Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2011 December 1; 81(5): 1328–1335. doi:10.1016/j.ijrobp.2010.07.1993.

The influence of total nodes examined, number of positive nodes, and lymph node ratio on survival after surgical resection and adjuvant chemoradiation for pancreatic cancer: A secondary analysis of RTOG 9704

Timothy N. Showalter¹, Kathryn A. Winter², Adam C. Berger³, William F. Regine⁴, Ross A. Abrams⁵, Howard Safran⁶, John P. Hoffman⁷, Al B. Benson⁸, John S. MacDonald⁹, and Christopher G. Willett¹⁰

¹Department of Radiation Oncology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA

²Radiation Therapy Oncology Group, RTOG Statistical Center, Philadelphia, PA

³Department of Surgery, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA

⁴Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD

⁵Department of Radiation Oncology, Rush University Medical Center, Chicago, IL

⁶Department of Medicine, The Miriam Hospital, Brown University Oncology Group, Providence, RI

⁷Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA

⁸Division of Hematology-Oncology, Northwestern University, Chicago, IL

⁹St. Vincent's Cancer Care Center, New York, NY

¹⁰Department of Radiation Oncology, Duke University Medical Center, Durham, NC

Abstract

Purpose—Lymph node status is an important predictor of survival in pancreatic cancer. We performed a secondary analysis of RTOG 9704, an adjuvant chemotherapy and chemoradiation trial, to determine the influence of lymph node factors—number of positive nodes (NPN), total nodes examined (TNE), and lymph node ratio (LNR—ratio of NPN to TNE)—on OS and disease-free survival (DFS).

Patient and Methods—Eligible patients from RTOG 9704 form the basis of this secondary analysis of lymph node parameters. Actuarial estimates for OS and DFS were calculated using Kaplan-Meier methods. Cox proportional hazards models were performed to evaluate associations

© 2010 Elsevier Inc. All rights reserved.

Corresponding Author: Adam C. Berger, MD, Department of Surgery Thomas Jefferson University, 1100 Walnut Street, MOB, Suite 500; Philadelphia, PA 19107; Phone: (215) 955-1622 ; Fax: (215) 923-8222 ; adam.berger@jefferson.edu.

Presented in part at these meetings: 2008 Annual Meeting of the American Society for Radiation Oncology (ASTRO) in Boston, Massachusetts; 2007 American Society of Clinical Oncology GI Cancer Symposium in Orlando, Florida.

Conflict of Interest Notification: The authors have no actual or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

of NPN, TNE, and LNR with OS and DFS. Multivariate Cox proportional hazards models were also performed.

Results—There were 538 patients enrolled in the RTOG 9704 trial. Of these, 445 patients were eligible with lymph nodes removed. Overall median NPN was 1 (min-max, 0-18). Increased NPN was associated with worse OS (HR=1.06, p=0.001) and DFS (HR=1.05, p=0.01). In multivariate analyses, both NPN and TNE were associated with OS and DFS. TNE > 12, and >15, were associated with increased OS for all patients, but not for node-negative patients (n =142). Increased LNR was associated with worse OS (HR=1.01, p<0.0001) and DFS (HR=1.006, p=0.002).

Conclusion—In patients who undergo surgical resection followed by adjuvant chemoradiation, TNE, NPN, and LNR are associated with OS and DFS. This secondary analysis of a prospective, cooperative group trial supports the influence of these lymph node parameters on outcomes after surgery and adjuvant therapy using contemporary techniques.

Keywords

lymph node; nodal ratio; pancreatic cancer; radiation therapy; pancreaticoduodenectomy

INTRODUCTION

Despite aggressive treatment, cancer mortality rates remain high for pancreatic cancer (PC) patients. In 2009, it was estimated that 42,470 people would be diagnosed with PC and that 35,240 deaths would occur as a result of PC (1). In an effort to improve survival for patients with resectable PC, adjuvant therapy is offered after definitive surgery. Postoperative chemotherapy (CT) and chemoradiotherapy (CRT) have improved survival in randomized trials, but trial results are conflicting, and there is controversy regarding the optimal adjuvant regimen (2-7). In the United States, CRT is commonly included in standard adjuvant approaches after surgery for resectable PC. The use of CRT is supported by the frequency and location of postoperative recurrence (8,9), and by results from single institutions and large databases (2,10-13). The Radiation Therapy Oncology Group (RTOG) conducted an intergroup trial, RTOG 9704, which enrolled PC patients after surgical resection and randomized patients to one of two CT regimens, containing gemcitabine (Gem) versus 5-fluorouracil (5-FU), before and after CRT with 5-FU. The results were reported recently and suggested a 3-year survival benefit for the addition of Gem CT, versus 5-FU CT, to 5-FU based CRT (14).

