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

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Abstract

Background Controversy still exis ts 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 using1:5 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.

Table 1
The comparison of clinicopathological factors between post-operative RT group and surgery alone group

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			
+	17	192	0.594
	96	893	
+	62	680	
Unknown	11	141	
TNM Stage			
+	86	1083	0.000
+	15	124	
Unknown	85	699	
Tumor size(CM)			

Variable	post-operative RT group (n = 186)	surgery group (n = 1906)	P value
≤ 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).

Table 2
The comparison of clinicopathological factors between post-operative RT group and surgery alone group,After Propensity Score Matching Analysis

	Standardized Difference		Matched Analysis	P value	
Variable	Unadjusted	PSM	post-operative RT group (n=184)	surgery group (n=783)	
Age(year)	-0.162	0.0288			0.210
≤65			90	343	
>65			94	440	
Sex	0.1243	-0.0445			0.078
Male			73	367	
Female			111	416	
Race	-0.0808	0.0154			
White			163	692	0.996
Black			14	61	
Asian			7	30	
Insurance status	0.2461	-0.0154			
Any Medicaid			2	32	0.110
Insured			67	238	
Uninsured			1	8	
Unknown			115	505	
Tumor differentiation	-0.0649	-0.1155			0.259
□			17	48	
□			94	366	
□+□			62	313	
Unknown			11	52	
TNM Stage	0.2875	-0.0725			0.001
□+□			86	350	
□+□			13	42	

Unknown			85	391	
Tumor size(CM)	0.175	0.0061			
≤ 3			25	105	0.897
3~ 5			55	228	
≥ 5			17	61	
Unknown			87	389	
Lymph node invasion	0.161	-0.0194			0.266
No			76	314	
Yes			106	467	
Unknown			2	2	

Os In The Baseline Cohort

The OS time for patients who underwent post-operative RT after surgery and **in the bas**underwent 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 aprognostic-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).

Table 3
Univariate and multivariate analyses of overall survival in all patients

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)

Characteristic	Univariate analysis	Multivariate analysis
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 35.4vs 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

Acknowledgements

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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

