Adjuvant Chemoradiation Therapy for Pancreatic Adenocarcinoma: Who Really Benefits?

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Abstract

BACKGROUND—The role of adjuvant chemoradiation therapy (CRT) in pancreatic cancer remains controversial. The primary aim of this study was to determine if CRT improved survival in patients with resected pancreatic cancer in a large, multiinstitutional cohort of patients.

STUDY DESIGN—Patients undergoing resection for pancreatic adenocarcinoma from seven academic medical institutions were included. Exclusion criteria included patients with T4 or M1 disease, R2 resection margin, preoperative therapy, chemotherapy alone, or if adjuvant therapy status was unknown.

RESULTS—There were 747 patients included in the initial evaluation. Primary analysis was performed between patients that had surgery alone (n = 374) and those receiving adjuvant CRT (n

= 299). Median followup time was 12.2 months and 14.5 months for survivors. Median overall survival for patients receiving adjuvant CRT was significantly longer than for those undergoing operation alone (20.0 months versus 14.5 months, p = 0.001). On subset and multivariate analysis, adjuvant CRT demonstrated a significant survival advantage only among patients who had lymph node (LN)-positive disease (hazard ratio 0.477, 95% CI 0.357 to 0.638) and not for LN-negative patients (hazard ratio 0.810, 95% CI 0.556 to 1.181). Disease-free survival in patients with LN-negative disease who received adjuvant CRT was significantly worse than in patients who had surgery alone (14.5 months versus 18.6 months, p = 0.034).

CONCLUSIONS—This large multiinstitutional study emphasizes the importance of analyzing subsets of patients with pancreas adenocarcinoma who have LN metastasis. Benefit of adjuvant CRT is seen only in patients with LN-positive disease, regardless of resection margin status. CRT in patients with LN-negative disease may contribute to reduced disease-free survival.

There will be an estimated 37,170 new cases of pancreas cancer, with nearly as many deaths in the US in 2008. Although this accounts for only 2% of all newly diagnosed malignancies, pancreas cancer is the fourth leading cause of cancer death.[1] Most patients with pancreatic cancer present with advanced disease at the time of diagnosis, and only 10% to 15% of patients are candidates for potentially curative resection.[2–4] The rationale for adjuvant therapy is based on the high incidence of tumor recurrence both locally and at distant sites, presumably because of the presence of micrometastatic disease after surgical resection.

The Gastrointestinal Study Group (GITSG) first studied the role of adjuvant chemoradiation therapy (CRT) for pancreas cancer.[5] The study was closed early because of the slow accrual of only 43 patients over 8 years, and the interim analysis showed a statistically significant benefit for the adjuvant therapy arm. Based on this, the GITSG trial established CRT as a viable option after pancreatic cancer resection within the US, but less so elsewhere. Since the GITSG trial, other trials have suggested that adjuvant chemotherapy alone may be beneficial in the adjuvant setting for pancreas cancer,[6–8] but no randomized trial has been able to convincingly support the role of radiation therapy, and this issue sparks considerable debate throughout the world.

Multiple reasons exist as to why these trials have failed to obtain a greater understanding of the role of CRT in pancreas cancer. Limitations of these randomized trials include small numbers of patients in the treatment arms,[5] poor compliance with the treatment regimens,[5,7] variable pathologic criteria for study entry including combining patients with pancreatic adenocarcinoma with other periampullary malignancies,[6,7] and flawed randomization schemes.[7] In addition, patients with positive (R1) and negative (R0) margins of resection and positive and negative lymph nodes (LN) are assessed as a uniform group. So patient populations vary considerably among these trials and comparative analysis becomes impossible.

Recent large single-institution studies[9,10] and data from the Surveillance, Epidemiology, and End Results (SEER) database,[11] however, have suggested a significant benefit for adjuvant CRT after surgery for pancreas cancer. These studies, although analyzing large numbers of patients, are limited by institutional biases and by analysis of patients treated over many

years, during which time our diagnostic capabilities, operative morbidity and mortality, and techniques for delivery of radiation and chemotherapy have improved substantially.[4,12]

The primary aim of this study was to determine if adjuvant CRT improves survival in patients with resected pancreatic cancer in a large, multiinstitutional cohort of patients. This analysis dilutes the biases of individual institutions and allows for independent analysis of subsets of patients. We sought to determine if adjuvant CRT benefits only a subset of patients who are LN positive or those with R1 resection margins.

METHODS

This is an institutional review board-approved, multiinstitutional review of prospectively maintained databases from seven academic medical centers of the Central Pancreas Consortium. Patients with pancreas adenocarcinoma who underwent surgical resection from January 2000 to December 2006 from five centers and from January 1996 to December 2006 from two centers were analyzed. Patients were excluded if they were found to have T4 or M1 disease or R2 resection margins at the time of operation, if they received preoperative therapy, or if their adjuvant therapy status was unknown. A total of 747 patients were included in the initial evaluation. Of these, 374 patients had surgery alone, 299 patients received adjuvant CRT, and 74 patients received adjuvant chemotherapy alone. Adjuvant radiation therapy alone was identified as a treatment regimen in six patients; these patients were included in the CRT group. Primary analysis for this study was performed between patients who had surgery alone (n = 374) and those receiving adjuvant CRT (n = 299). Patients receiving chemotherapy alone were excluded from the primary analysis.

All pathology and operative reports were reviewed to determine the extent of resection. Resection margins were considered positive (R1) if the carcinoma was close (within 1 mm) or present at the final pancreatic neck, uncinate process, bile duct, or duodenal or retroperitoneal soft tissue margin, consistent with American Joint Committee on Cancer (AJCC) definitions.[13] Perineural and lymphovascular invasion were not recorded routinely, so were not included in the final analysis. Tumor grade was consistently reported and included. Because of the update to the American Joint Committee on Cancer staging manual in 2002, staging was inconsistent throughout the study period, so was not evaluated.

All patients underwent surgical resection at the centers involved in this study. Being tertiary referral centers, many patients received their adjuvant therapy at outside hospitals, so specific adjuvant therapy regimens were not able to be determined for all patients, but the majority of patients received 5-fluorouracil (5-FU)-based chemotherapy with conformal radiation therapy. Only patients who had verification of their therapy were included the study.

