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Safety and Feasibility of Carboplatin and Paclitaxel followed by Fluoropyrimidine Analogs and Radiation as Adjuvant Therapy for Gastric Cancer

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Key Words
Paclitaxel · Carboplatin · Adjuvant · Gastric · Radiation

Abstract
Background: Adjuvant 5-fluorouracil (5FU)-based chemo-radiotherapy is currently considered a standard of care for the treatment of gastric cancer. The impact of 5FU-based adjuvant therapy on the rate of distant recurrence has been modest. In order to improve the systemic effects of adjuvant therapy, we have been treating patients with resected gastric cancer with carboplatin and paclitaxel followed by fluoropyrimidine analogue and radiation.
Methods: We report on the outcomes of 21 consecutive gastric cancer patients treated off protocol with adjuvant carboplatin (area under the curve 5 mg/ml × min) and paclitaxel (175–200 mg/m^2) every 3 weeks, followed by concurrent pyrimidine analogs (either capecitabine 1,600–2,000 mg/m^2/day in 17 patients, or 5FU 200 mg/m^2/day in 4 patients) and radiation (45–50.4 Gy). Patients received a total of 4–6 cycles of carboplatin and paclitaxel.
Results: The median age at diagnosis was 60 years. Sixteen patients had stage 3 disease and 7 of them had positive surgical margins (6 with R1 and 1 with R2 resection), 3 patients were stage 2, and 2 patients were stage 1 (all had R0 resection). All patients had D1/D2 (4 had D2 and 17 had D1) lymph node dissection. The incidence of grade 3 or higher overall, hematologic, or gastrointestinal toxicity in the patients receiving carboplatin and paclitaxel was 57, 48 and 10%, respectively. No treatment-related deaths

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were observed. After adjuvant treatment 15 patients developed recurrent disease, 10 of whom had distant metastases. The median recurrence-free survival (RFS) was 12.3 months. The median overall survival (OS) was 16.0 months. Patients with R0 resection had significantly longer OS than did those with positive surgical margins (log-rank p = 0.0060). Median OS for the R0 resection group was 28.8 months.
Conclusions: Carboplatin and paclitaxel added to radiation plus fluoropyrimidine analogs is a well-tolerated regimen in the adjuvant setting. The activity of this regimen in this relatively high-risk group of gastric cancer patients is of interest for future development.

Introduction

Gastric cancer has a high mortality with a current 5-year survival rate of 24% [1]. A decline in distal gastric cancer incidence was accompanied by a simultaneous rise of proximal cancers and of gastro-esophageal junction tumors [2]. Proximal cancers are associated with significantly worse prognosis. They usually present with a more advanced stage, more aggressive histology, and are markedly harder to resect [2–5].

Although surgery remains the only curative therapy in gastric cancer, its 5-year overall survival (OS) rate ranges from 10 to 30% [6]. Both locoregional and distant relapses after resection are common [7–9]. In order to improve the surgical outcome in gastric cancer patients, adjuvant and neo-adjuvant approaches have been explored utilizing chemotherapy, radiotherapy (RT) or both. Adjuvant chemoradiotherapy utilizing bolus 5-fluorouracil (5FU) was evaluated in the Southwest Oncology Group/Intergroup 0116 (INT-0116) trial [10]. A significant improvement in median relapse-free survival (30 vs. 19 months) and median OS (36 vs. 27 months) was observed. Although this study established adjuvant chemoradiotherapy as a standard treatment for gastric/gastro-esophageal junction tumors, the high rate of observed toxicities and the modest impact on distant recurrence suggests that a more effective and tolerable chemotherapeutic regimen may be needed in the adjuvant setting.

Single agent paclitaxel has encouraging activity in patients with advanced gastric cancer [11, 12]. In preclinical models, paclitaxel has synergistic effects with platinum compounds when applied in a schedule-dependent course [13]. Of the platinum compounds, carboplatin has an improved safety profile over cisplatin. The combination of paclitaxel and carboplatin has been shown to be tolerable and active in many solid tumors [14]. The activity and safety of the carboplatin-paclitaxel combination was tested in patients with advanced gastric cancer and has shown a response rate of 22 to 33% and a median time to progression of 3.5 to 4.9 months [15–17].