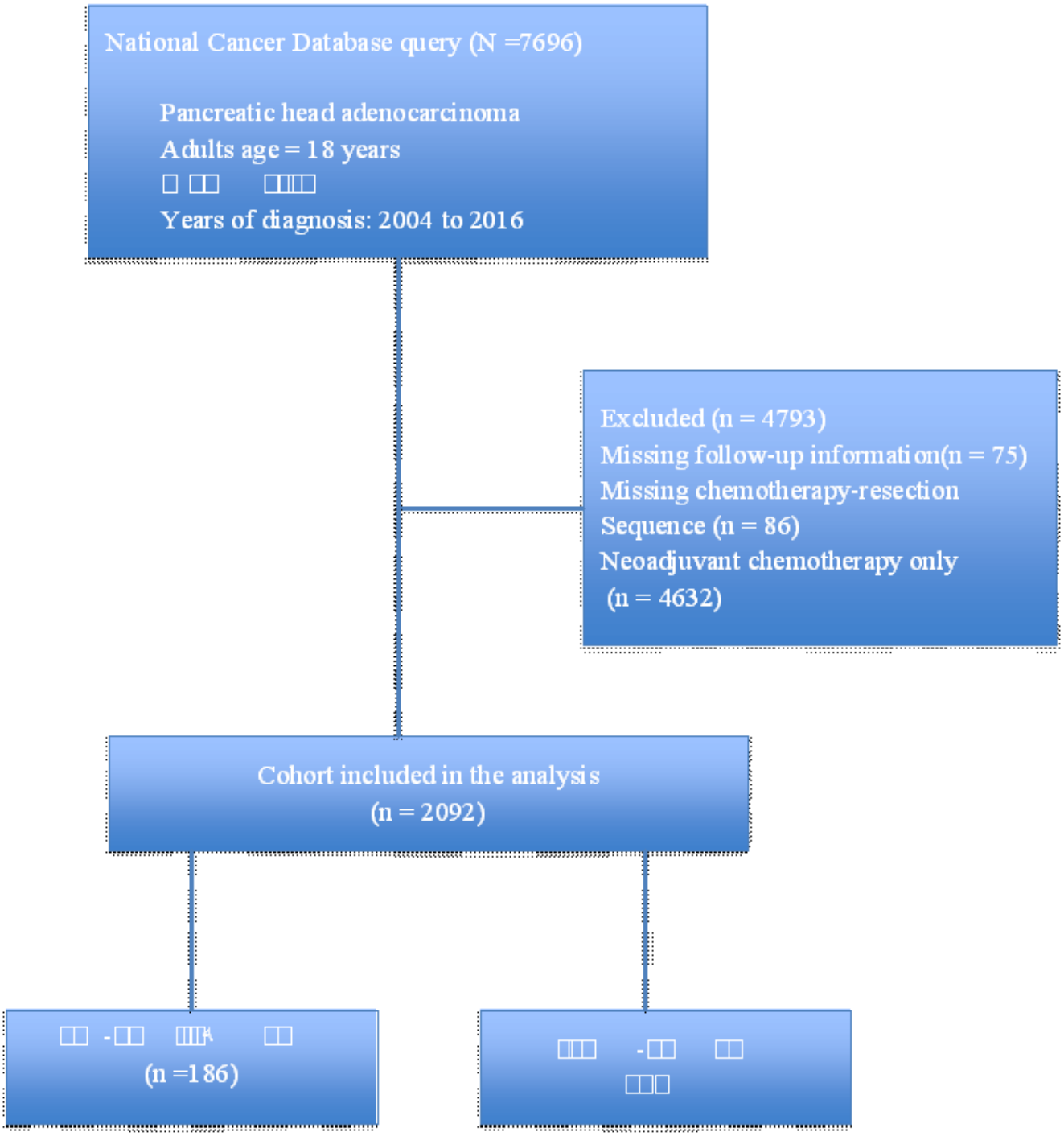

Figure 1

Flowchart representing selection process of patients included in this study

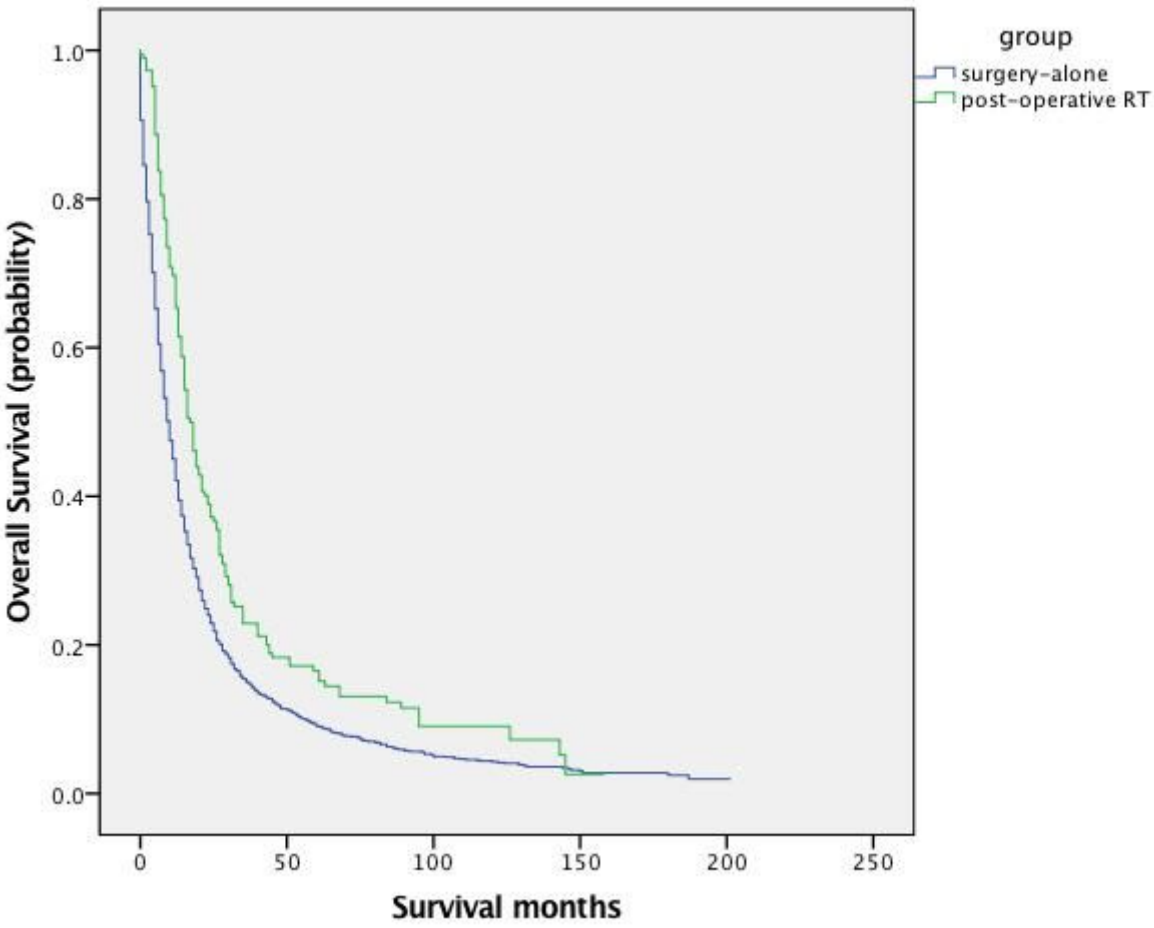