Statistical analysis

The Wilcoxon test and the Fisher's exact test were used as appropriate to test for differences in patient characteristics between the two treatment groups. Overall survival (OS) was defined as the time from operation to death for any reason. For OS, patients alive at last contact were censored at their last followup time. Disease-free survival (DFS) was defined

as the time of operation to time of first recurrence or death for any reason. Patients alive and recurrence-free were censored at last followup. Survival distributions were estimated using the method of Kaplan and Meier. The proportions of individuals surviving up to 2 and 5 years were estimated, and standard errors for 95% confidence intervals were estimated using Greenwood's formula. Survival comparisons by treatment arm were performed using the log rank test. The impact of multiple prognostic variables on OS and DFS were assessed using the Cox (proportional hazards) regression model stratifying by institution. Comparisons with p values < 0.05 were considered statistically significant.

RESULTS

Median followup time for all patients was 12.2 months and 14.5 months for survivors. Demographic data for patients are shown in Table 1, including the number of patients in each treatment arm by institution. The mean age for the entire cohort of patients was 65.0 ±11.3 years. Patients receiving adjuvant CRT were younger than those undergoing surgery alone (CRT, 63.0 ± 10.3 years versus surgery, 67.0 ± 11.7 years, $p < 0.001$). There was an equal distribution of men and women. Tumors were larger in patients who received CRT (3.03 ± 1.36 cm versus 3.28 ± 1.45 cm, $p = 0.048$). Other tumor characteristics such as grade and location were similar between the two groups. Patients in the CRT arm had a greater incidence of LN-positive disease (CRT, 65% versus surgery, 56%, $p = 0.027$) and R1 resections (CRT, 33% versus surgery, 20%, $p = 0.00014$). The complication rates were similar between both groups. Length of stay was significantly longer in patients who underwent surgery alone compared with those who received adjuvant CRT (CRT, 9 ± 6.0 days versus surgery, 10 ± 9.4 days, $p < 0.001$).

Overall survival

Table 2 shows the median OS for the entire group of patients treated with adjuvant CRT or surgery alone and patients stratified by resection margin status (R0 versus R1) and by LN status (LN positive versus LN negative). When comparing the entire cohort of patients by treatment arm, OS was significantly improved for patients receiving CRT after surgery compared with those undergoing surgery alone (20 months versus 14.5 months, $p = 0.001$). Comparison of the subset of patients with R0 versus R1 resection margin and LN-positive or LN-negative disease allows for analysis of which patients may truly benefit with adjuvant CRT. Patients receiving adjuvant CRT showed significantly improved OS compared with patients undergoing surgery alone, regardless of margin status. Patients who had either R0 (CRT, 23.4 months versus surgery, 15.9 months, $p = 0.001$) or R1 (CRT, 15.9 months versus surgery, 8.9 months, $p = 0.003$) resection margins benefitted significantly with adjuvant CRT. On the other hand, there were no statistically significant differences in OS between patients with LN-negative disease who received adjuvant CRT and those who underwent operation alone (22.9 months versus 24.2 months, respectively, $p = 0.774$); patients with LN-positive disease showed a significant improvement in OS with adjuvant CRT compared with those undergoing operation alone (19.4 months versus 10.4 months, $p < 0.001$).

Figure 1 shows the Kaplan-Meier survival curves for OS by treatment group. Two and 5-year OS rates for patients receiving adjuvant CRT were 43.2% (95% CI, 37.2% to 50.2%)

and 15.6% (95% CI, 10.0% to 24.4%), respectively, and for those undergoing surgery alone were 33.5% (95% CI, 28.5% to 39.5%) and 19.0% (95% CI, 14.3% to 25.4%), respectively. Figure 2 shows the overall survival curves for treatment groups stratified by resection margin and LN status.

To assess the impact of resection margin and LN status together, we stratified patients into the following sub-groups: R0, LN −; R0, LN + ; R1, LN−; and R1, LN+ (Table 2). This analysis showed that LN-negative patients had no statistically significant benefit with adjuvant CRT compared with those undergoing surgery alone, regardless of their resection margin status. Lymph node-negative patients with either R0 (CRT, 29.6 months versus surgery, 24.4 months, $p = 0.441$) or R1 (CRT, 15.6 months versus surgery, 15.4 months, $p = 0.761$) resection margins had similar OS in both treatment arms. On the other hand, LN-positive patients showed a statistically significant benefit to receiving adjuvant CRT compared with patients undergoing surgery alone with either R0 (CRT, 23.3 months versus surgery, 10.8 months, $p < 0.001$) or R1 (CRT, 14.4 months versus surgery, 8.5 months, $p = 0.002$) resection margins.

To adjust for competing risk factors, we performed a multivariate analysis to assess whether adjuvant CRT would remain a predictor of OS among LN-positive patients (Table 3). After adjusting for age, gender, tumor location, size, grade, blood loss, transfusions, surgical complications, and margin and node status as an interaction term, adjuvant CRT still demonstrated a significant survival advantage compared with surgery alone among patients who were LN positive (hazard ratio 0.477, 95% CI 0.357 to 0.638). There was insufficient evidence to suggest that adjuvant CRT provided a survival advantage compared with surgery alone among patients who were LN negative (hazard ratio 0.810, 95% CI 0.556 to 1.181). Other prognostic variables for OS included age, tumor size, advanced tumor grade, increased blood loss, and R1 resection margin. Variables that did not affect OS included tumor location, need for blood transfusion, vein resection, or complications within 30 days. CRT, as seen in Table 2, significantly improved median OS in R0 patients by 7.5 months ($p = 0.001$) and by 6.1 months in R1 patients ($p = 0.003$). This differential treatment (interaction) effect with resection status of 1.4 months was tested in a separate regression model and was not statistically significant ($p = 0.980$).

