Survival Benefit of Post-Operative Radiotherapy in Patients with Resectable Pancreatic Head Adenocarcinoma

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Abstract
Background Controversy still exists with regard to the beneficial effects of adjuvant radiotherapy (RT) on patients with resectable pancreatic head adenocarcinoma. The aim was to investigate the role of post-operative RT in resectable pancreatic head adenocarcinoma.

Methods A total of 2092 patients with resectable pancreatic head adenocarcinoma were enrolled from 2004 to 2016. The data of these patients were obtained from the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute. The propensity score matching method was used to avoid selection bias of the treatment. A multivariable Cox proportional hazards model was used in analyzing the survival benefit from the utilization of post-operative RT.

Results In total, 186 patients received post-operative RT after pancreatic head adenocarcinoma resection. Compared with patients who only underwent surgery (n = 1906), the subjects who had postoperative RT were younger (P = 0.000) and had a greater TNM stage (P = 0.00). The baseline characteristics of the two groups were well matched, and more notable in the clinicopathologic and demographic aspects. Before and after matching, the patients who received post-operative RT after pancreatic head adenocarcinoma resection had a higher survival rate than those who underwent only resection (P = 0.00). Subgroups analyses revealed that this benefit was restricted to patients with Lymph node invasion (P = 0.00).

Conclusions Pancreatic head adenocarcinoma resection followed by post-operative RT demonstrated considerable survival benefit in relation to surgery alone.

Background
Pancreatic ductal adenocarcinoma (PDAC) is a serious life-threatening disease with poor prognosis, and is associated with the lowest survival rate among all other malignancies worldwide [1]. The mortality of PDAC increases by 2030 and is ranked as the second leading cause of cancer deaths around the world [2]. According to the statistics, approximately 80% of PDACs are derived from the head of the pancreas. Fewer, i.e., 10–20%, pancreatic cancers that are confirmed at an early-stage could be effectively treated [3, 4]. The current standard therapy for patients with early-stage pancreatic cancer is surgical resection of the tumor followed by adjuvant chemotherapy (CT), which
notably decreases the relapse and improves the survival rate of patients [5-15]. However, high rates of distant metastases (more than 80%) and local recurrence (more than 20%) are detected after surgery combined with adjuvant CT [12-17]. Thus, the addition of post-operative radiotherapy (RT) is thought to control the local relapse and improve the survival rate of patients. Yet the benefits of routine post-operative adjuvant RT still remain a controversy [18-20]. No consensus has been reached till date on the optimal adjuvant therapy for the combination of RT [21-25]. Until now, there are no randomized trials that elucidated the efficacy of post-operative adjuvant RT combination. Based on the aforementioned reasons, the current study was conducted by obtaining the data from the Surveillance, Epidemiology, and End Results (SEER) database to address whether the patients who received post-operative RT showed an improvement in the overall survival (OS) when compared to those patients who did not.

Methods
Data source
Data from the SEER database of the National Cancer Institute were used for analysis [26]. The SEER database provides authoritative information based on the cancer incidence and survival among the population in the USA. All data including public data, RT and CT data, and all variable information were obtained.

Patients
We retrieved the data for patients with pancreatic head adenocarcinoma from the SEER database version 8.3.6 for the period 2004 to 2016. The main inclusion criteria were as follows: diagnosis of patients was based on (1) the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), histology code: 8140/3; (2) ICD-O-3 site code C25.0; (3) confirmed biopsy; (4) the ones receiving Whipple procedure; and (5) sufficient follow-up data using the relevant extraction codes. Patients were excluded if they (1) were subjected to second primary cancer; (2) received CT; (3) had incomplete information about their survival, follow-up period, grading, TNM staging, tumor size, etc.; (4) aged < 18 years; and (5) were not newly or pathologically diagnosed. Data selection was presented in Fig. 1.

Data Collection
Demographic and clinical information of patients including age, gender, insurance recode, tumor size, pathologic results, metastatic lymph node, TNM stage, RT recode, clinical prognosis, etc. were extracted from the SEER database. With regard to allocation, the patients were divided into two groups either < 65 years or ≥65 years, with metastatic lymph node negative or positive, and with or without RT recode. OS, with no restriction on the cause of death, was calculated from the date of diagnosis till death or the last follow-up date. TNM stage according to the 7th edition of the AJCC TNM staging manual. All RT included was beam RT, and the patients were divided into two groups based on the therapy received (post-operative RT group and surgery-alone group). All patients received the Whipple procedure, but none of them had CT.

