p = 0,242).

py include immediate definitive resection and accurate pathologic staging information before beginning ionizing radiation. The disadvantages of postoperative radiation therapy include possible delay in adjuvant radiation therapy if postoperative complications ensue, no effect on tumor cell spread at the time of surgery and decreased effect of radiation in tissues with surgically-induced hypoxia. Published randomized trials suggest that preoperative or postoperative radiation therapy appears to have a significant impact on local recurrence but does not increase survival rates.[14-15]

A recent systematic review suggested that preoperative chemoradiotherapy for patients with stage II and III resectable rectal cancer gives better complete response rates compared to radiotherapy alone but it also results in higher toxicity.[16] Moreover, according to a recent large phase III Italian study, addition of oxaliplatin (Eloxatin) to standard preoperative radiochemotherapy does not lead to tumor shrinkage in patients with locally advanced rectal cancer, although this does not necessarily mean that the drug does not have an effect on micrometastases at distant sites.[17]

The application of an optimal treatment plan for patients with rectal cancer involves a complex decision-making process. Strong consideration should be given to the intent of surgery, possible functional outcome and preservation of anal continence as well as genitourinary function. Remarkable progress has been achieved during the past 20 years in understanding the pathogenesis of rectal cancer and improving treatment. However, areas of uncertainty do exist and larger multicenter clinical trials of newer chemotherapy regimens and radiotherapy strategies will specify the best therapeutic options for each patient.

REFERENCES

1. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 355: 1114–1123.
2. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. N Engl J Med 2000; 342: 792.
3. Mayer RJ. Gastrointestinal Tract Cancer. In: Fauci AC, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J eds: Harrison's Principles of Internal Medicine.17th ed. New York: McGraw Hill 2008; 697.
4. Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. N Engl J Med 2005; 352: 476.
5. Weitz J, Koch M**,** Debus J**,** Hφhler T**,** Galle PR**,** Bóchler MW. Colorectal cancer. Lancet 2005; 365: 153.
6. Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. JAMA 2000; 284: 1008–1015.
7. Ngan SY, Burmeister BH, Fisher R, et al. Early toxicity from preoperative radiotherapy with continous infusion 5-fluorouracil for resectable adenocarcinoma of the rectum: a Phase II trial for the Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2001; 50:883.
8. Bosset JF, Magnin V, Maingon P, et al. Preoperative radiochemotherapy in rectal cancer: long-term results of a phase II trial. Int J Radiat Oncol Biol Phys 2000; 46: 423.
9. Rich TA, Skibber JM, Ajani JA, et al. Preoperative infusional chemoradiation therapy for stage T3 rectal cancer. Int J Radiat Oncol Biol Phys 1995; 32: 1025.
10. Jim Cassidy, Josep Tabernero, Chris Twelves, et al. XELOX (Capecitabine Plus Oxaliplatin). Active First-Line Therapy for Patients with Metastatic Colorectal Cancer. J Clin Oncol 2004; 22:2084-2091.
11. Glen H, Cassidy J. Redefining adjuvant chemotherapy in patients with stage III colon cancer: X-ACT trial. Expert Rev Anticancer Ther 2008; 8: 547-551.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-481.
13. Cox DR. Regression models and life-tables. J R Stat Soc [B]

1972; 34: 187-220.
14. Cagi B. Rectal Cancer. Available at http://emedicine.medscape.com/article/ 281237-overview. Accessed 30 August 2009.
15. van Helmond J, Beart RW. Cancer of the rectum: Operative management and adjuvant therapy. In: Current Therapy in Colon and Rectal Surgery. 2nd ed. Philadelphia, Pa: Mosby; 2005.
16. Latkauskas T**,** Paskauskas S**,** Dambrauskas Z, et al. Preoparetive chemoradiation versus radiation alone for stage II and III resectable rectal cancer: a meta-analysis. Colorectal Dis 2009 (in print).
17. Printz C. Preoperative oxaliplatin does not shrink rectal tumors. Cancer 2009; 115: 3818-3819.