Disease-free survival

There was no significant difference seen in DFS between patients receiving adjuvant CRT compared with those undergoing surgery alone when assessing the entire cohort of patients (CRT, 12.8 months versus surgery, 10.8 months, $p = 0.552$), (Table 2). No differences in DFS were seen with either R0 or R1 resection margin status by treatment arm (R0 CRT, 15.0 months versus surgery, 12.0 months, $p = 0.429$; R1 CRT, 10.1 months versus surgery, 6.5 months, $p = 0.156$). Interestingly, patients with LN-negative disease showed a significantly worse DFS with adjuvant CRT compared with those undergoing surgery alone (CRT, 14.5 months versus surgery, 18.6 months, $p = 0.034$). Patients with LN-positive disease, however, showed a significantly improved DFS with adjuvant CRT (CRT, 12.3 months versus surgery, 7.2 months, $p < 0.001$).

When assessing the impact of resection margin and LN status together, no differences in DFS were seen in patients with LN-negative disease regardless of resection margin status between the two treatment arms (Table 2). A trend toward worse DFS was seen in R0 and LN-negative patients who received adjuvant CRT, but this did not achieve statistical significance (CRT, 15.0 months versus surgery, 18.8 months, p = 0.072). Patients with LN-positive disease who had an R0 resection showed a significant improvement in DFS with adjuvant CRT (CRT, 15.4 months versus surgery, 9.0 months, p = 0.001), however, LN-positive patients with R1 resections showed no difference in DFS between the two treatment arms.

Kaplan-Meier survival curves for DFS by treatment group are shown in Figure 3. Two- and 5-year DFS rates for patients receiving adjuvant CRT were 25.2% (95% CI, 20.3% to 31.2%) and 10.3% (95% CI, 6.6% to 16.0%), respectively, and for those undergoing surgery alone were 28.7% (95% CI, 24.1% to 34.3%) and 15.9% (95% CI, 11.7% to 21.6%), respectively. Figure 4 shows the survival curves for treatment groups stratified by resection margin and LN status.

Although there was no difference in DFS between patients receiving adjuvant CRT and those undergoing surgery alone by log rank analysis, on multivariate analysis, after adjusting for the variables listed in Table 4, and once again including an interaction term for lymph node status, adjuvant CRT demonstrated a significant DFS advantage compared with surgery alone among patients with positive LNs (hazard ratio 0.566, 95% CI 0.437 to 0.733). There was no evidence to suggest adjuvant CRT provided a survival advantage compared with surgery alone among patients who were LN negative (hazard ratio 1.170, 95% CI 0.832 to 1.645). Other prognostic variables for DFS were similar to those for OS and included age, tumor size, advanced tumor grade, increased blood loss, and R1 resection margin. Variables that did not affect DFS included tumor location, need for blood transfusion, vein resection, or complications within 30 days. CRT, as can be seen in Table 2, improved median DFS by 3 months and 3.6 months for R0 (p = 0.429) and R1 patients (p = 0.156), respectively. This differential treatment (interaction) effect with resection status of 0.6 months was tested in a separate regression model and was not statistically significant (p = 0.600).

DISCUSSION

This large multiinstitutional study emphasizes the importance of analyzing subsets of patients with pancreas adenocarcinoma who have LN metastasis and R1 resection margins. This study suggests that patients receiving adjuvant CRT after surgical resection for pancreatic adenocarcinoma achieve a significant OS benefit as compared with those undergoing surgery alone. Subset analysis, however, revealed that the benefit of adjuvant CRT is seen only in patients with LN-positive disease. Although patients with R0 or R1 resection margin showed a significant survival advantage with adjuvant CRT, this benefit was not seen in patients with LN-negative disease and was seen only in LN-positive patients. Similarly, for DFS, comparison of the entire group of patients revealed no significant differences between patients receiving adjuvant CRT compared with those undergoing surgery alone, but on subset analysis, a DFS advantage is seen only in patients who have LN-positive disease and are receiving adjuvant CRT. In addition, the DFS in

patients with LN-negative disease who received adjuvant CRT was actually significantly worse than that in patients who had surgery alone.

Significant risk factors for recurrence after surgical resection for pancreas adenocarcinoma include LN-positive disease and involved surgical margins.[7,8,10] Outcomes for these patients are significantly worse than those for patients with negative resection margins and LN-negative disease. This finding was confirmed in our study. Clinical trials of adjuvant therapy for pancreas cancer include 17% to 45% of patients who had an R1 resection and 45% to 80% of patients who have LN-positive disease.

Other pathologic criteria for study entry into clinical trials have also varied significantly. The GITSG trial excluded LN-negative patients,[5] the European Organization for Research and Treatment of Cancer (EORTC) trial excluded patients with T3 or T4 tumors,[6] and the Charité Onkologie (CONKO)-001 trial excluded patients with postoperative CA19–9 or carcinoembryonic antigen values greater than 2.5 times normal.[8] The comparison of these heterogeneous patient populations limits the evaluation of the role of adjuvant CRT in pancreas cancer.

Results from the several published prospective and retrospective series evaluating the role of adjuvant CRT are shown in Table 5. In the US, adjuvant CRT has been considered to be the standard of care for more than 20 years by many clinicians. The rationale for this, however, lies in the findings of the randomized GITSG study initially published in 1985.[5] This trial has been extensively criticized because of its small numbers, slow accrual, and use of outdated split course radiation, and should, at this time, be considered only in historical context.

The only other prospective study in the US that compared adjuvant CRT with surgical resection alone for pancreas adenocarcinoma is a nonrandomized study from Johns Hopkins.[14] Patients were allowed to choose between standard therapy (similar to that used in the GITSG study), intensified therapy (intensified radiation therapy to pancreatic bed and liver with infusional 5-FU), or observation alone. The majority of patients chose standard therapy and those that received adjuvant CRT showed an improvement in OS (CRT, 19.5 months versus surgery, 13.5 months, p = 0.003), with no difference seen between the two CRT arms.

Data from European trials show a significant role for adjuvant systemic chemotherapy, but fail to support a role for adjuvant CRT in pancreatic adenocarcinoma. The randomized EORTC trial, consisting of both pancreatic cancers and periampullary tumors, also failed to show a significant benefit with the use of CRT[6] Even when analyzed for patients with pancreatic adenocarcinoma alone, there was no benefit with the use of CRT.

