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Research Article

Evaluating the Effect of Post-Operative Radiotherapy on Long Term Survival of Testicular Seminomas: A Population Based Study

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Abstract

Objectives: To assess the effect of post-operative radiotherapy (PORT) on long term survival in Testicular Seminoma (TS) patients and factors may effect the prognosis of PORT patients.

Results: 12957 patients with a median age of 36.00 (13.00-107.00) years were pathologically diagnosed as primary TS. PORT was performed in 3407 patients. Patients with clinical stages I, II, and III testicular cancer accounted for 70.69% (n=9159), 8.30% (n=1075), and 5.72% (n=741) of all patients, respectively. According to results of multivariate Cox proportional hazard model, lower risk of cancer specific mortality was related with PORT in all patients (HR=0.40 95% CI=0.25-0.63 p<0.0001). However, no benefit in survival (p>0.05) was brought by PORT in either clinical stage. Aging, elevated human chorionic gonadotropin and lactate dehydrogenase level were related with higher risk of cancer specific mortality in PORT patients (p>0.05). Furthermore, aging and elevated LDH were inversely related with the prognosis of CSI PORT patients. No significant risk factor was observed in CSII and III PORT patients.

Conclusion: PORT can be benefit to the long term survival in TS patients, however, it did not show significant advantage in patients of either clinical stage based on the results of our study. Elevation of human chorionic gonadotropin and lactate dehydrogenase levels and elder age related with higher risk of CSM in PORT patients. Utilization of PORT in the management of TS should be considered comprehensively.

Keywords: Post-operative radiotherapy; Testicular tumor; Testicular seminoma

Introduction

Testicular tumor is a relatively rare disease of urogenital system, accounting for 1% of all tumors in male and 5% of all urological neoplasms [1]. The predominant pathological subtype of testicular tumor is testicular Seminoma (TS), which accounted for approximately 70% of all testicular tumors. Its incidence in Chinese population is approximately 1 case per 100 000 person-years, which is lower than that of western countries and showed a slight increase over the past decades [1,2].

As a result of the progression in diagnosis and treatment techniques, therapeutic regimens improved through these years [1]. Most patients with TS can be cured with orchiectomy and, if necessary, subsequent chemotherapy or Post-Operative Radiotherapy (PORT) [1]. Although accurate diagnosis and advanced multimodal treatment significantly contribute to good prognosis, controversies regarding various side effects of PORT for the treatment of TS and its efficacy on patients' long term survival still exists [1,3-7].

We conducted this study based on the information from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database (2006-2016) aims at assessing the effect on the long term survival of PORT in TS patients and evaluate risk factors related with the prognosis of PORT patients.

Materials and Methods

Study population, variables and outcomes

With Institutional Review Board approval, we identified men with TSs from 2006 to 2016 from cancer registries captured by the SEER Program. Tumors containing elements other than TSs, patients with neoplasms in other sites and received radiotherapy in other time points (before surgery or intrasuegery) were excluded. Demographic data including region, marital status, age, race, year of diagnosis, Clinical Stage (CS), TNM stage, serum tumor markers (Alpha Fetoprotein (AFP), Human Chorionic Gonadotropin (hcG), Lactate Dehydrogenase (LDH)), and regimens of surgery and PORT were obtained from the database. All patients had AJCC staging assignments [8]. The independent variable of interest was PORT. Outcomes included cancer-specific mortality (CSM; deaths caused by TSs).

Statistical analysis

Firstly, we assessed the distribution of baseline characteristics with two-sample t test and chi-square test to compare continuous and categorical variables, respectively. Data were presented as median (min-max) for continuous variables and as frequency (%) for

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categorical variables.

Secondly, Kaplan-Meier survival estimate was used to compare survival of patients of different subgroups.

Thirdly, a multivariable Cox proportional hazard model was used for analyses of CSM after adjusting race, marital status and year of diagnosis.

Statistical analysis was conducted with Empower Stats 2.0.