Several factors have been associated with outcomes after adjuvant therapy for resected PC. These prognostic factors include tumor size, tumor stage, surgical margin status, CA 19-9 levels, and lymph node status (13,15-17). The influence of postoperative CA 19-9 levels on outcomes in RTOG 9704 has been reported (18). In the primary report of RTOG 9704, lymph node positivity was associated with worse overall survival (OS), with hazard ratio (HR) of 1.53 (p=0.001) (14). Number of positive nodes (NPN), total nodes examined (TNE), and lymph node ratio (LNR) are three lymph node parameters that have been associated with survival after surgery in pancreatic cancer, as well as in other gastrointestinal malignancies. Increasing NPN has been associated with lower OS for patients with node-positive PC (19), and increasing TNE has been shown to predict for longer OS among patients with node-negative PC (20-22). LNR, the ratio of the NPN to the TNE, has demonstrated a prognostic relationship with OS for resected PC (19,23,24), as well as other gastrointestinal cancers (25-28).

Previous published reports of TNE, NPN, and LNR have examined data from single institutions or large databases, including patients who received surgery alone or followed by

a variety and mixture of non-standardized adjuvant regimens. The current report is the first analysis of TNE, NPN, and LNR in PC for patients who received adjuvant CRT according to guidelines of a prospective trial, which included contemporary therapies and required prospective quality assurance of radiation therapy (29). The purpose of this secondary analysis is to examine the impact of NPN, TNE, and LNR on survival for a large cohort of patients treated with CRT on RTOG 9704, a randomized, phase III Intergroup trial.

METHODS

RTOG 9704

The experimental design and primary results of the RTOG 9704 trial have been reported. (14) Patients with resectable pancreatic adenocarcinoma were entered onto the trial after surgery, and were stratified according to nodal status (involved vs. uninvolved), tumor diameter (< 3 cm vs. ≥ 3 cm), and surgical margins (negative vs. positive vs. unknown). Patients were randomly assigned to one of two adjuvant therapy arms, which consisted of 5-fluorouracil (5-FU) versus gemcitabine (Gem) CT delivered before and after CRT, and treatment started between 3 and 8 weeks after surgery. All eligible patients from this study that had lymph nodes removed are included in this secondary analysis of lymph node parameters, specifically NPN, TNE, and LNR (ratio of NPN to TNE).

Statistical Methods

Overall survival (OS) was measured from the date of randomization to the date of death or last follow-up. The failure event for disease-free survival (DFS) was defined as disease relapse (either local or regional), distant disease (including ascites and peritoneal seeding), second primary, or death due to any cause. DFS was measured from the date of randomization to the date of first failure event occurrence. Reported median survival times are the times (in years) at which the estimated survival rate reaches 50%. LNR was calculated by dividing the number of positive lymph nodes in the surgical specimen by the number of lymph nodes examined. NPN, TNE and LNR were continuous variables in the analyses. Separate analyses were performed for NPN (0 vs. 1-3 vs. >3) and TNE (0-12 vs. >12 , and 0-15 vs. >15) in all patients, and for LNR in node positive patients (by thirds of the group: $\leq 15\%$, $>15-33\%$, and $>33\%$) as categorical variables. A 1-sided log-rank test for a trend in increased (decreased) OS and DFS was performed for the ordered NPN and LNR categories.

Cox proportional hazards models were utilized to explore associations of NPN, TNE, and LNR with OS and DFS. In addition to the lymph node parameters, multivariate analyses included the following variables: treatment arm (Gem vs. 5-FU), age (≤ 62 vs. > 62 years), gender (female vs. male), primary tumor location (head vs. other locations), surgical T-stage (T1/T2 vs. T3/T4), tumor diameter (< 3 cm vs. ≥ 3 cm), KPS (90-100 vs. 60-80), and surgical margin status (negative vs. positive vs. unknown). All variables were coded such that a hazard ratio (HR) greater than 1 indicates an increased risk for the second level of the variable. For example, tumor diameter was coded such that a HR > 1 indicates an increased risk for tumors ≥ 3 cm. A backwards selection procedure was used to select variables for inclusion in the multivariate model.

RESULTS

Patients

Among the 538 patients who enrolled on RTOG 9704 from 7/20/98 – 7/26/02, 451 were eligible for the study, and of those, 445 patients had lymph nodes removed and were included in these analyses. Of the 93 excluded cases, there were 85 patients deemed

ineligible for the clinical trial, 2 patients who withdrew study consent, and 6 patients who had no lymph nodes removed. Among the 445 patients, 303 patients were node-positive and 142 patients were node-negative. There were 382 patients with head-of-pancreas (HOP) tumors among the 445 patients included in this study. Patient characteristics are displayed in Table 1. T-stage was the only characteristic that showed a significant association with treatment arm ($p=0.041$).

