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ORIGINAL ARTICLE – HEALTHCARE POLICY AND OUTCOMES

Impact of Radiation Therapy Sequence on Survival Among Patients With Resected Pancreatic Head Ductal Carcinoma

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ABSTRACT

Background. Neoadjuvant therapy for pancreatic cancer is increasingly studied, but no randomized data is available to address its clinical utility. The purpose of this study is to compare the impact of the sequencing of radiation therapy and surgery on overall survival (OS) of patients, who received both pancreaticoduodenectomy and radiation therapy.

Methods. Surveillance, Epidemiology, and End Results data on pancreatic head carcinoma patients diagnosed between 1991 and 2007 was used. OS of patients receiving neoadjuvant (nRT, $n = 111$) versus adjuvant radiation therapy (aRT, $n = 1839$) was the primary end point. Excluded were cases in which resection or radiation therapy were omitted.

Results. The groups were comparable with respect to age (63 ± 9 vs. 62 ± 10 years, $P = 0.490$) and gender distribution. Median OS was similar in the nRT and aRT groups (19 vs. 20 months, $P = 0.688$). On multivariate analysis, nodal status (hazard ratio [HR] 1.35, $P < 0.001$) and age (HR 1.01/year, $P < 0.001$) were predictive of OS, but RT sequence was not.

Conclusions. Survival of patients undergoing pancreaticoduodenectomy for pancreatic head carcinoma does not seem to be affected by sequence of perioperative radiation therapy. This finding would imply that prospective studies comparing nRT to aRT is warranted to examine potential clinical benefits of nRT and can be carried out without compromising patient outcome.

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Pancreatic cancer remains the most challenging gastrointestinal malignancy in terms of local control and overall survival (OS). Given the high rates of early local and distant recurrence after seemingly curative surgery, some have advocated for the routine delivery of neoadjuvant therapy to potentially resectable patients with pancreatic adenocarcinoma, borderline resectable carcinoma, and locally advanced disease.[1–14] Advocates of this approach argue that it may result in selecting a population of patients most likely to benefit from surgical resection by eliminating those who progress through neoadjuvant treatment. Additionally, with the suggestion that trimodality treatment is associated with better outcomes than surgery alone, administration of chemoradiation preoperatively makes it far more likely that all 3 elements of therapy will be completed.[15–17] Currently, a significant number of surgery-first patients never complete the desired postoperative adjuvant treatment.[17,18]

Despite the favorable early clinical results and theoretical appeal, the neoadjuvant approach does not yet enjoy widespread adoption. Resistance to postponing surgery is primarily due to a lack of ample phase III data refuting the firmly entrenched standard of care, represented by a "surgery-first" approach. This skepticism is fueled by concerns about the limited efficacy of current chemoradiotherapy, which may be perceived to only delay "curative" resection.

Given the absence of prospective data and limited comparative retrospective data outside of single-institution reports, we used the Surveillance, Epidemiology, and End Results (SEER) database to compare nRT and aRT strategies.[11,19,20] While we acknowledge that almost all of the recent trials of neoadjuvant treatment have used chemoradiation, the SEER program does not include information on the inclusion of chemotherapy. Chemoradiation is the only recognized neoadjuvant approach in pancreatic cancer in the United States, with very limited data on neoadjuvant chemotherapy from non-US institutions.[21] Therefore, we

feel it is reasonable for the purposes of our study to consider radiation therapy as a surrogate for radiation and chemoradiation therapy alike in the neoadjuvant setting.

In these settings we address whether OS with resected pancreatic head ductal carcinoma is different among patients undergoing nRT versus those with aRT.

MATERIAL AND METHODS

SEER Program data from 1991 to 2007 were used.[20] The study is exempt from human subjects research as defined by Code of Federal Regulations [§46.102(f)].

Histological classification of tumors in the SEER database is based on diagnosis codes from the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3). To capture all ductal carcinomas of the pancreas, we included histological codes 8010, 8020, 8021, 8022, 8140, 8141, 8490, and 8500 with documented invasion. Intraductal papillary mucinous neoplasm, mucinous cystic carcinomas, mucin-producing carcinomas, neuroendocrine, ampullary, and acinar carcinomas were excluded.

Pancreatic head location was determined by tumor site code C25.0, which designates pancreatic head malignancy. Cases were considered pancreatic head malignancy if the site within pancreas was not specified, but pancreaticoduodenectomy was used to treat the patient. For the purpose of this report, pancreatic head resection (Whipple procedure) or total pancreatectomy was considered pancreaticoduodenectomy. Radiation therapy sequence before or after resection was analyzed. Cases with intraoperative, combined preoperative and postoperative, and unspecified sequence were not included (Fig. 1).