Statistical Analysis
All continuous data were presented as means±SD and analyzed using Student’s t test. Chi-square test and Fisher’s exact test were applied for comparing the categorical data. Univariate and multivariate analyses were performed using the Cox regression model, and the hazard ratio (HR) and associated 95% confidence interval (CI) were presented. The Kaplan–Meier method was used in analyzing to analyze the OS.

The propensity score matching (PSM) method was adopted to reduce selection bias between the post-operative RT group and the surgery-alone group. The propensity scores were calculated using age, gender, insurance recode, tumor grade, tumor size, metastatic lymph node, and RT procedures. Propensity score matching was performed using matching package (Matchit) in R using 1:5 nearest neighbor match criterion with caliper length of 0.02. Between the counterparts, the absolute standardized differences in means and proportions of those variables were less than 0.10, and should be balanced between patients in the two groups. Between the counterparts, the absolute standardized differences in means and proportions of those variables were less than 0.10, and should be balanced between patients in the three groups. All statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). PSM was performed using R 3.4.2. P < 0.05 was considered statistically significant and all reported P values were two-sided.

Results
Patient characteristics in the baseline cohort and the matched cohort
A total of 2092 eligible patients who underwent the Whipple procedure and were without CT were included, and the patients were divided into two groups (post-operative RT and surgery-alone). There were 186 patients who received post-operative RT with surgery, and 1906 who had only surgery. Table 1 demonstrates the baseline characteristics of the two groups. Significant differences were found in age, sex, insurance recode, TNM stage, tumor size, and lymph node invasion. There exists no difference in the rate of poor tumor differentiation (P = 0.594) and race recode (P = 0.149) between the post-operative RT group and the surgery-alone group. The aforementioned variables were used for PSM.

| Variable                        | post-operative RT group (n = 186) | surgery group (n = 1906) | P value |
|---------------------------------|-----------------------------------|--------------------------|---------|
| Age (year)                      |                                   |                          |         |
| ≤ 65                            | 92                                | 634                      | 0.000   |
| > 65                            | 94                                | 1272                     |         |
| Sex                             |                                   |                          |         |
| Male                            | 113                               | 921                      | 0.001   |
| Female                          | 73                                | 985                      |         |
| Race                            |                                   |                          |         |
| White                           | 165                               | 1588                     | 0.149   |
| Black                           | 14                                | 195                      |         |
| Asian                           | 7                                 | 123                      |         |
| Insurance status                |                                   |                          | 0.0     |
| Any Medicaid                    | 2                                 | 130                      |         |
| Insured                         | 67                                | 752                      |         |
| Uninsured                       | 1                                 | 20                       |         |
| Unknown                         | 116                               | 1004                     |         |
| Tumor differentiation           |                                   |                          |         |
| I+II                            | 17                                | 192                      | 0.594   |
| II                              | 96                                | 893                      |         |
| III+IV                          | 62                                | 680                      |         |
| Unknown                         | 11                                | 141                      |         |
| TNM Stage                       |                                   |                          |         |
| I+II                            | 86                                | 1083                     | 0.000   |
| II                              | 15                                | 124                      |         |
| Unknown                         | 85                                | 699                      |         |
| Tumor size (CM)                 |                                   |                          |         |
| ≤ 2                             | 25                                | 288                      | 0.147   |
| 2 ~ 4                           | 55                                | 669                      |         |
| ≥ 4                             | 19                                | 222                      |         |
| Unknown                         | 87                                | 727                      |         |
| Lymph node invasion             |                                   |                          | 0.465   |
| Yes                             | 106                               | 1093                     |         |
| No                              | 78                                | 805                      |         |
| Unknown                         | 2                                 | 8                        |         |