Total Nodes Examined (TNE)

The median TNE was nine (min-max: 1-46) and 11 (min-max: 1-56) in the 5-FU and Gem treatment arms, respectively. Increased TNE was not statistically significantly associated with improved OS (HR=0.99, 95% CI (0.97, 1.001), $p=0.068$) or DFS (HR=0.99, 95% CI (0.98, 1.002), $p=0.113$) on univariate analysis. The median OS times were 17.7 months and 18.1 months for those patients with 0-12 nodes ($n = 284$) and > 12 nodes examined ($n = 161$), respectively (log-rank $p = 0.195$). The median DFS was 10.3 months and 10.8 months for patients with 0-12 nodes and > 12 nodes examined, respectively (log-rank $p = 0.327$). The median OS times were 16.9 months and 20.9 months for patients with 0-15 nodes ($n = 333$) and > 15 nodes ($n = 112$) examined, respectively, representing a statistically significant decrease in OS for patients with ≤ 15 examined nodes (log-rank $p = 0.03$) (Figure 1). The median DFS times were 10.1 months and 12.3 months for patients with ≤ 15 nodes and > 15 nodes, respectively (log-rank $p = 0.091$). A separate analysis of TNE categories was performed for patients with negative lymph nodes ($n = 142$). There were no statistically significant differences in OS and DFS in the 12 and 15 node cut-point groupings.

Number of Positive Nodes (NPN)

Median NPN for all patients was one (min-max, 0-18). Increased NPN, as a continuous variable, was associated with worse OS (HR=1.06, 95% CI (1.03, 1.10), $p=0.001$) and DFS (HR=1.05, 95% CI (1.01, 1.08), $p=0.01$). Two-year actuarial OS for 0, 1-3, and >3 NPN was 47%, 35%, and 31%, respectively (log-rank $p=0.0001$) (Figure 2). Two-year actuarial DFS for the NPN categories (0, 1-3, >3) was 33%, 22%, and 17%, respectively (log-rank $p=0.003$) (Figure 3).

Lymph Node Ratio (LNR)

In the univariate analyses of LNR as a continuous variable, increased LNR was associated with decreased OS (HR=1.009, 95% CI (1.004, 1.013), $p=0.0004$) and DFS (HR=1.007, 95% CI (1.002, 1.011), $p=0.005$). Analysis of LNR by categories ($\leq 15\%$, 15-33%, and $>33\%$) demonstrated a decreasing MST (16.3 months, 20.8 months, and 12.7 months) and 2-year OS with increasing LNR (39%, 38%, and 25%, respectively). The results show a significant trend in decreased OS with increasing LNR category ($p=0.0005$, Figure 4), as evaluated by 1-sided log-rank test for trend. There was also a decrease in median DFS time and 2-year DFS with increasing LNR by quartiles: 10.8 months, 10.1 months, and 8.8 months, and 29%, 21%, and 12%, respectively. There was a statistically significant association of decreased DFS with increasing LNR ($p=0.0019$, Figure 5).

Multivariate Analyses

TNE and NPN as Continuous Variables—In multivariate Cox proportional hazards models, after adjusting for the other variables in the models, the increase in TNE was associated with improved OS (HR=0.98, 95% CI (0.96, 0.99), $p=0.001$) and DFS (HR 0.98, 95% CI (0.97, 0.996), $p=0.013$). On the other hand, the increase in NPN was associated with worse OS (HR=1.08, 95% CI (1.04, 1.12), $p<0.0001$) and DFS (HR=1.06, 95% CI (1.02, 1.10), $p=0.005$, Table 2).

NPN as a Categorical Variable—In multivariate analyses, patients with 0 positive nodes had better OS than patients with 1 to 3 positive nodes (HR=0.62, 95% CI (0.48, 0.81), $p=0.0003$, Table 3). There was no difference in OS, however, for patients with > 3 positive nodes compared to patients with 1 to 3 positive nodes. No association was found between NPN and DFS.

TNE as a Categorical Variable—Multivariate analyses were performed using TNE as a categorical variable. Greater than 12 nodes examined (vs. ≤ 12 nodes) was associated with improved OS after adjusting for age, KPS, tumor diameter, and positive nodes (HR = 1.32, 95% CI (1.05, 1.66), $p=0.019$, Table 4). Greater than 12 nodes examined was not associated with DFS (HR=1.17, 95% CI (0.95, 1.45), $p=0.151$) in the multivariate model (Table 3). Tumor diameter (< 3cm vs. ≥ 3 cm) (HR=1.32, 95% CI (1.07, 1.63), $p=0.009$) and T-stage (T1/T2 vs. T3/T4) (HR=1.39, 95% CI (1.09, 1.77), $p=0.008$), however, were associated with DFS (Table 3). Greater than 15 nodes examined (vs. ≤ 15 nodes) was associated with prolonged OS (HR=1.47, 95% CI (1.14, 1.89), $p=0.003$), but not DFS (HR = 1.24, 95% CI (0.98, 1.58), $p=0.071$, Table 5) after adjusting for all variables in the models.