We analyzed age at diagnosis, lymph node status, and radiation therapy sequence (preresection vs. postresection). Survival was measured from the date of diagnosis, and data were current as of November 2009.[20] Staging of pancreatic tumors using the American Joint Committee on Cancer (AJCC) system was not an integral part of SEER until 2004. Extent of disease data used in the SEER program does not allow for unequivocal reconciliation of the AJCC stage for cases entered before 2004 according to the definitions of the 7th edition. Therefore, nodal status was used to stage all resectable carcinomas.

Values are expressed as mean ± standard deviation (median). Kaplan–Meier estimates of survival were plotted, and survival differences were analyzed using the log-rank test. Proportional-hazards assumptions were tested using Schoenfeld's residuals. Multivariable survival analysis was performed using Cox proportional hazard model. Statistical significance was assumed at $P \leq 0.05$. Stata 10 (StataCorp, College Station, TX) was used for the analysis.

RESULTS

A total of 1950 cases were available for analysis, with 111 receiving nRT and 1839 receiving aRT.

Age was similar between the groups (63 ± 9 vs. 62 ± 10 years, $P = 0.490$), as well as gender distribution (1005 males total, of which 57 received neoadjuvant therapy, compared with 54 women; $P = 0.968$). The neoadjuvant group featured significantly fewer recovered lymph nodes (9.0 ± 7.2, median 7 vs. 11.6 ± 8.6, median 10; $P = 0.0072$), and a higher proportion of patients with no lymph nodes in the specimen (6.5 vs. 0.5%, $P < 0.001$). Among patients with known number of recovered lymph nodes, the neoadjuvant group had significantly fewer metastatic lymph nodes (0.8 ± 1.6, median 0 vs. 1.9 ± 2.4, median 1; $P < 0.001$) and fewer cases classified as lymph node positive (39 vs. 66%, $P < 0.001$).

To assess proportion of patients with stage III disease (arterial involvement), we had to limit the analysis to cases diagnosed in 2004 and later, since prior years' cases had equivocal extent of disease coding. A total 676 cases were available, with 58 cases undergoing nRT, of which 9 were stage III. Overall, the nRT group had significantly more stage III patients compared with the aRT group (15.5 vs. 4.8%, $P < 0.001$).

Median OS was similar between nRT and aRT (19 vs. 20 months, $P = 0.688$, Fig. 2). In multivariate modeling, nodal status and age were predictive of OS, but RT sequence was not (Table 1). Power analysis suggests that the dataset has 80% power to detect hazard ratio of 0.78 or less at α level 0.05. When sensitivity analysis was performed on a limited dataset with complete staging available (diagnosis in 2004 and after), RT sequence again was not predictive of OS (Table 2).

DISCUSSION

This study showed that among pancreatic head carcinoma patients treated by both the radiation therapy and resection, the treatment sequence has no effect on overall survival. We feel this study provides an impetus for a phase III trial examining neoadjuvant and adjuvant treatment strategies. Given the fact that this is a retrospective population-based study of highly selected patients, no immediate recommendations for clinical practice can be made.

The role of RT in pancreatic cancer remains controversial, primarily because of the mixed results from randomized trials examining the role of aRT. The routine use of aRT is based on the original Gastrointestinal Tumor Study Group data, which showed a near-doubling of median survival with adjuvant treatment despite using what is now considered suboptimal chemotherapy and RT.[15]