In the European Study Group for Pancreatic Cancer (ESPAC-1) trial,[7] patients in the 2×2 factorial design who received adjuvant CRT actually fared significantly worse than those undergoing surgery alone. In contrast, however, those who received adjuvant systemic chemotherapy had an increased OS compared with those who underwent surgery alone. When both the 2×2 factorial arm and single-randomization arms were analyzed for prognostic factors, the benefit of chemotherapy appeared most pronounced in patients with

well-differentiated tumors, LN-positive disease, and margin-negative resection. The detrimental effects of CRT, meanwhile, appeared to be most pronounced in patients with moderately differentiated tumors, LN-positive disease, and negative resection margins. Although this study has led to the virtual abandonment of adjuvant CRT in Europe, it has been widely criticized in the US because of its complicated design, the lack of statistical power in the 2×2 design, and the lack of radiation quality controls.

Recently, large retrospective series from Johns Hopkins and Mayo Clinic have suggested that use of adjuvant CRT significantly improves OS compared with that in patients undergoing surgery alone.[9,10] In the study from Johns Hopkins, analysis of 616 patients showed that the benefit of CRT was independent of several risk factors including tumor size, grade, margin, and nodal status. Similar to results of this study, adjuvant CRT improved survival for both margin-negative and margin-positive patients. In addition, LN-positive patients appeared to have a significant benefit with adjuvant CRT, and LN-negative patients did not. But by multivariate analysis, the interaction between nodal status and treatment was not significant.

The recently reported Mayo Clinic experience of 472 patients who underwent R0 resection also showed a significant survival benefit with the use of adjuvant CRT. This benefit was present for both LN-positive and LN-negative disease. Although both these trials support the findings of a benefit of adjuvant CRT, they were both nonrandomized single-institution studies.

In this study, the presence of involved LNs was 60%, consistent with several other randomized and nonrandomized series shown in Table 5. Also consistent with other published series, the presence of positive LNs was associated with decreased survival. The survival benefit of adjuvant CRT was seen only in LN-patients and not in LN-negative patients and was consistent with the findings of John Hopkins study. In the Mayo Clinic study, which evaluated only R0 resected patients, adjuvant CRT led to an improvement in survival in both LN-negative and LN-positive patients. However the randomized ESPAC-1 trial adjuvant CRT was actually harmful in both LN-positive and LN-negative patients. The decrease in DFS with adjuvant CRT for LN-negative patients seen in our study is an intriguing finding and similar to the findings of the ESPAC-1 trial suggesting that these patients may actually be harmed or certainly not helped with the use of adjuvant CRT.

The incidence of positive microscopic margins (R1) was 26% in this study. An R1 resection margin was independently associated with worse OS and DFS, consistent with the findings in several other studies.[7,8,10] Although the use of adjuvant CRT improved OS in patients with R0 and R1 margins in this study, this benefit was seen only in patients with LN-positive disease. In the study from Johns Hopkins, the use of adjuvant CRT also showed a survival advantage in patients with both positive and negative resection margins independent of nodal status.

Despite the maturation of a number of randomized trials, little improvement in overall survival or understanding of the appropriate adjuvant therapy in pancreas cancer have materialized. This lack of progress is not simply the result of ineffective systemic therapies,

but in part, the result of poor trial design and calls for a more disciplined approach to designing future trials.[15,16] Other critical factors necessary to improve the quality of data obtained from future studies of adjuvant therapy include a systematic approach to the selection of patients for surgery with the use of high quality pretreatment imaging and defined radiographic criteria for resectability,[17,18] and the use of a meticulous and reproducible system for pathologic evaluation of resection margins.[18] A recent consensus conference sponsored by the Society of Surgical Oncology and the American Hepato-Pancreatico-Biliary Association addressed these important issues and this article is forthcoming. Future trials must also carefully define inclusion criteria and ensure better quality control of treatment delivery, including standardized surgical technique, especially for dissection along the superior mesenteric artery, where the majority of positive margin resections occur.

This multiinstitutional study helps to overcome many of the limitations associated with studies exploring the role of adjuvant CRT described earlier. It limits institutional biases and evaluates large numbers of patients who had their surgical resection at experienced, high-volume centers that treat pancreas cancer using a multidisciplinary approach. It is, however, limited by its inherent retrospective approach. Many of the quality measures discussed earlier could not be evaluated prospectively and could not be confirmed, particularly for the adjuvant treatments, because many patients received their treatment at facilities other than the primary institution where the surgical resection was performed.

Although no randomized trial has demonstrated the benefit of adjuvant CRT in resected pancreas cancer, substantial data exist in a large number of patients to suggest that it may be beneficial in certain high-risk subsets of patients (R1 resection margin and/or LN-positive disease) and does not exclude the possibility of a therapeutic contribution of this treatment strategy. Our results suggest that this benefit is limited to patients with LN-positive disease. Data also exist from our study and that of the ESPAC-1 trial to suggest that in some patients, particularly LN-negative patients, adjuvant CRT may actually be harmful. These data emphasize the importance of determining which subsets of patients truly benefit from this therapy and are not harmed by the morbidity of ineffective therapy.

Future studies will need to continue to assess the benefits of adjuvant chemotherapy and CRT and should include stratification schemes to investigate the effects of adjuvant therapy depending on resection margin status and LN status. Optimal staging, standardization and quality control of surgical technique, pathologic evaluation and treatment delivery will also need to be key components of trial design. The design of these trials should take into account the lessons learned from previous trials so that data generated are not flawed by the same limitations.