In separate multivariate analyses of TNE as a categorical variable in node-negative patients ($n=142$), >12 nodes examined (vs. 0-12 nodes) was not associated with OS (HR=1.26, 95% CI (0.76, 2.11), $p=0.371$) or DFS (HR=1.21, 95% CI (0.77, 1.92), $p=0.413$). Similarly, > 15 nodes examined (vs. 0-15 nodes) was not associated with OS (HR=1.12, 95% CI (0.65, 1.92), $p=0.684$) or DFS (HR=1.12, 95% CI (0.68, 1.82), $p=0.660$).

LNR as a Continuous and a Categorical Variable—In the multivariate analysis of LNR as a continuous variable, increased LNR was associated with worse OS (HR=1.01, 95% CI (1.004, 1.013), $p=0.001$) and DFS (HR=1.01, 95% CI (1.002, 1.011), $p=0.005$, Table 6). Multivariate analysis of LNR as a categorical variable demonstrated associations of LNR >33% with worse OS and DFS (Table 7). In these models, there was an association with worse OS for patients on the CRT+5-FU arm when LNR was treated as either continuous or categorical.

DISCUSSION

This secondary analysis of the influence of lymph node parameters on survival for patients enrolled on the RTOG 9704 trial confirms the associations of NPN, TNE, and LNR with survival in PC treated with surgery and contemporary adjuvant therapy. Previous reports regarding the relationship of these lymph node factors with survival in PC have evaluated data that included heterogeneous adjuvant treatments (19-22,30). The current study demonstrates the significance of NPN, TNE, and LNR in PC patients who received protocol-based treatment with surgery followed by adjuvant CT (5-FU or Gem) and CRT. Prospective quality assurance of radiation therapy fields was required for patients enrolled on RTOG 9704. Central review of surgical and pathology reports were performed, but centralized review of surgical specimens was not a component of the clinical trial (14). In the primary report of results from RTOG 9704, Gem CT improved 3-year overall survival for patients with head of pancreas tumors on multivariate analysis. Nodal status was also associated with overall survival (HR 1.53, 95% CI (1.18, 1.97), $p=0.001$) (14).

The current study provides added insight on the relationships of TNE, NPN and LNR with survival for patients with surgically-resected PC. This analysis is limited by the lack of central pathology review and by the number of patients included, in comparison to larger databases, but it does add value through the evaluation of patients treated relatively homogeneously in the context of a prospective, clinical trial.

For PC patients treated with surgical resection followed by adjuvant chemotherapy and CRT on RTOG 9704, increased NPN was associated with worse OS and DFS, when considered as either a continuous or a categorical variable. NPN >3, compared to 0 or 1-3 positive lymph nodes, was associated with inferior OS and DFS. Furthermore, the significant association of NPN with survival persisted in the multivariate analysis; patients with >3 positive lymph nodes, compared to 0, were associated with inferior OS. These patients, however, were not statistically significantly different compared to patients with 1 to 3 positive nodes in the multivariate analysis. Schwarz and Smith identified a similar relationship between NPN and overall survival in their evaluation of the Surveillance, Epidemiology, and End Results (SEER) database (20). They did not report an NPN cut-point that could be used to define discrete prognostic groups. House *et al.* observed a linear decrease in OS with increasing NPN from 1 to 8 nodes positive using a single-institution database; two positive nodes was their most effective cut-point for determining prognosis based on NPN (19). Therefore, the present analysis of patients enrolled on RTOG 9704 supports the association of increasing NPN with decreased survival after resection and adjuvant therapy.

Greater than 12 nodes and greater than 15 nodes examined were associated with improved OS in analyses of all patients in the current study. Schwarz and Smith found a survival benefit for higher TNE in their analysis of PC patients in the SEER database. When only node-negative patients were considered, the greatest survival differences were identified for TNE greater than 10 or 15 (20). In a separate SEER database study of node-negative patients who underwent surgery for PC, Tomlinson *et al.* found that OS was extended for patients with 15 or more nodes examined, suggesting that staging was improved by the higher TNE (30). Twelve or more nodes was identified by Slidell *et al.* (21), and more than 10 nodes was identified by Hellan *et al.* (22), as the minimal number of nodes required for accurate staging of node-negative PC. The significant OS improvement observed for > 15 TNE in the univariate analysis (Figure 1), which was not observed in the parallel analysis of > 12 versus ≤ 12 TNE, suggests that the preferred TNE cut-point may be 15. However, in multivariate analyses of TNE categories in the current study, both > 12 and >15 TNE were independent predictors of overall survival. These TNE cut-points, 12 and 15, were selected for the current analysis based upon the published literature with these numbers (20,21,30). When considering the explanation for improved OS, it seems unlikely that higher TNE provided a therapeutic benefit for patients enrolled on RTOG 9704, since clinical trials of extended lymphadenectomy for PC have failed to identify a clear survival benefit (31-35). Potential explanations for the influence of TNE on survival for PC patients likely relate to accuracy of staging, which may be impacted by surgical quality (22,30) and extent of pathologic assessment (36,37). In the previously published reports of TNE in PC (20-22,30), higher TNE was associated with prolonged DFS and OS in node-negative patients, which suggests that the influence of TNE on OS and DFS is related to more accurate pathologic staging. A similar association between TNE and DFS or OS was not observed for the subset of node-negative patients analyzed in the current study, which may be related to the relatively small number of node-negative patients in this analysis (n=142). Furthermore, the population analyzed in the current study received rigorously controlled CT and CRT in a cooperative group trial, which is different from the variable adjuvant regimens for subjects in previously published reports that utilized institutional and SEER databases (20-22,30). Although the present analysis supports the association of higher TNE with improved survival after surgical resection for PC, and though it may generate hypotheses regarding the significance of TNE, our study was not designed to elucidate the causes of this relationship.