Figure 2

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

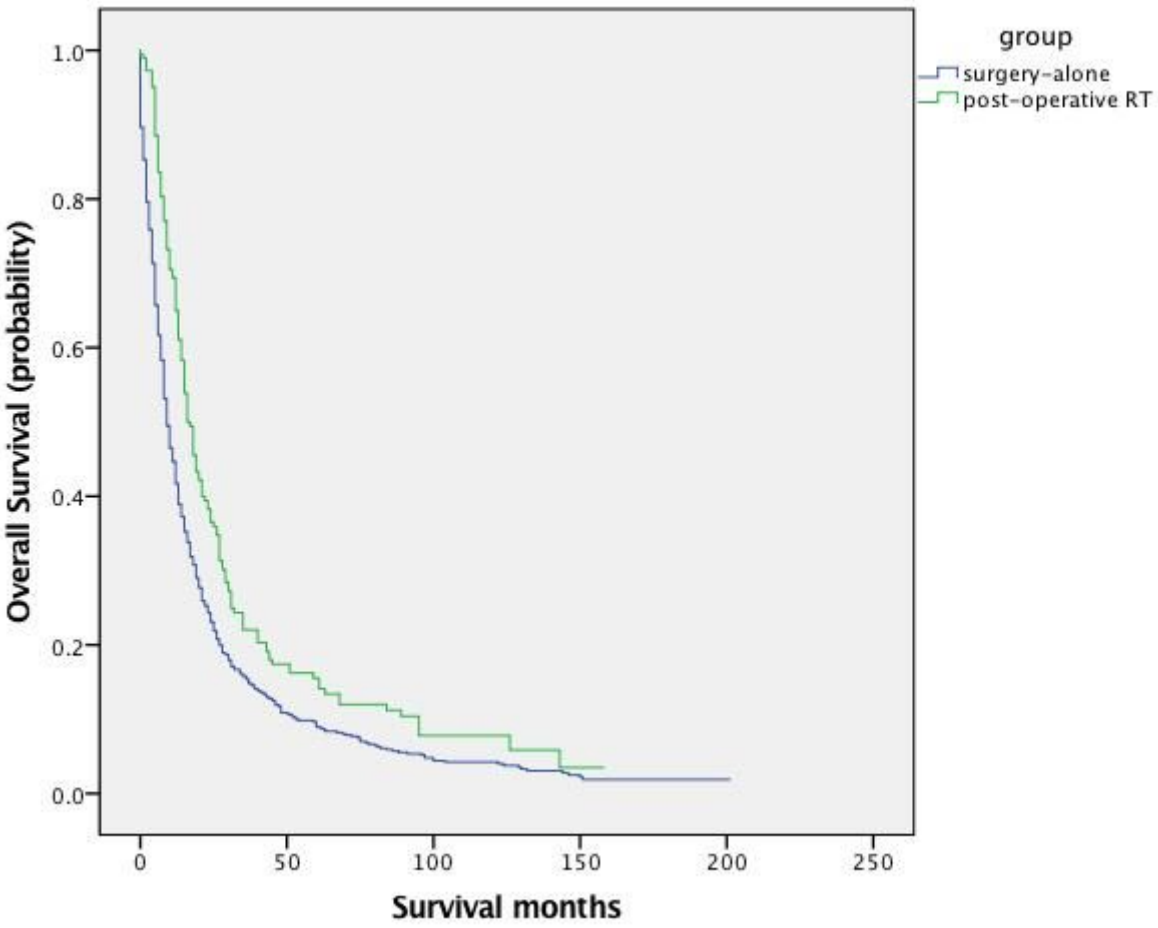

Figure 3