Abbreviations and Acronyms

CRT   chemoradiation therapy

DFS   disease-free survival

ESPAC   European Study Group for Pancreatic Cancer

| **GITSG** | Gastrointestinal Study Group |
| **LN** | lymph node |
| **OS** | overall survival |

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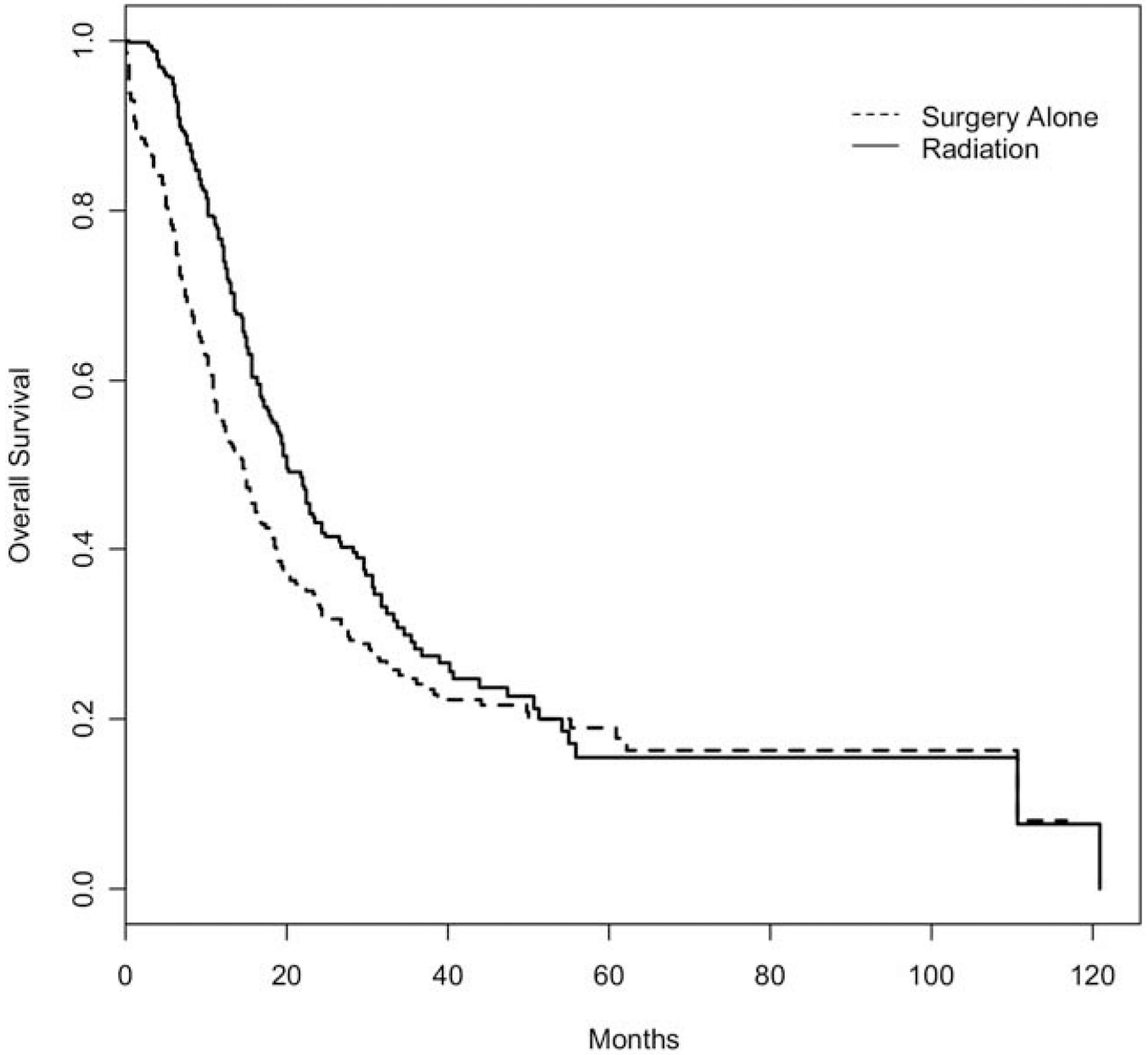
Figure 1.
Kaplan-Meier survival curves for overall survival by treatment group. Two and 5-year overall survivals for patients receiving adjuvant chemoradiation therapy (n = 299) were 43.2% (95% CI, 37.2% to 50.2%) and 15.6% (95% CI, 10.0% to 24.4%), respectively, and for those undergoing surgery alone (n = 374) were 33.5% (95% CI, 28.5% to 39.5%) and 19.0% (95% CI, 14.3% to 25.4%), respectively. Overall survival with chemoradiation therapy versus surgery, p = 0.001 by log rank analysis.
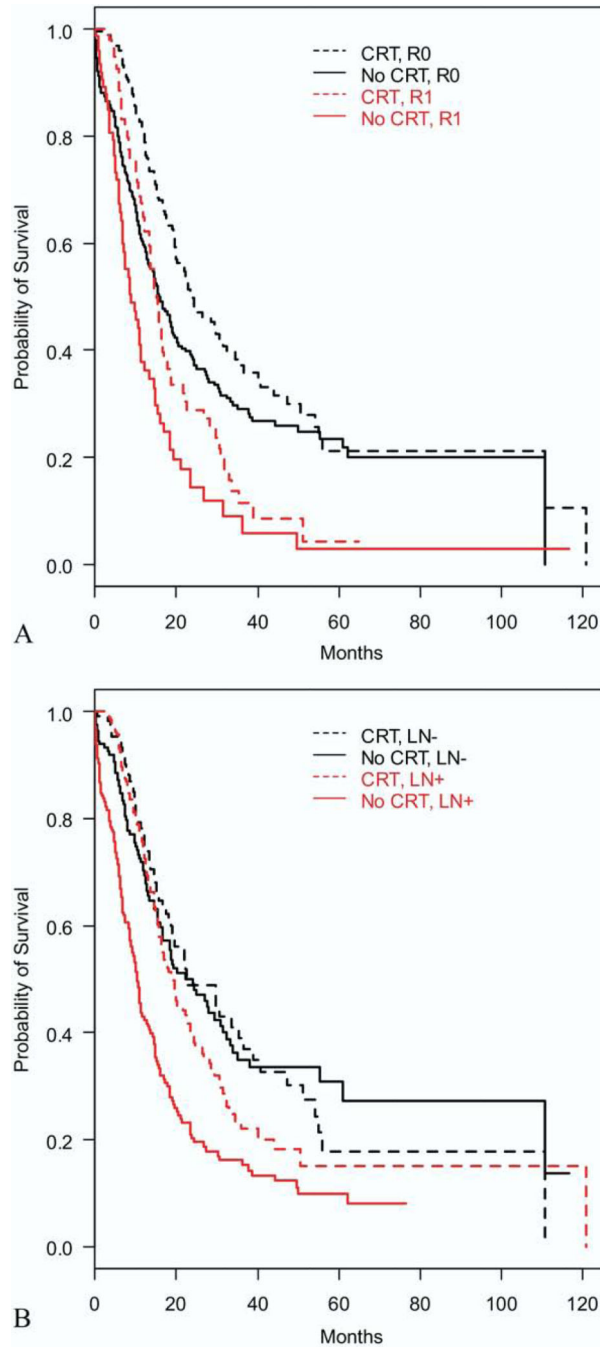
Figure 2.
Kaplan-Meier survival curves for overall survival for treatment groups stratified by resection margin and lymph node (LN) status. (A) Patients with either R0 or R1 resection margin benefitted significantly from adjuvant chemoradiation therapy (CRT) compared with those undergoing surgery alone (R0 CRT [n = 200] versus R0 surgery [n = 298], p = 0.001; R1 CRT [n = 99] versus R1 surgery [n = 76], p = 0.003). (B) Only patients with LN-positive disease benefitted from adjuvant CRT compared with patients undergoing surgery alone; LN-negative patients showed no benefit with adjuvant CRT (LN+ CRT [n = 193] versus LN