Increased LNR, both as continuous variable and as categorical variable, was associated with decreased OS and DFS in univariate and multivariate analyses. LNR has been described as a powerful predictor of survival for patients with positive lymph nodes in both institutional

reports and a SEER database analysis (21,23,24). LNR is particularly useful as a lymph node parameter for determining prognosis, as it includes information that is hypothesized to reflect surgical and/or pathological quality (TNE) and extent of disease (NPN) (21). LNR has been reported to be prognostic for survival in a variety of cancers, including breast (38), esophageal (27,39,40), gastric (41), and colon (28). The results of the current study confirm the association on LNR with survival after surgery and adjuvant therapy for resectable PC, and LNR greater than 33% was associated with inferior OS and DFS.

In conclusion, for patients who undergo surgical resection followed by adjuvant CRT for PC, the lymph node parameters TNE, NPN, and LNR are associated with OS and DFS. The current study represents the first analysis of TNE, NPN, and LNR for PC patients who received relatively uniform treatment on a cooperative group trial of postoperative, adjuvant therapy. Greater than 12 or 15 nodes examined were associated with prolonged survival, and 15 TNE is recommended as the preferred target number for future study of TNE in PC. LNR greater than 33% was associated with worse OS and DFS. These LN factors should be considered when estimating prognosis and, in the future, when designing clinical trials to incorporate experimental treatments. These findings also generate hypotheses for future investigation regarding potential explanations for the influence of TNE on prognosis, which may include surgical quality, extent of pathologic examination, or other patient-related factors.

Acknowledgments

Supported by RTOG U10 CA21661, CCOP U10 CA37422, and Stat U10 CA32115 grants from the National Cancer Institute (NCI). This manuscript's contents are the sole responsibility of the authors and do not necessarily represent the official views of the NCI.

REFERENCES

1. Jemal A, Siegal R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin.* 2009; 59:225–249. [PubMed: 19474385]
2. Garofalo M, Flannery T, Regine W. The case for adjuvant chemoradiation for pancreatic cancer. *Best Pract Res Clin Gastroenterol.* 2006; 20:403–416. [PubMed: 16549335]
3. Garofalo MC, Regine WF, Tan MT. On statistical reanalysis, the EORTC trial is a positive trial for adjuvant chemoradiation in pancreatic cancer. *Ann Surg.* 2006; 244:332–333. [PubMed: 16858208]
4. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection for pancreatic cancer. *Cancer.* 1987; 59:2006–2010. [PubMed: 3567862]
5. Kalser MH, Ellenberg SS. Pancreatic cancer: adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg.* 1985; 120:899–903. [PubMed: 4015380]
6. Klinkenbijl JH, Jeekel H, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and perampullary region: Phase III trial of the EORTC Gastrointestinal Tract Cancer Cooperative Group. *Ann Surg.* 1999; 230:776–784. [PubMed: 10615932]
7. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* 2004; 350:1200–1210. [PubMed: 15028824]
8. Foo ML, Gunderson LL, Nagorney DM, et al. Patterns of failure in grossly resected pancreatic ductal adenocarcinoma treated with adjuvant irradiation +/- 5 fluorouracil. *Int J Radiat Oncol Biol Phys.* 1993; 26:483–489. [PubMed: 8390422]
9. Hishinuma S, Ogata Y, Tomikawa M, et al. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg.* 2006; 10:511–518. [PubMed: 16627216]

10. Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. *Ann Surg.* 1997; 225:621–633. [PubMed: 9193189]
11. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol.* 2008; 26:3503–3510. [PubMed: 18640931]
12. Hazard L, Tward JD, Szabo A, et al. Radiation therapy is associated with improved survival in patients with pancreatic adenocarcinoma: Results of a study from the Surveillance, Epidemiology, and End Results (SEER) Registry data. *Cancer.* 2007; 110:2191–2201. [PubMed: 17918259]
13. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. *Ann Surg.* 2003; 237:74–85. [PubMed: 12496533]
14. Regine WF, Winter K, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. *JAMA.* 2008; 299:1019–1026. [PubMed: 18319412]
15. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas - 616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg.* 2000; 4:567–579. [PubMed: 11307091]
16. Cleary SP, Gryfe R, Guindi M, et al. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. *J Am Coll surg.* 2004; 198:722–731. [PubMed: 15110805]
17. Smith RA, Bosonnet L, Ghaneh P, et al. Preoperative CA 19-9 levels and lymph node ratio are independent predictors of survival in patients with resected pancreatic ductal adenocarcinoma. *Dig Surg.* 2008; 25:226–232. [PubMed: 18577869]
18. Berger AC, Garcia M Jr, Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol.* 2008; 26:5918–5922. [PubMed: 19029412]
19. House MG, Gonen M, Jarnagin WR, et al. Prognostic significance of pathologic nodal status in patients with resected pancreatic cancer. *J Gastrointest Surg.* 2007; 11:1549–1555. [PubMed: 17786531]
20. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. *Ann Surg Oncol.* 2006; 13:1189–1200. [PubMed: 16955385]
21. Slidell MB, Chang DC, Cameron JL, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. *Ann Surg Oncol.* 2008; 15:165–174. [PubMed: 17896141]
22. Hellan M, Sun C-L, Artinyan A, et al. The impact of lymph node number on survival in patients with lymph node-negative pancreatic cancer. *Pancreas.* 2008; 37:19–24. [PubMed: 18580439]
23. Pawlik TM, Gleisner AL, Cameron JL, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. *Surgery.* 2007; 141:610–618. [PubMed: 17462460]
24. Berger AC, Watson JC, Ross EA, et al. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am Surg.* 2004; 70:235–240. [PubMed: 15055847]
25. Falconi M, Crippa S, Dominguez I, et al. Prognostic relevance of lymph node ratio and number of resected nodes after curative resection of Ampulla of Vater carcinoma. *Ann Surg Oncol.* 2008; 15:3178–3186. [PubMed: 18712568]
26. Hurtuk MG, Hughes C, Shoup M, et al. Does lymph node ratio impact survival in resected periampullary malignancies? *Am J Surg.* 2009; 197:348–352. [PubMed: 19245913]
27. Mariette C, Piessen G, Briez N, et al. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg.* 2008; 247:365–371. [PubMed: 18216546]

28. Berger AC, Sigurdson ER, LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol.* 2005; 23:8706–8712. [PubMed: 16314630]
29. Abrams, RA.; Winter, KA.; Regine, WF., et al. RTOG 9704 - Radiotherapy Quality Assurance (QA) Review and Survival; American Society for Radiation Oncology Annual Meeting; Philadelphia, PA. 2006;
30. Tomlinson JS, Jain S, Bentrem DJ, et al. Accuracy of staging node-negative pancreas cancer: A potential quality measure. *Arch Surg.* 2007; 142:767–774. [PubMed: 17709731]
31. Michalski CW, Kleeff J, Wente MN, et al. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. *Br J Surg.* 2007; 94:265–273. [PubMed: 17318801]
32. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. *Ann Surg.* 1998; 228:508–517. [PubMed: 9790340]
33. Reddy SK, Tyler DS, Pappas TN, et al. Extended resection for pancreatic adenocarcinoma. *Oncologist.* 2007; 12:654–663. [PubMed: 17602057]
34. Farnell MB, Aranha GV, Nimura Y, et al. The role of extended lymphadenectomy for adenocarcinoma of the head of the pancreas: strength of the evidence. *J Gastrointest Surg.* 2008; 12:651–656. [PubMed: 18085343]
35. Glanemann M, Shi B, Liang F, et al. Surgical strategies for treatment of malignant pancreatic tumors: extended, standard or local surgery? *World J Surg Oncol.* 2008; 6:123. [PubMed: 19014474]
36. Staley CA, Cleary KR, Abbruzzese JL, et al. The need for standardized pathologic staging of pancreaticoduodenectomy specimens. *Pancreas.* 2006; 12:373–380. [PubMed: 8740405]
37. Adsay NV, Basturk O, Altinel D, et al. The number of lymph nodes identified in a simple pancreatoduodenectomy specimen: comparison of conventional vs orange-peeling approach in pathologic assessment. *Mod Pathol.* 2009; 22:107–112. [PubMed: 18820663]
38. van der Wal BCH, Butzelaar RMJM, van der Meij S, et al. Axillary lymph node ratio and total number of removed lymph nodes: predictors of survival in stage I and II breast cancer. *EJSO.* 2002; 28:481. [PubMed: 12217299]
39. Altorki NK, Zhou XK, Stiles B, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. *Ann Surg.* 2008; 248:221–226. [PubMed: 18650631]
40. Greenstein AJ, Litle VR, Swanson SJ, et al. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. *Cancer.* 2008; 112:1239–1246. [PubMed: 18224663]
41. Inoue K, Nakane Y, Iiyama H, et al. The superiority of ratio-based lymph node staging in gastric carcinoma. *Ann Surg Oncol.* 2002; 9:27–34. [PubMed: 11829427]

Figure 1.
OS by TNE category (0-15 vs. >15).