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

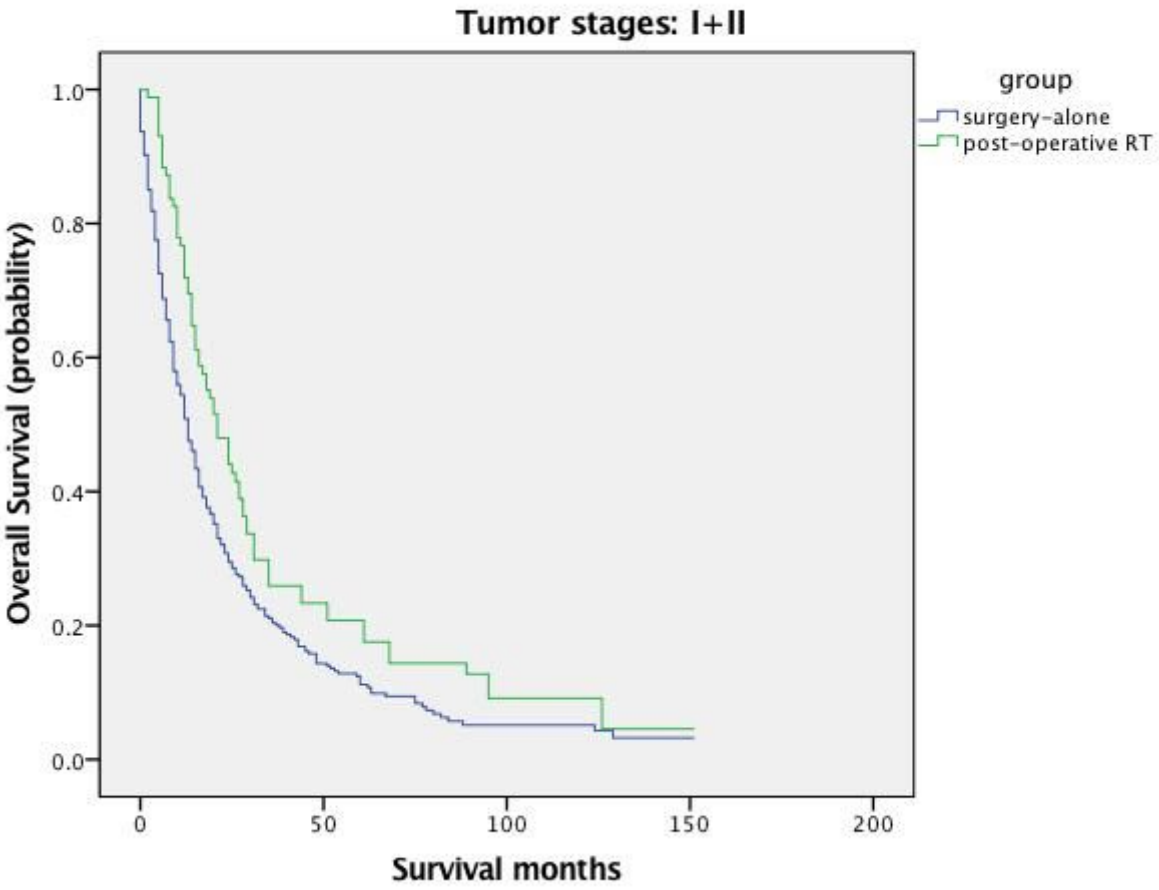

Figure 4

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