The matched cohort consisted of 783 patients in the post-operative RT group and 184 patients in the surgery group. In the matched cohort, no differences existed in the clinical variables among the three groups, except the TNM stage variable (P = 0.001), (Table 2).
The comparison of clinicopathological factors between post-operative RT group and surgery alone group, After Propensity Score Matching Analysis

| Variable                      | Standardized Difference | Matched Analysis | P value |
|-------------------------------|-------------------------|------------------|---------|
|                               | Unadjusted | PSM | post-operative RT group (n=184) | surgery group (n=783) |         |
| Age(year)                     | -0.162      | 0.0288 | 90 | 343 | 0.210 |
| ≤65                           |            |       |    |     |      |
| >65                           |            |       |    |     |      |
| Sex                           | 0.1243      | -0.0445 | 73 | 367 | 0.078 |
| Male                          |            |       |    |     |      |
| Female                        |            |       |    |     |      |
| Race                          | -0.0808     | 0.0154 | 163 | 692 | 0.996 |
| White                         |            |       |    |     |      |
| Black                         |            |       |    |     |      |
| Asian                         |            |       |    |     |      |
| Insurance status              | 0.2461      | -0.0154 | 2 | 32 | 0.110 |
| Any Medicaid                  |            |       |    |     |      |
| Insured                       |            |       |    |     |      |
| Uninsured                     |            |       |    |     |      |
| Unknown                       | -0.0649     | -0.1155 | 115 | 505 | 0.259 |
| Tumor differentiation         |            |       |    |     |      |
| I                             |            |       |    |     |      |
| II                            |            |       |    |     |      |
| III+IV                        |            |       |    |     |      |
| Unknown                       |            |       |    |     |      |
| TNM Stage                     | 0.2875      | -0.0725 | 86 | 350 | 0.001 |
| I+II                          |            |       |    |     |      |
| III+IV                        |            |       |    |     |      |
| Unknown                       |            |       |    |     |      |
| Tumor size(CM)                | 0.175       | 0.0061 | 25 | 105 | 0.897 |
| ≤3                            |            |       |    |     |      |
| ≥5                            |            |       |    |     |      |
| Unknown                       |            |       |    |     |      |
| Lymph node invasion           | 0.161       | -0.0194 | 76 | 314 | 0.266 |
| No                            |            |       |    |     |      |
| Yes                           |            |       |    |     |      |
| Unknown                       |            |       |    |     |      |

**Os In The Baseline Cohort**

The OS time for patients who underwent post-operative RT after surgery and in the basunderwent only surgery were 33.4 months and 22.8 months, respectively. Patients with post-operative RT had longer OS (P = 0.000) than those who had only surgery treatment (Fig. 1).

Propensity score-matched analyses

The matched apragnostic-relevant characteristics of patients were well matched (Table 2). The mean OS time for the matched post-operative RT group and the only surgery group were 32.1 months and 22.1 months, respectively. Patients with post-operative RT had longer OS (P = 0.000) in the two groups (Fig. 2). Effect of the treatment approach was consistent in both clinical stages I + II and III + IV (stage I + II: 36.6 months v 25.2 months; P = .003; stage III + IV: 30.7 months v 10.7 months; P = 0.007)(Fig. 3.4). Overall survival 1, 3, and 5 years was 76%, 33%, and 16% in the post-operative RT
group, and 65%, 24%, and 12% in the only surgery group, respectively. Overall mortality was increased in the post-operative the only surgery group, with an estimated hazard ratio (HR) of 1.32 (95% CI, 1.12 to 2.03).

Univariate and multivariate analyses of effects of factors on OS in the baseline cohort

A total of 2092 patients with known prognostic data were included in the multivariate and univariate analyses. The Kaplan–Meier method revealed varied significance of each demographic or clinical factor that it has on patients’ OS (Table 3).