Figure 2.
OS by NPN category (0 vs. 1-3 vs. >3).

Figure 3.
DFS by NPN category (0 vs. 1-3 vs. >3).

Figure 4.
OS by LNR category in node-positive patients ($\leq 15\%$ vs. $>15\%$ - 33% vs. $>33\%$).

Figure 5.
DFS by LNR category in node-positive patients ($\leq 15\%$ vs. $>15\%-33\%$ vs. $>33\%$).

Table 1

Patient characteristics for patients included in the analysis

	CRT + 5-FU (n=226)	CRT + Gemcitabine (n=219)				
Age						
Median	62	61				
Min, Max	36-81	33-84				
Gender			n	%	n	%
Male			135	60	117	53
Female			91	40	102	47
Primary Tumor Location in Pancreas						0.415
Head			197	87	185	85
Body/Tail			29	13	34	15
KPS						0.726
90-100			145	36	137	37
60-80			81	64	82	63
T-stage (surgical)						0.041
T1			26	12	11	5
T2			39	17	32	14
T3			138	61	157	72
T4			23	10	19	9
N-stage (surgical)						0.162
N0			79	35	63	29
N1			147	65	156	71
AJCC Stage (5th Edition)						0.245
Stage I			35	15	21	10
Stage II			38	17	42	19
Stage III			130	58	137	63
Stage IV A			23	10	19	9
Tumor Diameter						0.327
< 3 cm			97	43	84	38

Gender	n		%		p-value
	n	%	n	%	
≥ 3 cm	129	57	135	62	

Abbreviations: CRT, chemoradiation

Table 2

Multivariate Cox Proportional Hazards Model with Number of Positive Nodes and Total Nodes Examined (n=445).

Endpoint	Adjustment Variables	Comparison	Adjusted HR	p-value [†]
OS	Positive Nodes	Continuous	1.08 (1.04, 1.12)	<0.0001
	Total Nodes Examined	Continuous	0.98 (0.96, 0.99)	0.001
	Age (Median)	≤ 62 vs. > 62	0.78 (0.63, 0.97)	0.022
	KPS	90-100 vs. 60-80	1.31 (1.06, 1.64)	0.015
	T-stage (surgical)	T1/T2 vs. T3/T4	1.31 (1.02, 1.70)	0.037
DFS	Positive Nodes	Continuous	1.06 (1.02, 1.10)	0.005
	Total Nodes Examined	Continuous	0.98 (0.97, 0.996)	0.013
	Tumor Diameter	< 3 cm vs. ≥ 3 cm	1.26 (1.02, 1.56)	0.031
	T-stage (surgical)	T1/T2 vs. T3/T4	1.38 (1.09, 1.77)	0.009

Abbreviations: OS, Overall Survival; DFS, Disease-Free Survival; HR, Hazard Ratio; KPS, Karnofsky Performance Status

[†] p-value from Chi-square test using the Cox proportional hazards model

Table 3

Multivariate Cox Proportional Hazards Model with Total Nodes Examined (continuous) and Number of Positive Nodes (0 vs. 1-3 Nodes vs. >3) (n=445).

Endpoint	Adjustment Variables	Comparison	Adjusted HR	p-value [†]
OS	Positive Nodes	1 to 3 Nodes vs. 0 Nodes	0.62 (0.48, 0.81)	0.0003
		1 to 3 Nodes vs. > 3 Nodes	1.20 (0.91, 1.58)	0.208
	Total Nodes Examined	Continuous	0.98 (0.96, 0.99)	0.001
	Age (Median)	≤ 62 vs. >62	0.78 (0.63, 0.97)	0.026
	KPS	90-100 vs. 60-80	1.35 (1.09, 1.69)	0.007
DFS	Positive Nodes	1 to 3 Nodes vs. 0 Nodes	0.83 (0.65, 1.06)	0.131
		1 to 3 Nodes vs. > 3 Nodes	1.26 (0.96, 1.66)	0.093
	Total Nodes Examined	Continuous	0.98 (0.97, 0.99)	0.013
	T-stage (surgical)	T1/T2 vs. T3/T4	1.33 (1.04, 1.71)	0.024
	Tumor Dimension	< 3 cm vs. ≥ 3cm	1.25 (1.01, 1.55)	0.037

Abbreviations: OS, Overall Survival; DFS, Disease-Free Survival; HR, Hazard Ratio; KPS, Karnofsky Performance Status

[†] p-value from Chi-square test using the Cox proportional hazards model

Table 4

Multivariate Cox Proportional Hazards Model with Total Nodes Examined (0-12 vs. > 12) and Positive Nodes (Yes vs. No) as Categorical Variables (n=445).