Due to the lack of a clinical trial for adjuvant therapy in gastric cancer, oncologists in our institution adopted an adjuvant approach of carboplatin and paclitaxel followed by concurrent fluoropyrimidine analogue and radiation for treatment of gastric cancer and gastro-esophageal junction adenocarcinoma patients. This study is a retrospective review of our patients who have been treated adjuvantly with this regimen. The primary objective of this study is to assess the safety and feasibility of the paclitaxel/carboplatin chemoradiotherapy regimen in patients with resectable gastric cancer. The secondary objective is to evaluate efficacy.

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Materials and Methods

Patient Identification and Data

After obtaining Wayne State University Institutional Review Board approval, we identified patients with resected gastric cancer who were treated adjuvantly with carboplatin-paclitaxel-based regimens. A chart review was performed. Data collected included the age, race, gender, pathological stage, resection margins, extent of lymph node resection, histopathologic type of the tumor, number of the lymph nodes examined, lymph node status, lymphovascular invasion, treatment administration, radiation port and dose, toxicity from the carboplatin and paclitaxel combination, relapse status, and survival.

Treatment Plan

The treatment plan included adjuvant administration of carboplatin and paclitaxel before and after concurrent chemo-radiation utilizing 5FU. The doses of paclitaxel and carboplatin for the first cycle were 175–200 mg/m^2 and area under the curve (AUC) 5 mg × min /ml, respectively. Paclitaxel infusion preceded the administration of carboplatin. After the initial 2–3 cycles of paclitaxel-carboplatin, patients were given RT with a planned dose of 4,500 cGy delivered at 1.8 Gy/fraction, 5 days/week over a median period of 5 weeks. The typical radiation fields encompassed the gastric remnant, gastric bed, anastomosis and regional lymph nodes using a multiportal technique with customized blocking that included the oblique or lateral fields. Along with RT, patients received a fluoropyrimidine analog, either a continuous infusion of 5FU (200 mg/m^2/day) or oral capecitabine (approximately 1,600 mg/m^2/day administered in twice daily dosing on the days of radiation). After completion of RT, patients received another 2–3 cycles of carboplatin-paclitaxel. Patients were evaluated for toxicity after each cycle, and appropriate dose adjustments were made for hematologic and non-hematologic toxicities. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, Version 2.0. After completion of adjuvant therapy, patients were followed every 3 months by physical examination and every 6 months with imaging studies.

Statistical Methods

Descriptive statistics were used to summarize the patient characteristics and toxicity data. Recurrence-free survival (RFS) was measured from surgery to the date of clinically documented disease recurrence or death from any cause, whichever came first. Surviving patients still recurrence-free as of the date of their last tumor assessment were censored on that date. OS was measured from surgery to the date of death from any cause. Surviving patients were censored as of the last date on which they were known to be still alive. Patients censored for either RFS or OS with censoring dates >6 months prior to the data collection were recorded as lost to follow-up (LFU), but still treated as censored patients in the statistical analyses. Median follow-up time for each time-to-event endpoint (RFS or OS) was computed using only the censored patients for that endpoint to more accurately assess data maturity. Kaplan-Meier (K-M) estimates of the censored RFS and OS distributions were computed. From the K-M analysis, the median and its 90% confidence interval (CI) were derived. Due to the small sample sizes, survival statistics (e.g., median, 1-year rate, etc.) were estimated more conservatively using linear interpolation among successive event times on the K-M curves [18]. RFS and OS were compared by surgical margins status via the log-rank test. Surgical margins status was recorded for each patient. An R0 resection is defined as one in which all margins are histologically free of tumor. An R1 resection is one in which there is microscopic residual disease. An R2 resection is defined as gross residual disease.

Results

Patient Characteristics

Between the years 1999 and 2006, we identified 21 gastric cancer patients who were treated with a carboplatin-paclitaxel-based regimen in the adjuvant setting. Patient characteristics are shown in **table 1**. Of the 21 patients, 4 (19%) had gastro-esophageal

junction tumors and the remaining 17 patients (81%) had gastric cancer. All patients had clinically limited disease (stages 1–3, American Joint Committee on Cancer TNM staging). Sixteen patients (76%) had stage 3 disease, 3 patients (14%) stage 2, and 2 patients (10%) stage 1. Review of the surgical and pathological reports showed that poorly differentiated adenocarcinoma was found in 12 of the 21 patients. Half of the patients had signet ring cell histology. Of the 21 patients, 7 (33%) had positive margins (R1 in 6 patients and R2 resection in 1 patient) and all were clinically staged as stage 3. The remaining 14 had negative margins. 17 patients underwent D1 lymph node dissection and 4 patients had D2 lymph node dissection.