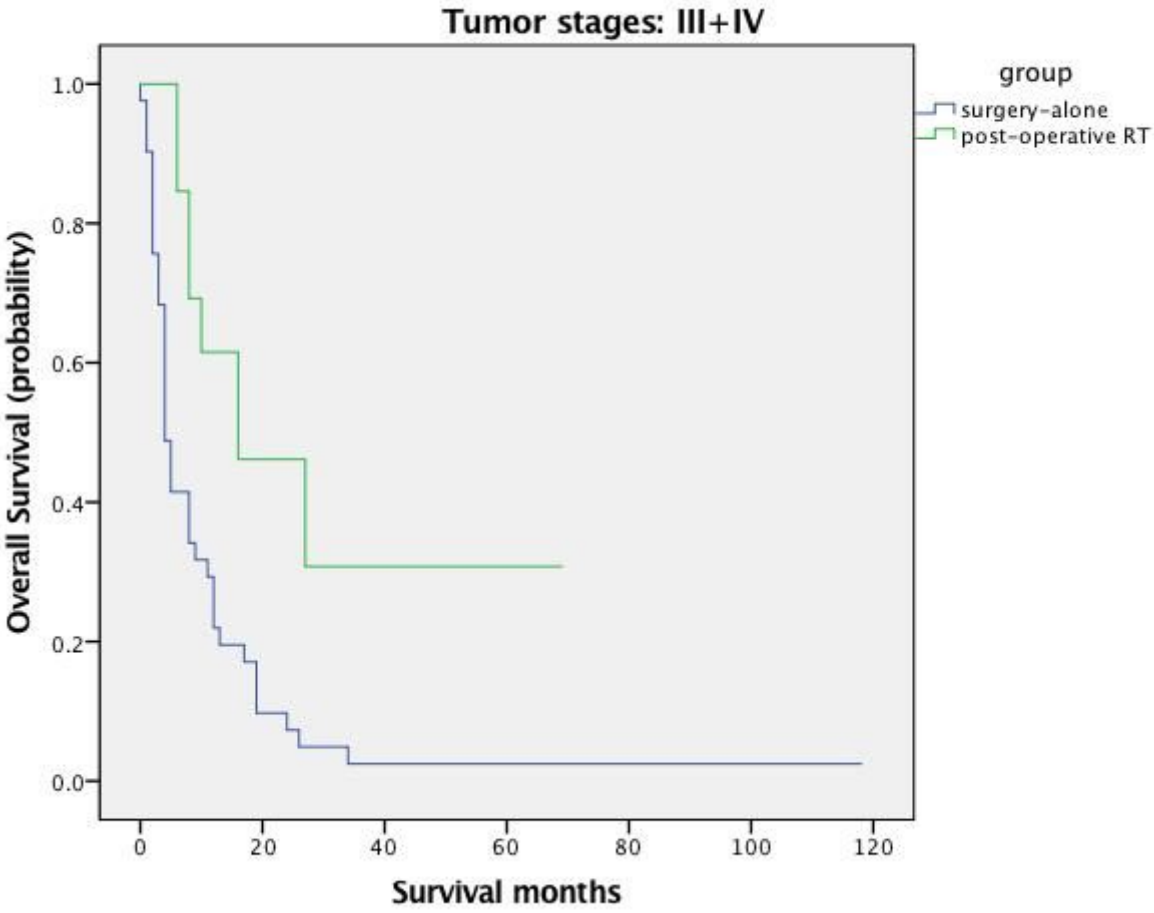

Figure 5

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

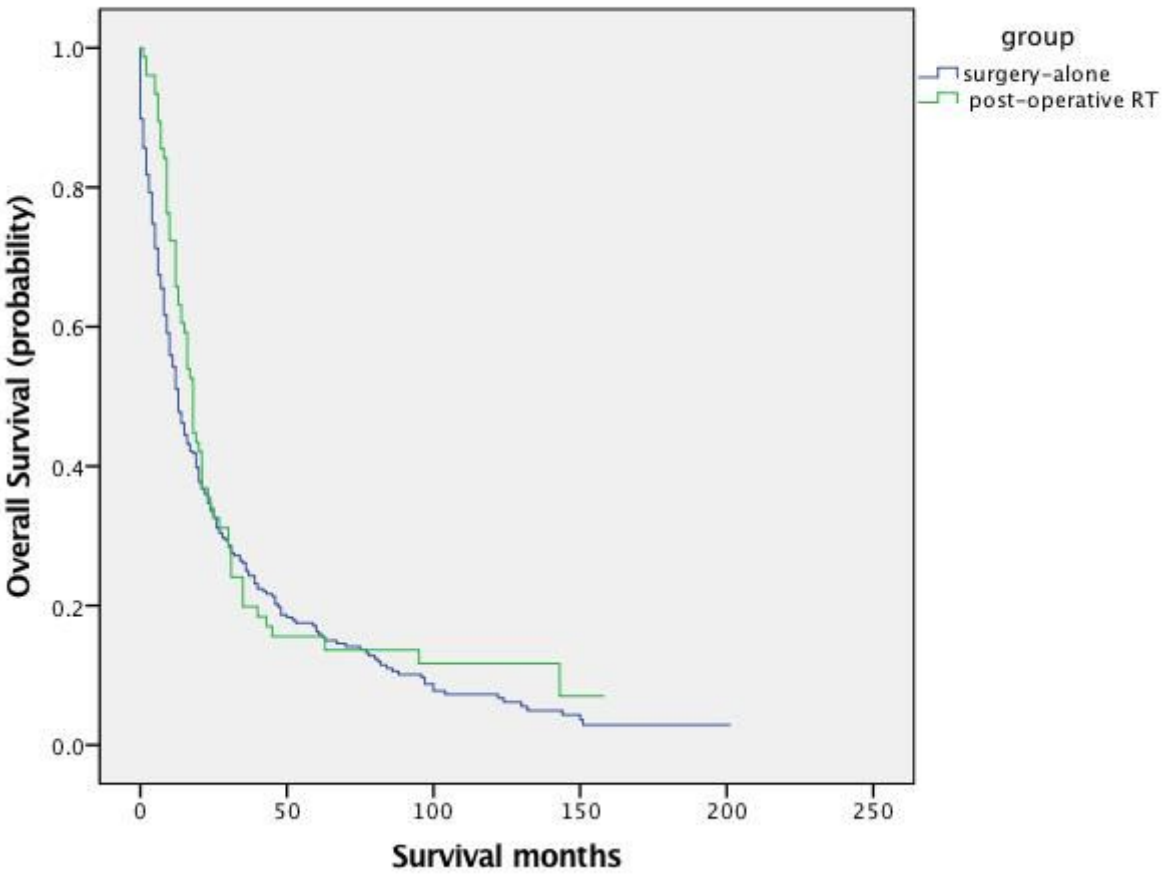

Figure 6