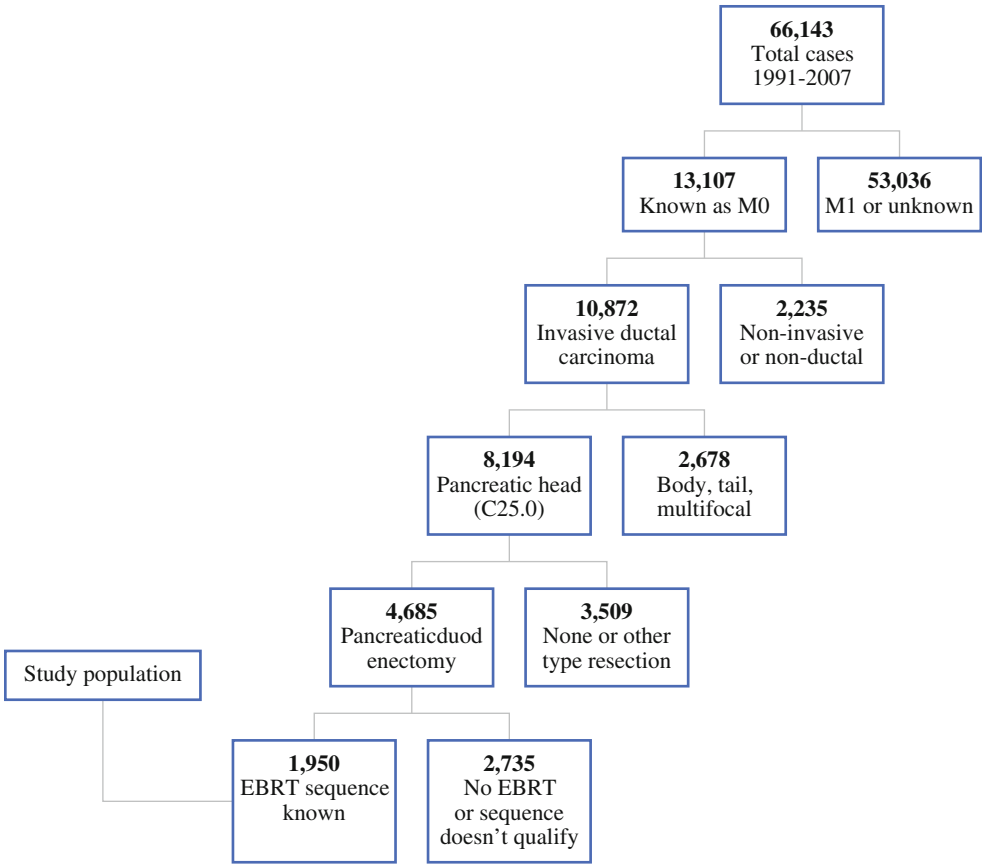

FIG. 1 Selection process flowchart. TNM M status is designated as M0 and M1. *EBRT* external beam radiation therapy

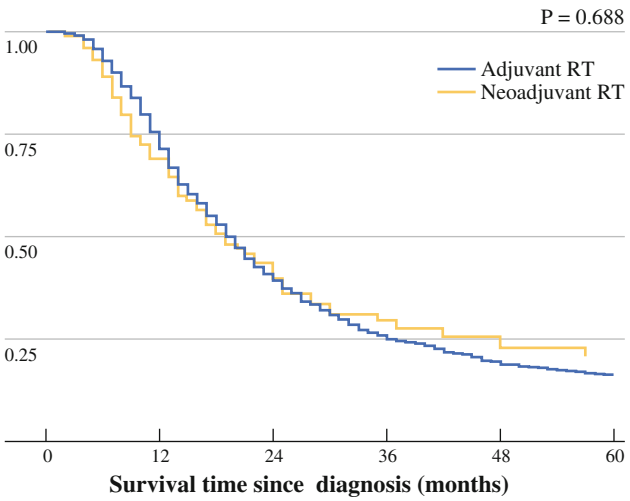

FIG. 2 Kaplan–Meier plot of neoadjuvant vs adjuvant radiation therapy (RT) group

Additionally, large retrospective series from leading institutions demonstrate significant benefit of adjuvant radiation therapy.[16,17] However, some randomized trials demonstrate no benefit or even detriment of aRT in resected pancreatic cancer.[3,18,22] A large pooled analysis of 5 randomized trials

TABLE 1 Multivariate modeling on a complete dataset (diagnosis 1991–2007)

	HR	*P* value	95% CI
RT sequence (nRT vs. aRT)	1.017049	0.896	0.7887157–1.311484
LN status (N0 vs. N1)	1.358567	0.000	1.216282–1.517498
Age (years)	1.011931	0.000	1.006787–1.017102

1918 cases available for this analysis of 1950 cases treated in this time period. *RT* radiation therapy, *aRT* adjuvant radiation therapy, *nRT* neoadjuvant radiation therapy, *95% CI* 95% confidence interval

TABLE 2 Multivariate modeling on a limited dataset with complete staging available (diagnosis in year 2004 and later)

	HR	*P* value	95% CI
RT sequence (nRT vs. aRT)	1.159217	0.561	0.7045938–1.907174
LN status (N0 vs. N1)	1.392697	0.010	1.080654–1.794844
Age (years)	1.013908	0.023	1.001872–1.026089
Stage (I/II vs. III)	1.638283	0.053	0.9941908–2.699653

644 cases were available for this analysis of 676 cases treated in this time period. *RT* radiation therapy, *aRT* adjuvant radiation therapy, *nRT* neoadjuvant radiation therapy, *95% CI* 95% confidence interval

also suggests that aRT is not helpful in the management of pancreatic cancer, but this analysis has been strongly influenced by the inclusion of the heavily criticized ESPAC-1 trial.[3,18,23]

Conversely, nRT remains an important and commonly used modality for pancreatic cancer, whether for initially unresectable locally advanced disease, borderline resectable, or potentially resectable disease.[5–11,13,14,19] While the indication for its use in inoperable locally advanced disease is well accepted, the latter indications remain controversial in general community practice. The hesitancy to employ nRT is reflected in the results of our population analysis where only about 5% of all resected patients underwent preoperative therapy.