Treatment Outcome

At the time of analysis, follow-up for RFS identified 15 patients with recurrence, 1 patient still recurrence-free, and 5 patients lost to (clinical) follow-up. The median follow-up time of the 6 patients censored for RFS was 12.4 months. Ten patients (67%) of the 15 who had recurrent disease had distant metastases, 2 had loco-regional recurrence, and for 3 patients the site of recurrence could not be determined. The median RFS was 12.3 months (90% CI: 9.7–16.0 months) (**fig. 1**). Patients with negative surgical margins had a median RFS of 12.6 months (90% CI: 12.0–28.7) compared to only 9.1 months (90% CI: 5.0–15.5) for the patients with positive surgical margins. Length of censored RFS was significantly different between these two groups (log-rank test $p = 0.0278$).

Of our 21 patients, 14 had died, 3 were still alive at the time of analysis, and 4 were lost to (survival) follow-up. The median follow-up time of the 7 patients censored for OS was 30.4 months. The median OS was 16.0 months (90% CI: 13.3–28.8 months) (**fig. 2**). Patients with negative surgical margins had a median OS of 28.5 months (90% CI: 13.4–upper limit not estimable) compared to only 12.7 months (90% CI: 10.9–15.4) for the patients with positive surgical margins. Length of censored OS was significantly different between these two groups (log-rank test $p = 0.0060$) (**fig. 3**).

Toxicities

A total of 91 cycles of carboplatin-paclitaxel were administered with a median of 4 cycles per patient (range: 1–6 cycles/patient). Eighteen of the 21 patients received 4 or more cycles of the carboplatin-paclitaxel combination. Only 3 patients received <3 cycles. One of those 3 patients developed a reaction during the first treatment and chemotherapy was discontinued. Of the 21 patients who received this regimen, dose reduction for carboplatin and paclitaxel was performed in 10 patients. The most common cause for dose reduction was hematologic toxicity. 17 patients received concurrent chemo-radiation utilizing capecitabine, and 4 patients utilizing 5FU. Dose reduction for the fluoropyrimidine was needed in 4 patients, one of them was taking 5FU and the other 3 were taking capecitabine. Gastrointestinal side effects of fluoropyrimidine drugs were observed in 8 patients (38%).

Table 2 summarizes the toxicity data. The grade 3 and 4 toxicities were seen in 8 (24%) and 7 (33%) patients, respectively. Hematologic toxicities were the most common. Neutropenia was found in 10 patients (48%), with grade 3 to 4 neutropenia observed in 6 patients (29%). No neutropenic fever was reported. None of the patients received hematopoietic growth factors. Anemia was found in 10 patients (48%) but no grade 3–4 anemia was reported. Thrombocytopenia was found in 4 patients (19%) with only one of

them at grade 4. Non-hematologic toxicities included grade 4 nausea and vomiting in 1 patient, grade 3 nausea in 2 patients, grade 3 diarrhea in 3 patients, and grade 4 fatigue in 2 patients. The total number of patients with grade 3 or 4 gastrointestinal (GI) toxicities (nausea, vomiting or diarrhea) was 6 (28%). Hand-foot syndrome grade 2 was observed in 1 patient who was taking capecitabine. Grade 1 neuropathy was reported in 5 patients. Overall, the therapy was very well tolerated. No treatment-related deaths were reported.