| Characteristic             | Univariate analysis | Multivariate analysis |
|----------------------------|---------------------|-----------------------|
|                            | p       | HR (95%CI)             |
| Age (years)                | 0.000   |                       |
| < 60                       |         |                       |
| ≥ 60                       | 0.777   | (0.705–0.856)          |
| Sex                        | 0.237   |                       |
| Male                       |         |                       |
| Female                     |         |                       |
| Insurance Recode           | 0.367   |                       |
| Insured                    |         |                       |
| Uninsured                  |         |                       |
| unknown                    |         |                       |
| Tumor differentiation      | 0.000   |                       |
| I                          |         |                       |
| II                         | 0.975   | (0.805–1.179)          |
| III+IV                     | 1.271   | (1.045–1.546)          |
| Unknown                    | 2.651   | (1.382–5.083)          |
| TNM Stage                  | 0.000   |                       |
| I+II                       |         |                       |
| III+IV                     | 1.082   | (0.772–1.610)          |
| Unknown                    | 1.781   | (1.222–2.597)          |
| Tumor size(cm)             | 0.000   |                       |
| ≤ 2                        |         |                       |
| 2 ~ 4                      | 0.988   | (0.725–1.347)          |
| ≥ 4                        | 1.238   | (0.893–1.718)          |
| Radiation therapy          | 0.000   |                       |
| No                         |         |                       |
| Yes                        | 1.137   | (0.6-2.156)            |
| Lymph node invasion        | 0.000   |                       |
| No                         |         |                       |
| Yes                        | 1.106   | (0.584-2.098)          |
| Unknown                    |         | 1.610 (0.846-3.062)    |

The univariate analysis indicated that age, tumor differentiation, TNM staging, tumor size, and metastatic lymph node showed significant association with OS (Table 3).

To identify the potential risk factors as independent prognostic indicators, the Cox survival analysis was performed (Table 3). Among all the characteristics, five factors (such as age, tumor differentiation, TNM stage, tumor size, and Lymph node invasion were confirmed as independent prognostic indicators for OS (Table 3).

Interaction Between Post-operative Rt And Lymph Node Invasion
Interaction analyses were performed to further understand the impact of adjuvant RT by Lymph node invasion. In matched analysis, there was no significant difference in survival between post-operative RT group and surgery-alone group (median 35.4 vs 31.3 months, P = 0.182) in patients without Lymph node invasion (Fig. 6). In contrast, patients with Lymph node invasion receiving post-operative RT had significantly longer survival than patients underwent only surgery (median 29.9 vs 15.9 months, P = 0.000; Fig. 7).

Discussion
Previous studies indicated that almost one-third of the curatively resected PDAC patients would experience a local relapse, but without distant metastases [26, 27]. The rationale underlying the RT combination involves decreasing of the local relapse, which possesses the same lethality as that of distant metastasis. However, the true impact of RT still remains questionable. Based on the PSM analysis, the current study investigated the survival outcomes between patients undergoing postoperative RT after surgery and patients who underwent surgery alone for resectable pancreatic head cancer.

The treatment process of patients undergoing postoperative RT in the surgery group and the surgery-alone group was shown in Figs. 2 and 3. In baseline cohort and matched cohort, the median OS of patients in the postoperative RT group was longer than that of patients in the surgery-alone group.

Although there were fewer patients in the postoperative RT group who underwent surgical resection than in the surgery-alone group, the results showed that patients with resectable pancreatic head cancer with postoperative RT therapy obtained a survival advantage over those who have undergone surgery alone. Subset analyses revealed that this benefit was restricted to patients with Lymph node invasion. Patients without lymph node invasion already had a relatively impressive median survival of 31 months, and post-operative RT was not associated with additional benefit in this group. As such, these data highlight the need for more intensive study of the potential benefit of RT in the multidisciplinary treatment of pancreatic head adenocarcinoma.