+ surgery [n = 208], p < 0.001; LN– CRT [n = 106] versus LN surgery [n = 164], p = 0.774).

Figure 3.
Kaplan-Meier survival curve for disease-free survival by treatment group. Two- and 5-year disease-free survivals for patients receiving adjuvant CRT (n = 299) were 25.2% (95% CI, 20.3% to 31.2%) and 10.3% (95% CI, 6.6% to 16.0%), respectively, and for those undergoing surgery alone (n = 374) were 28.7% (95% CI, 24.1% to 34.3%) and 15.9% (95% CI, 11.7% to 21.6%), respectively. Disease-free survival with chemoradiation therapy versus surgery, p = 0.552 by log rank analysis.
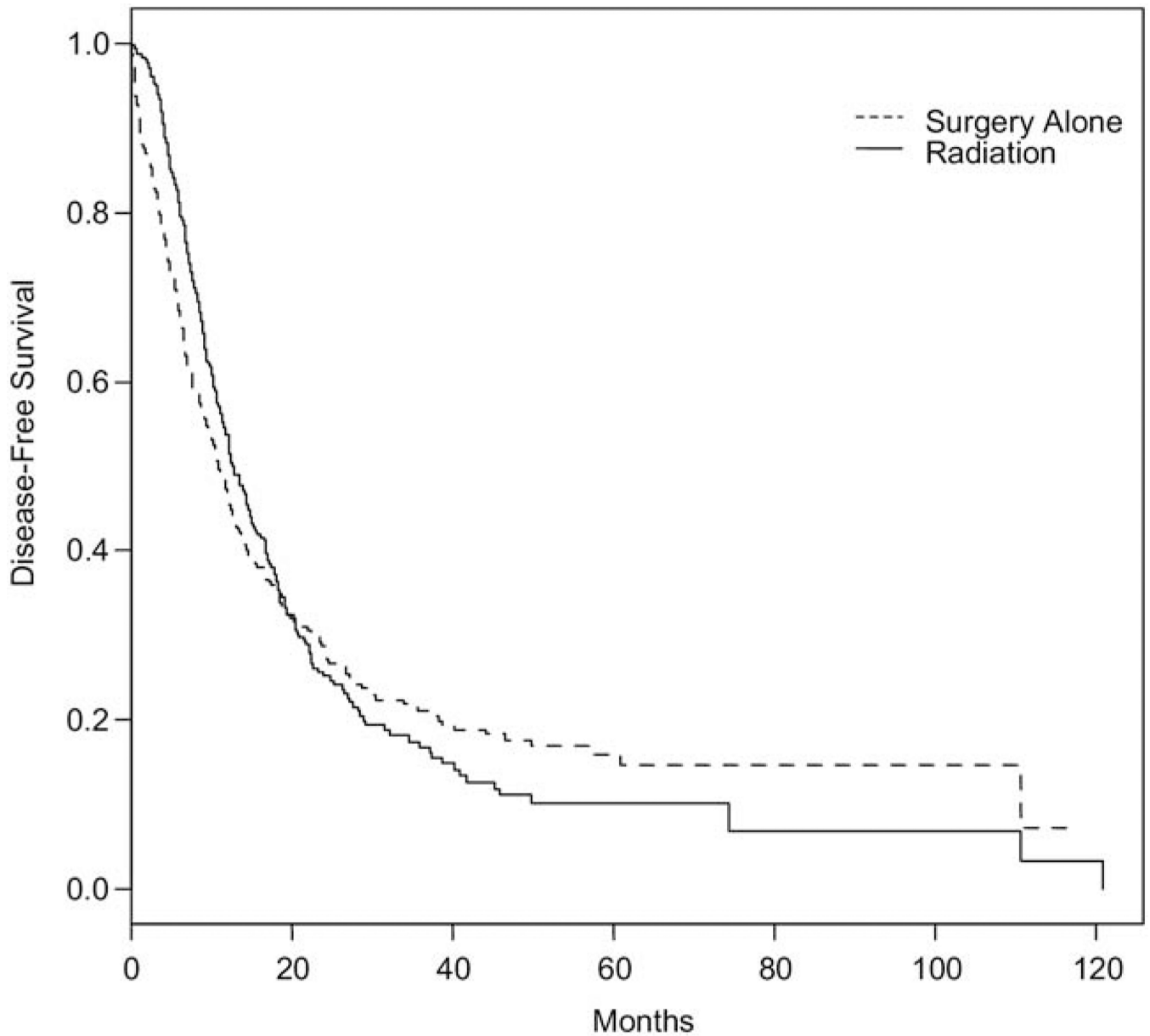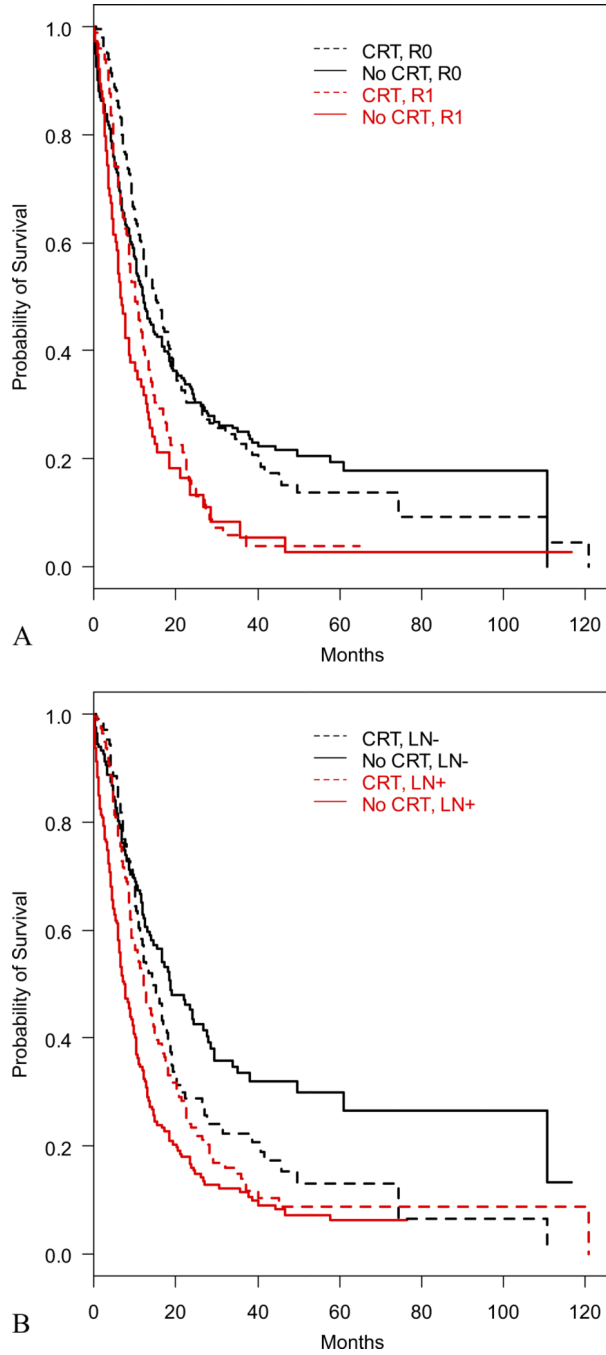
Figure 4.
Kaplan-Meier survival curves for disease-free survival for treatment groups stratified by resection margin and lymph node (LN) status. (A) Patients with either R0 or R1 resection margin showed no differences in disease-free survival with adjuvant chemoradiation therapy (CRT) compared with those undergoing surgery alone (R0 CRT [n = 200] versus R0 surgery [n = 298]), p = 0.429; R1 CRT [n = 99] versus R1 surgery [n = 76], p = 0.156. (B) Patients with LN-negative disease who received adjuvant CRT had significantly worse disease-free survival compared with patients undergoing surgery alone (LN− CRT [n = 106] versus LN−