Clear-cut answers regarding the applicability of RT can only be provided by prospective randomized trials, but such data are not presently available and likely will not be available for years to come. Single-arm small prospective studies have demonstrated favorable perioperative and longer-term oncologic outcomes for nRT.[6,7,9] Evans et al. proposed a neoadjuvant approach to all potentially resectable pancreatic cancer cases in hopes of avoiding futile surgery in those patients who are destined to develop recurrence during or shortly after their neoadjuvant therapy is completed.[6] Indeed, early local or distant recurrence after a Whipple procedure is rather common, even in settings of margin-negative resection.[1,4,18,24] Also, 40% of patients with no adjuvant therapy and margin-negative resection recur locally within 6 months, and almost all recurrences occur within 24 months of resection.[1,2]

In this regard, our results show no detriment to delaying resection in the nRT group, bolstering the logic that underlies the approach of Evans and others, namely that neoadjuvant therapy's major contribution may be that it serves as a selection tool by which the surgical group is enriched with patients whose tumors do not yet have a distant metastatic phenotype.[6,8,9]

Patients with potentially resectable pancreatic cancer experience an approximately 10%–19% progression rate on neoadjuvant chemoradiation, but at least 1 study reported a much higher rate of 41%.[5,7–9,14,19] An additional fraction of the patients, usually about 5%, have sufficient decline in performance status on restaging evaluation, such that surgery is then felt to be contraindicated, and a further 10–15% are identified to have unsuspected metastatic disease upon laparotomy.[7] Overall, the resection rate of "initially resectable" patients with preoperative radiation therapy is approximately 75%, ranging from 41 to 85% depending on study population.[7–9,19]

Median survival of potentially resectable patients treated with nRT ranges widely, but the largest studies report survivals of about 23 months, remarkably similar to that of 20 months reported in the adjuvant GITSG study, and longer than the 15.9 months in the adjuvant ESPAC-1 trial.[3,7,11,15,18] Median survival among patients treated in this study was 19 months for neoadjuvant and 20 months for adjuvant radiotherapy. However, our study reports only on cases successfully undergoing both modalities and cannot be directly compared with the intent-to-treat trials cited previously.

Neoadjuvant treatment has been examined in population databases previously and with inconsistent results. Neoadjuvant RT has been linked to improved overall survival in one report, but not in another.[25,26] The most recent report analyzed patients in Los Angeles County cancer registry and considered neoadjuvant chemotherapy as a definition of neoadjuvant treatment.[27] Only a minority of those neoadjuvantly treated patients received RT, but survival of the neoadjuvant cohort was longer than those with adjuvant therapy (34 vs. 19 months). All 3 of the mentioned studies examined pancreatic cancer without limitation as to the location of the primary cancer, whereas the current report focuses on proximal carcinomas only.[25–27] This report also has by far the largest neoadjuvant cohort of 111 patients, comparing favorably with other reports with 70, 39, and 23 patients, respectively.[25–27]

A few institutional retrospective studies have examined outcomes of direct-to-surgery approach vs neoadjuvant treatment.[11,19] Since population characteristics (indication for neoadjuvant vs. surgery decision, amount of adjuvant therapy, etc.) were substantially different, no firm conclusions can be made. Data from the current study suggest that patients treated with both RT and pancreaticoduodenectomy have similar survival, irrespective of the sequence used. However, because the neoadjuvant approach is often used in medically or technically borderline patients, this bias could have introduced an increased proportion of patients with unfavorable characteristics into the nRT group. Indeed, a higher proportion of stage III patients was observed in that group, a limitation only partially addressed by a multivariable Cox model (Table 2). The fact that OS was equal despite nRT being offered to patients with more advanced disease potentially bodes well for nRT in the setting of a head-to-head trial, but this of course remains to be determined. Cohorts in this study do not represent an intent-to-treat approach, and therefore one has to abstain from practice-changing recommendations. On the other hand these results, as noted previously, support the safety and rationale for a phase III trial, testing an adjuvant vs neoadjuvant strategy for pancreatic cancer.

Limitations of this study include its retrospective character, lack of intention-to-treat analysis, no assessment of the duration of adjuvant and neoadjuvant therapy, concomitant chemotherapy if any, and knowledge of margin status. Many of these limitations are, unfortunately, universal to all population database inquiries such as this one. On the other hand, this is the only population study directly and

contemporaneously comparing aRT and nRT among patients with resected pancreatic head carcinoma; most other studies are single-armed comparisons against historical controls.

CONCLUSION

OS of patients with pancreaticoduodenectomy for pancreatic head carcinoma does not seem to be affected by sequence of perioperative radiation therapy, as long as both modalities are used. Prospective study comparing nRT to aRT is warranted to examine potential clinical benefits of nRT among patients with potentially resectable pancreatic head carcinoma.

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