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

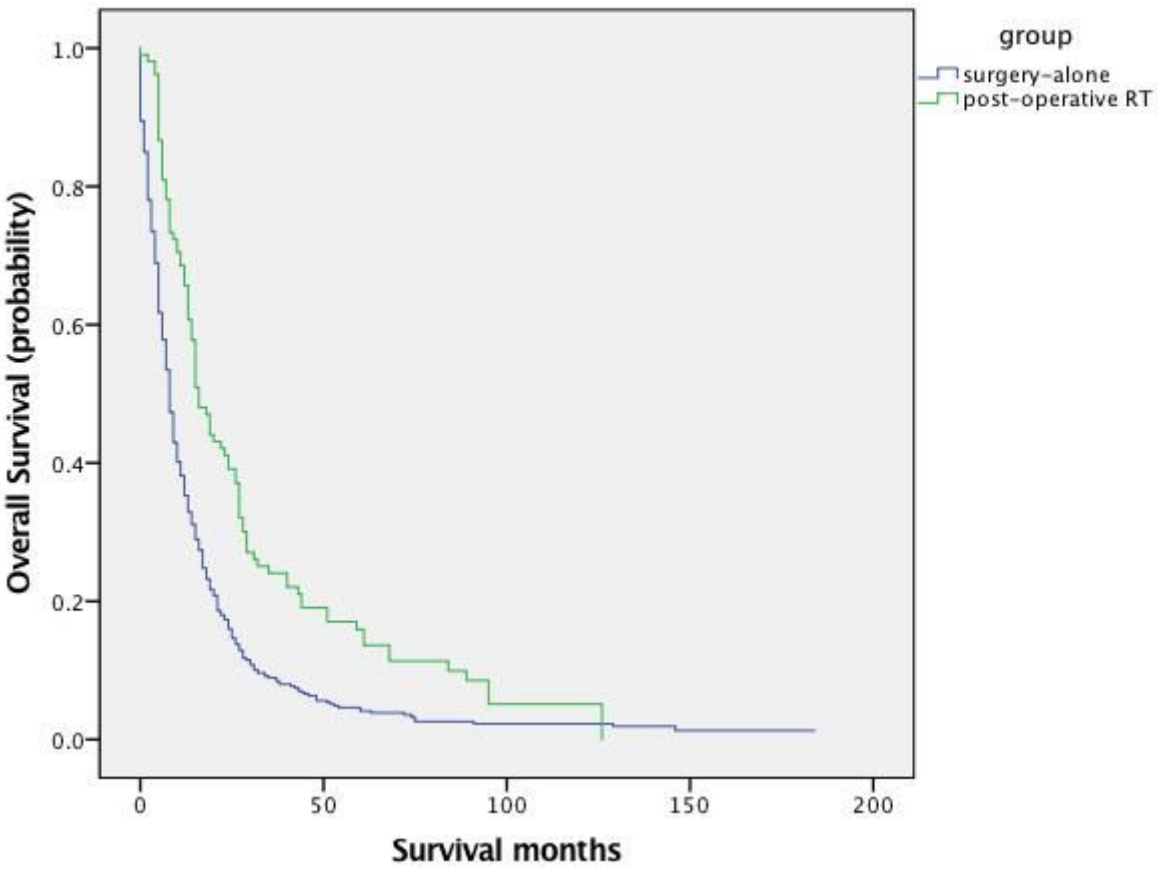

Figure 7

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