Discussion

Surgical resection of localized gastric cancer is clearly not sufficient as a sole therapy. Significant controversy continues regarding the best approach to patients with resectable gastric cancer with respect to adjuvant vs. neo-adjuvant and chemotherapy vs. chemoradiotherapy. On the basis of the SWOG/INT-0116 trial, adjuvant chemoradiotherapy has become an established standard treatment for gastro-esophageal junction [10]. Despite this improvement in outcome, over 40% of the patients in the chemoradiotherapy arm had disease relapse. Furthermore, the incidence of distant relapse was similar in both treatment arms, suggesting the need for a more systemically active chemotherapy regimen in the adjuvant setting. The incidence of toxicity observed in INT-0116 also concerned grade 3 or higher overall toxicities reported in 73% of cases. The major observed toxicities included GI (grade 3 in 29% and grade 4 in 3%) and hematologic toxicities (grade 3 in 26% and grade 4 in 28%). Factors that could have contributed to the high rate of toxicities included: (1) the use of parallel-opposed anterior and posterior field arrangements in the radiotherapy treatment planning; (2) the use of bolus rather than infusional 5FU; and (3) decreased tolerance of therapy after partial or complete gastrectomy. Therefore, improvement in the outcome of adjuvant therapy is dependent on the use of more active and tolerable chemotherapy regimens.

Since platinum-based chemotherapy is considered the standard of care for advanced-stage gastric cancer, several phase II trials have evaluated the feasibility and safety of these regimens in the adjuvant setting. RTOG-0114 evaluated paclitaxel, cisplatin and 5FU (PCF) or paclitaxel and cisplatin (PC) in the adjuvant setting [19]. The incidence of grade 3 or higher overall, hematologic, or GI toxicity in the PCF arm was 97, 67, and 68%, respectively. The incidence of grade 3 or higher overall, hematologic, or GI toxicity in the PC arm was 73, 40, and 34%, respectively [19]. Leong et al. reported on the use of epirubicin, cisplatin, and infusional 5FU in adjuvant gastric cancer [20]. The incidence of grade 3 or higher overall, hematologic, or GI toxicity in the patients receiving ECF was 45, 22, and 17%, respectively.

The results of our study suggest that carboplatin and paclitaxel before and after chemoradiotherapy can be safely administered in the adjuvant setting. The incidence of grade 3 or higher overall, hematologic, or GI toxicity in the patients receiving carboplatin and paclitaxel was 71, 33, and 28%, respectively. The use of carboplatin instead of cisplatin improved the GI toxicity profile. The increased incidence of hematological toxicities with carboplatin in comparison to cisplatin was mainly due to grade 3 neutropenia. No episodes of febrile neutropenia were reported. Therefore, the observed toxicities compare favorably with previously reported results from INT-0114 and platinum-based regimens. The use of capecitabine instead of infusional 5FU also appears to be feasible and safe. After partial or complete gastrectomy, patients were able to tolerate the oral intake of capecitabine. Hand-foot syndrome was observed in only one patient (5%). Furthermore, the use of capecitabine in this setting eliminates the need for central venous access.

The carboplatin and paclitaxel regimen appears to have moderate activity when used in gastric cancer patients. However, the evaluation of activity of this regimen is limited by the small number of patients and the high-risk features of patients in our series in comparison to the previously published studies. Similar to the SWOG/INT-0116 trial [10], most patients in our study were stage 3 (76%) [11]. However, in contrast to our study, patients with positive R1/R2 margins were not allowed on the SWOG trial. Seven patients (33%) treated with our regimen had positive margins, since this treatment was adopted for all high-risk patients. This fact partially explains the higher chance of recurrence and the worse outcome observed in our patients with a median OS of 16 months. To this point, and as expected, when OS was compared based on surgical margins (fig. 3), patients with negative margins had significantly longer survival. The new median OS of 28.5 months for negative margins patients is comparable to the reported literature in adjuvant gastric cancer [10] taking into account the higher risk profile with our patients as outlined in table 1.

The regimen of carboplatin and paclitaxel before and after concurrent chemo-radiation with capecitabine in the adjuvant setting for resected gastric or gastro-esophageal junction tumors is feasible and safe. The toxicity profile compares favorably with previously reported bolus 5FU or cisplatin-based regimens. Future trials evaluating this regimen in a randomized setting would be needed to evaluate the efficacy.