surgery [n = 164], p = 0.034). For LN-positive patients, a significant benefit was seen with adjuvant CRT compared with patients undergoing surgery alone (LN+ CRT [n = 193] versus LN+ surgery [n = 208], p < 0.001).

Table 1

Demographics

Variable	Operation alone (n = 374)	CRT (n = 299)	p Value
Age at operation, y[*]	67 ± 11.7	63 ± 10.3	<0.001
Male gender, n (%)	211 (56)	160 (54)	0.586
Institution, n (%)			
1	12 (3)	20 (7)	
2	80 (21)	60 (20)	
3	103 (27)	75 (25)	
4	106 (28)	22 (7)	
5	13 (3)	13 (4)	
6	42 (11)	37 (12)	
7	22 (6)	72 (24)	
Tumor size, cm[*]	3.03 ± 1.36	3.28 ± 1.45	0.048
Tumor grade, n (%)			
1	32 (9)	27 (9)	0.476
2	223 (59)	163 (55)	
3	108 (29)	100 (34)	
4	13 (3)	7 (2)	
Location of tumor, n (%)			
Head	352 (93)	269 (90)	0.135
Body	6 (2)	12 (4)	
Tail	20 (5)	18 (6)	
Vein resection, yes, n (%)	45 (12)	45 (15)	0.255
Margin, positive, n (%)	76 (20)	99 (33)	<0.001
Lymph nodes, positive, n (%)	210 (56)	193 (65)	0.027
Lymph nodes resected, n (range)	8.5 (0–58)	10 (0–41)	0.280
Blood loss, mL[*]	797 ± 826	832 ± 834	0.405
Transfusions, yes, n (%)	105 (28)	88 (30)	0.668
Complications, yes, n (%)	132 (35)	101 (34)	0.807
Length of stay, d[*]	10 ± 9.4	9 ± 6.0	<0.001

[*] Mean ± SD.

CRT, chemoradiation therapy.

Table 2

Overall and Disease-Free Survival

Patients	Treatment	n	Overall survival, mo	95% CI	p Value	Disease-free survival, mo	95% CI	p Value
All	CRT	299	20.0	18.0–24.3	0.001	12.8	11.2–15.0	0.552
	Surgery	374	14.5	12.0–16.5		10.8	9.3–12.6	
R0	CRT	200	23.4	20.0–32.3	0.001	15.0	12.3–18.2	0.429
	Surgery	298	15.9	13.4–19.3		12.0	10.4–14.6	
R1	CRT	99	15.0	13.4–17.8	0.003	10.1	8.5–13.4	0.156
	Surgery	76	8.9	6.8–13.4		6.5	5.4–10.2	
LN –	CRT	106	22.9	19.1–39.0	0.774	14.5	11.6–18.4	0.034
	Surgery	164	24.2	16.7–32.4		18.6	14.5–27.9	
LN +	CRT	193	19.4	16.3–23.3	<0.001	12.3	10.1–14.4	0.001
	Surgery	208	10.4	8.9–12.7		7.2	6.3–9.4	
R0, LN –	CRT	79	29.6	19.5–55.1	0.441	15.0	10.8–19.1	0.072
	Surgery	147	24.4	18.2–33.3		18.8	16.5–27.9	
R0, LN +	CRT	121	23.3	19.6–31.6	<0.001	15.4	12.3–19.4	0.001
	Surgery	150	10.8	9.6–15.0		9.0	6.4–10.4	
R1, LN –	CRT	27	15.6	12.1–39.0	0.761	13.4	10.6–22.2	0.819
	Surgery	17	15.4	7.4–inf		11.6	5.4–inf	
R1, LN +	CRT	72	14.4	13.5–17.0	0.002	8.7	6.6–11.7	0.131
	Surgery	58	8.5	6.6–11.2		6.5	4.6–8.5	

CRT, chemoradiation therapy; inf, infinity; LN, lymph node.