Endpoint	Adjustment Variables	Comparison	Adjusted HR	p-value [†]
OS	Examined Nodes	>12 vs. 0-12	1.32 (1.05, 1.66)	0.019
	Positive Nodes	No vs. Yes	1.56 (1.22, 1.99)	0.0004
	Age (Median)	≤ 62 vs. > 62	0.79 (0.63, 0.97)	0.027
	KPS	90-100 vs. 60-80	1.33 (1.07, 1.65)	0.012
	Tumor Diameter	< 3 cm vs. ≥ 3 cm	1.25 (1.00, 1.56)	0.047
DFS	Examined Nodes	>12 vs. 0-12	1.17 (0.95, 1.45)	0.151
	Tumor Diameter	< 3 cm vs. ≥ 3 cm	1.32 (1.07, 1.63)	0.009
	T-stage (surgical)	T1/T2 vs. T3/T4	1.39 (1.09, 1.77)	0.008

Abbreviations: OS, Overall Survival; DFS, Disease-Free Survival; HR, Hazard Ratio; KPS, Karnofsky Performance Status

[†] p-value from Chi-square test using the Cox proportional hazards model

Table 5

Multivariate Cox Proportional Hazards Model with Total Nodes Examined (0-15 vs. > 15) and Positive Nodes (Yes vs. No) as Categorical Variables (n=445).

Endpoint	Adjustment Variables	Comparison	Adjusted HR	p-value [†]
OS	Examined Nodes	>15 vs. 0-15	1.47 (1.14, 1.89)	0.003
	Positive Nodes	No vs. Yes	1.61 (1.27, 2.04)	0.0001
	Age (Median)	≤ 62 vs. > 62	0.79 (0.64, 0.98)	0.028
	KPS	90-100 vs. 60-80	1.36 (1.09, 1.69)	0.006
DFS	Examined Nodes	>15 vs. 0-15	1.24 (0.98, 1.58)	0.071
	Tumor Diameter	< 3 cm vs. ≥ 3 cm	1.31 (1.06, 1.61)	0.012
	T-stage (surgical)	T1/T2 vs. T3/T4	1.38 (1.08, 1.76)	0.010

Abbreviations: OS, Overall Survival; DFS, Disease-Free Survival; HR, Hazard Ratio; KPS, Karnofsky Performance Status

[†] p-value from Chi-square test using the Cox proportional hazards model

Table 6

Multivariate Cox Proportional Hazards Model with Ratio of Positive Nodes to Total Nodes Examined for node-positive patients (n=303).

Endpoint	Adjustment Variables	Comparison	Adjusted HR	p-value [†]
OS	Ratio of Positive Nodes to Total Nodes Examined	Continuous	1.01 (1.004, 1.013)	0.001
	RX	CRT + Gemcitabine vs. CRT + 5-FU	1.32 (1.02, 1.70)	0.036
	KPS	90-100 vs. 60-80	1.35 (1.04, 1.76)	0.023
DFS	Ratio of Positive Nodes to Total Nodes Examined	Continuous	1.01 (1.002, 1.011)	0.005

Abbreviations: OS, Overall Survival; DFS, Disease-Free Survival; HR, Hazard Ratio; KPS, Karnofsky Performance Status

[†] p-value from Chi-square test using the Cox proportional hazards model

Table 7

Multivariate Cox Proportional Hazards Model with Ratio of Positive Nodes to Total Nodes Examined as a Categorical Variable for node-positive patients Only ($\leq 15\%$ vs. $>15\%$ -33% vs. $>33\%$) (n=303).

Endpoint	Adjustment Variables	Comparison	Adjusted HR	p-value [†]
OS	Ratio of Positive Nodes to Total Nodes Examined	$\leq 15\%$ vs. $>15\%$ -33%	1.10 (0.79, 1.52)	0.576
		$\leq 15\%$ vs. $>33\%$	1.63 (1.21, 2.20)	0.001
	RX	CRT + Gemcitabine vs. CRT + 5-FU	1.32 (1.02, 1.70)	0.035
	KPS	90-100 vs. 60-80	1.35 (1.04, 1.76)	0.023
DFS	Ratio of Positive Nodes to Total Nodes Examined	$\leq 15\%$ vs. $>15\%$ -33%	1.09 (0.80, 1.49)	0.594
		$\leq 15\%$ vs. $>33\%$	1.53 (1.15, 2.04)	0.004

Abbreviations: OS, Overall Survival; DFS, Disease-Free Survival; HR, Hazard Ratio; KPS, Karnofsky Performance Status

[†] p-value from Chi-square test using the Cox proportional hazards model