Table 1. Characteristics of 21 patients

Characteristic	n (%) or median (range)
Age at diagnosis, years	60 (20–78)
Race	
Caucasian	8 (38%)
African-American	7 (33%)
Others	6 (29%)
Gender	
Male	9 (43%)
Female	12 (57%)
Primary tumor site	
Gastric	17 (81%)
Gastroesophageal junction	4 (19%)
Stage at the time of diagnosis	
Stage 1	2 (10%)
Stage 2	3 (14%)
Stage 3	16 (76%)
Lymph nodes examined	11 (4–13)
Histopathologic type	
Intestinal	4
Diffuse/signet ring cell	11
Papillary	2
Not available	4
Histopathologic grade	
Poorly differentiated	12

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Table 2. Adverse reactions in the patients who were evaluable for toxicity (N=21)

Toxicity (worst grade experienced)	Grade 1		Grade 2		Grade 3		Grade 4	
	n*	%	n*	%	n*	%	n*	%
Anemia	5	24	5	24				
Thrombocytopenia	2	10	1	5			1	5
Neutropenia	1	5	3	14	3	14	3	14
Nausea	11	52	8	38	2	10	1	5
Vomiting	7	33	5	24				
Diarrhea	5	24	2	10	3	14		
Weight loss	3	14	2	10				
Neuropathy	5	24						
Fatigue	6	29	2	10			2	10
Hand-foot syndrome			1	5				

* Number of patients whose worst degree of toxicity was at this grade.

Fig. 1. Kaplan-Meier graph of RFS for 21 gastric cancer patients treated with carboplatin and paclitaxel. Tick marks represent censored patients still recurrence-free, and the 90% confidence limits are shown as dashed lines. The median RFS was 12.3 months, with 90% CI 9.7–16.0 months. The 1-year RFS rate was 54%, with 90% CI 0.35–0.73. The 2-year RFS rate was 23%, with 90% CI 0.05–0.41. Two patients were still alive and recurrence-free beyond 2 years, at 30.4 and 63.0 months after surgery.

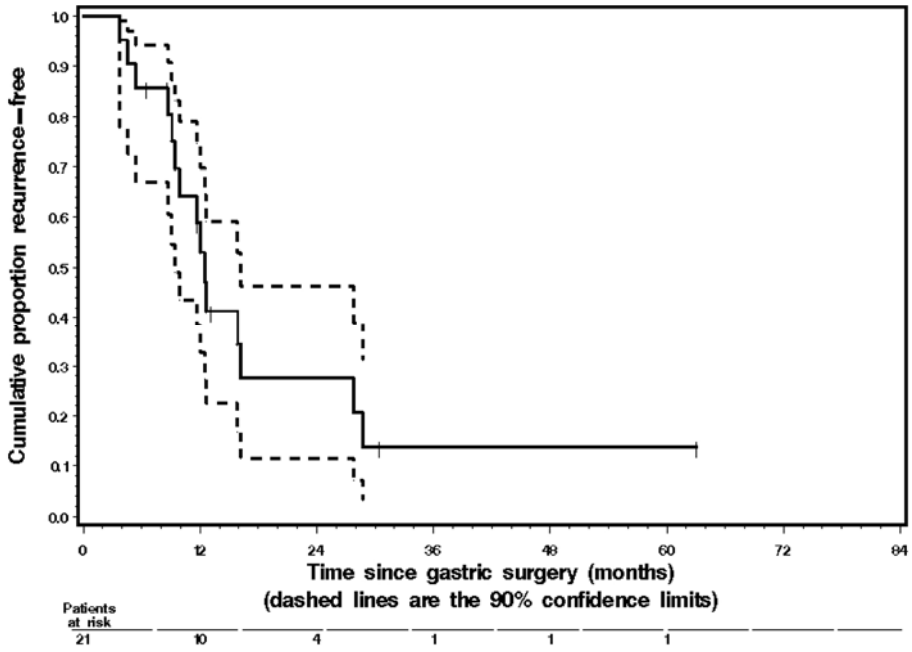


Fig. 2. Kaplan-Meier graph of OS for 21 gastric cancer patients treated with carboplatin and paclitaxel. Tick marks represent censored patients still alive, and the 90% confidence limits are shown as dashed lines. The median OS was 16.0 months, with 90% CI 13.3–28.8 months. The 1-year OS rate was 82%, with 90% CI 0.67–0.96. The 2-year OS rate was 35%, with 90% CI 0.17–0.55. Three patients were still alive beyond 3 years, at 46.8, 47.3, and 75.2 months after surgery.