Table 3

Cox Proportional Hazards Model for Overall Survival and Radiation

Variable	Hazard	95% CI	p Value
CRT versus operation, LN negative	0.810	0.556–1.181	0.270
CRT versus operation, LN positive[*]	0.477	0.357–0.638	<0.0001
Positive lymph nodes, yes/no	1.765	1.313–2.372	0.0002
Age at operation, y	1.012	1.002–1.023	0.021
Gender, versus female	1.028	0.827–1.278	0.800
Tumor size, cm	1.103	1.015–1.199	0.021
Tumor grade 2 versus 1	1.912	1.217–3.002	0.005
Tumor grade 3 versus 1	2.720	1.691–4.376	<0.0001
Tumor location body versus head	1.064	0.419–2.703	0.900
Tumor location tail versus head	1.078	0.647–1.798	0.770
Blood loss per 100U change	1.018	1.004–1.031	0.010
Transfusion versus none	1.189	0.916–1.542	0.190
Vein resection versus none	0.924	0.663–1.288	0.640
Complications in 30 d	1.169	0.911–1.499	0.220
Lymph nodes resected	0.995	0.977–1.012	0.540
Margin, positive versus negative	1.510	1.192–1.913	<0.001

[*] A single model with an interaction term between LN status and treatment generated the estimates in this table, and provided estimates of the treatment effect within LN groups. Although not shown in this table, this term had a hazard of 0.589, with a 95% CI of 0.378 to 0.916 and a p value of 0.0190. CRT, chemoradiation therapy; LN, lymph node.

Table 4

Cox Proportional Hazards Model for Disease-Free Survival and Radiation

Variable	Hazard	95% CI	p Value
CRT versus operation, LN negative	1.170	0.832–1.645	0.370
CRT versus operation, LN positive[*]	0.566	0.437–0.733	<0.0001
Positive lymph nodes, yes/no	1.971	1.491–2.605	<0.0001
Age at operation, y	1.011	1.001–1.020	0.028
Gender, versus female	0.992	0.815–1.208	0.940
Tumor size, cm	1.083	1.008–1.163	0.030
Tumor grade 2 versus 1	1.915	1.291–2.842	0.001
Tumor grade 3 versus 1	2.560	1.681–3.901	<0.0001
Tumor location body versus head	1.534	0.807–2.918	0.190
Tumor location tail versus head	1.104	0.715–1.705	0.650
Blood loss per 100U change	1.031	1.016–1.047	0.0001
Transfusion versus none	1.022	0.802–1.302	0.860
Vein resection versus none	1.083	0.806–1.456	0.600
Complications in 30 d	1.167	0.934–1.459	0.170
Lymph nodes resected	0.997	0.982–1.013	0.740
Margin, positive versus negative	1.437	1.156–1.787	0.001

[*] A single model with an interaction term between LN status and treatment generated the estimates in this table and provided estimates of the treatment effect within LN groups. While not shown in the table above, this term had a hazard of 0.484, with a 95% CI of 0.324 to 0.724 and a p value of 0.0004. CRT, chemoradiation therapy; LN, lymph node.

Table 5

Selected Major Prospective and Retrospective Studies of Adjuvant Therapy for Pancreatic Adenocarcinoma

Study, y	n Obs	n Adj	Adjuvant regimen	All patients R1, %	All patients LN+, %	All pts Obs	All pts Adj	R0 Obs	R0 Adj	R1 Obs	R1 Adj	LN− Obs	LN− Adj	LN+ Obs	LN+ Adj
GITSG, 1985[5]	22	21	5-FU (500 mg/m² bolus) + 40 Gy Split course XRT	0	0	11	20*	—	—	—	—	—	—	—	—
EORTC, 1999[6]	108	110	5-FU (25 mg/kg CI) + 40 Gy Split course XRT	21	46†	12	15.6†	—	—	—	—	—	—	—	—
ESPAC-1, 2001[7]	178‡	175	5-FU (500 mg/m² bolus) + 40 Gy Split course XRT	18	46	16.1‡	15.5	16.9‡	15.9	12.1‡	10.9	—	—	—	—
	235§	238	5-FU (425 mg/m²) + Leucovorin (20 mg/m²)	18	18	14.0	19.7*	15.3	20.7*	10.3	11.0	—	—	—	—
CONKO-001, 2007s	175	179	Gemcitabine (1,000 mg/m²)	17	72	20.2	22.8*	20.8	21.7	14.1	22.1	27.6	34*	18.2	18.5
Hopkins, 2008[14]	345	271	5-FU + 50 Gy XRT	45	80	14.4	21.2*	17	24.3*	11.4	18.3*	15.9	23.2	14.3	20.6
Mayo, 2008[10]	180	274	5-FU + 50.4 Gy XRT	NA	48	19.2	25.2*	19.2	25.2*	NA	NA	26.4	43.2*	14.4	20.4*
SEER, 2007[11]	1,513	1,123	XRT	NA	45	11	18*	NA	NA	NA	NA	—	—	8	17*
This study	374	299	Mainly 5-FU + XRT	26	60	14.5	20.0*	15.9	23.4*	8.9	15.0*	24.2	22.9	10.4	19.4*

*
$p < 0.05$.

†
Pancreatic adenocarcinoma only.

‡
No chemoradiation therapy group.

§
No chemotherapy group.

Adj, adjuvant; CONKO, Charite Onkologie; EORTC, European Organization for Research and Treatment of Cancer; ESPAC, European Study Group; for Pancreatic Cancer; GITSG, Gastrointestinal Study Group; LN, lymph node; obs, observation; pts, patients; SEER, Surveillance, Epidemiology, and End Results; XRT, radiation therapy.