The survival benefit of adjuvant postoperative RT was first revealed in the Gastrointestinal Tumor Study Group (GITSG) 9173 study [28]. However, A meta-analysis investigated 15 clinical trials and
reported that adjuvant postoperative RT could not improve disease-free survival (DFS), 2-year survival, or OS when compared to those with surgery alone, but adjuvant CT could improve all the three outcomes [29]. Another multi-center study analyzed 955 patients who underwent pancreatic cancer resections and concluded that adjuvant postoperative RT with CT improved patient's survival as compared to CT alone [30]. However, Morak et al. have suggested that neoadjuvant chemo(radio)therapy following resection showed no benefit in the OS of patients [31]. However, these trials lacked quality control of RT and had a selection bias. The ESPAC-1 study demonstrated that RT combined with adjuvant 5-FU CT might be redundant or even harmful [32]. Several concerns have been put forward about this trial criticizing their lack of attention to quality control for RT [33–35]. However, our large study, while still retrospective, used robust methods to avoid treatment selection bias, demonstrating survival benefit with adjuvant postoperative RT. Our study included patients who underwent treatment in the “real-world” setting as compared to the highly selected patients included in the clinical trials. Patients with adenocarcinoma histology and receiving the Whipple procedure were only included. To improve the reliability of the research, patients who received CT were excluded. The benefit of radiation was observed by conducting univariate and multivariate analyses. The radiation techniques have improved over time with more precise delivery to maximize the dose to the target tumor and minimize the dose to the normal tissues, daily integration of imaging before each fraction of the treatment, and identification of the variation in tumor position of the pancreatic tumor with respiration [36]. However, our study has several limitations. First, despite the use of PSM to address treatment selection bias, the potential for a residual bias still remained in this retrospective cohort study. Second, the adverse effects induced by the treatments cannot be addressed, and thus, the mortality estimation drawn based on such treatment might be biased. Also, the increased survival rates of the postoperative RT group in the present study might be underestimated. Third, the serum tumor marker of CA 19 – 9 that is associated with poor prognosis in patients with advanced PA receiving systemic CT [43,44] was absent in our study. Yet, whether the CA19-9 itself is considered to be vital in determining the survival in PDAC patients receiving postoperative RT remains controversial. Fourth,
dietary habits, socioeconomic status and body mass index, which might be the risk factors of mortality, were absent from the SEER database. Fifth, the SEER database did not include information on arterial or venous tumors involved or the presence of borderline resectable lesions. Therefore, we limited to using clinical stages. Sixth, the SEER database lacked the information regarding RT agents and the doses and combinations used, and therefore no specific recommendations could be drawn with respect to a specific RT protocol. Finally, we were unable to adopt the heterogeneity in the delivered treatment regimens, which were not available in the SEER database. Finally, as SEER did not include data on recurrence patterns, we could only speculate as to whether improved survival is associated with local or systemic disease control.

Conclusion
In summary, this study demonstrated that post-operative RT is related to enhanced survival after resection of pancreatic head adenocarcinoma. These results highlight the need for a renewed appraisal of postoperative RT in treating patients with pancreatic head adenocarcinoma. As the adjuvant and neoadjuvant treatment paradigms for pancreatic head adenocarcinoma continue to evolve, prospective evaluation of RT combined with modern systemic CT regimens should be done by considering the subgroup-specific effects.

Abbreviations
RT
radiotherapy ; CT:chemotherapy; CI:Confidence interval; HR:Hazard ratio; OS:Overall survival; PDAC:Pancreatic ductal adenocarcinoma; PSM:Propensity score matching; SEER:Surveillance, Epidemiology, and End Results

Declarations

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Author contributions
Gan yu. and Su.Song.: data acquisition and analysis; Gan yu and Fang cheng.: statistical analysis. Gan yu: drafted the article; Gan yu. and Li bo. study design; Li bo.: critical revision and final approval.

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**Availability of data and materials**

All primary data is available by sending email to: 454590225@qq.com or downloading from SEER database.

**Ethics approval and consent to participate**

This study is in accordance with the Declaration of Helsinki and has been approved by the Institutional Review Board at the affiliated hospital of southwest medical university. The data was retrieved after our application was approved by the SEER database.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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Figures

Flowchart representing selection process of patients included in this study
Figure 2

Kaplan-Meier survival curve of the patients in the post-operative RT group vs surgery-alone group in the baseline cohort.
Figure 3

Kaplan-Meier survival curve of the patients in the post-operative RT group vs surgery-alone group in the matched cohort.
Figure 4

Kaplan-Meier survival curve of the patients with stage I or II in the post-operative RT group vs surgery-alone group in the matched cohort.
Figure 5

Kaplan-Meier survival curve of the patients with stage III or IV in the post-operative RT group vs surgery-alone group in the matched cohort
Figure 6

Kaplan-Meier survival curve of the patients without Lymph node invasion in the post-operative RT group vs surgery-alone group in the matched cohort.
Figure 7

Kaplan-Meier survival curve of the patients with Lymph node invasion in the post-operative RT group vs surgery-alone group in the matched cohort.