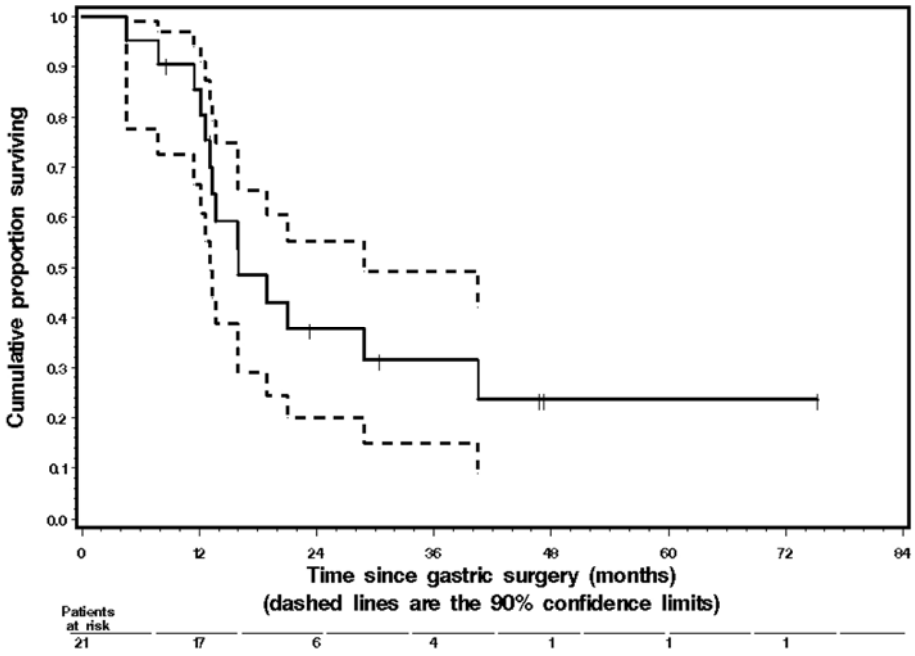
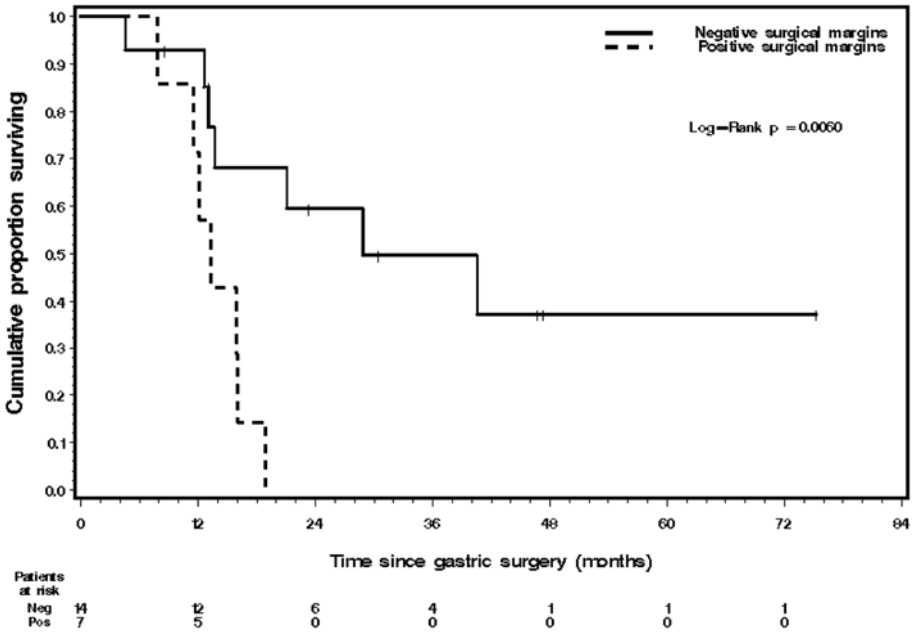


Fig. 3. Kaplan-Meier graph of OS for 14 gastric cancer negative margins patients versus 7 positive margins patients. Tick marks represent censored patients still alive. The median OS was 28.5 months (90% CI: 13.4–upper limit not estimable) for negative margins patients versus 12.7 months (90% CI: 10.9–15.4) for positive margins patients. The 1-year OS rate was 86% (90% CI: 0.70–1.00) for negative margins and 61% (90% CI: 0.30–0.91) for positive margins.



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