Results

Baseline characteristics

Data of 12957 TS patients were enrolled, with a median age of 36.00 (13.00-107.00) years. All patients were diagnosed based on pathological classification. Patients with clinical stage (CS) I, II, and III accounted for 70.67% (n=9181), 8.31% (n=1079), and 5.75% (n=747) of all, respectively. 3407 patients among all TS patients received PORT, 81.01% (n=2760) of them were CSI TS, 10.30% (n=351) were CSII and 1.82% (n=62) CSIII. Other baseline information was tabulated in Table 1.

Survival estimate

A total of 160 (1.23%) patients were confirmed died of this cancer during observation. The 5-year Cancer Specific Survival (CSS) rate of patients received no radiotherapy and patients received PORT was 99.36% and 98.26%, respectively. The median CSS time of PORT patients was significantly superior to those not (88(0-131) months *vs.* 43(0-131) months, p<0.001). Comparing CSSR of patients received PORT and those not, a significant advance was observed in PORT patients' CSSR (Figure 1). In all patients, the risk of CSM in patients received PORT was lower than those who did not (HR=0.40, 95% CI=0.25-0.63, p<0.0001). Considering its effect in patients in different clinical stage, we did not find statistical difference in the risk of CSM between patients received PORT or not in each CS (p >0.05).

Prognostic factors

Cox proportional hazard model was used to evaluate factors related with the prognosis of patients received PORT. Following the result of the Cox model: In all PORT patients, elder age, elevated hcG value more than 50000mIU/ml and LDH more than 10-fold of the

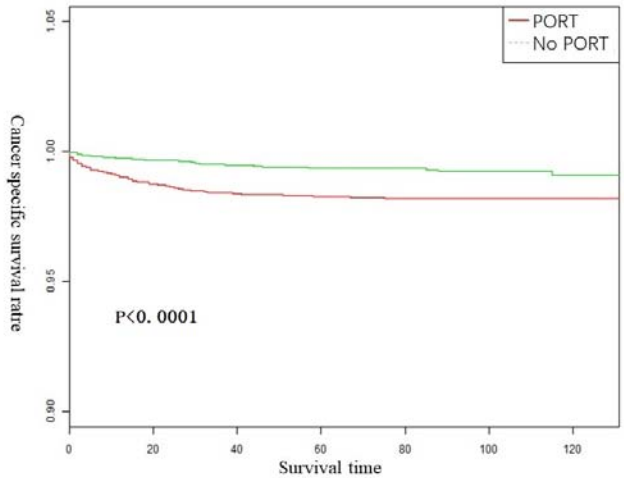

Figure 1: Cancer specific survival in patients received PORT or not.

Table 1: Clinical characteristics comparison between patients received PORT or not.

Radio therapy	none	Post-operative	P-value
N	9550	3407	
Age	36.00 (13.00-107.00)	37.00 (16.00-85.00)	0.065
Region			<0.001
Pacific Coast	5262 (55.10%)	1630 (47.84%)	
Alaska	21 (0.22%)	8 (0.23%)	
East	2900 (30.37%)	1194 (35.05%)	
Northern Plains	757 (7.93%)	322 (9.45%)	
Southwest	610 (6.39%)	253 (7.43%)	
Marital status			<0.001
Single (never married)/ Unmarried or Domestic Partner	3733 (39.09%)	1125 (33.02%)	
Married (including common law)	4519 (47.32%)	1896 (55.65%)	
divorced/seperated/ widowed	540 (5.65%)	234 (6.87%)	
NA	758 (7.94%)	152 (4.46%)	
Race			<0.001
White	8374 (87.69%)	3097 (90.90%)	
Black	326 (3.41%)	99 (2.91%)	
Asian or Pacific Islander	408 (4.27%)	118 (3.46%)	
American Indian/Alaska Native	120 (1.26%)	42 (1.23%)	
NA	322 (3.37%)	51 (1.50%)	
Year of diagnosis			<0.001
2006	476 (4.98%)	587 (17.23%)	
2007	534 (5.59%)	535 (15.70%)	
2008	674 (7.06%)	481 (14.12%)	
2009	745 (7.80%)	415 (12.18%)	
2010	818 (8.57%)	364 (10.68%)	
2011	846 (8.86%)	312 (9.16%)	
2012	918 (9.61%)	228 (6.69%)	
2013	1073 (11.24%)	157 (4.61%)	
2014	1180 (12.36%)	150 (4.40%)	
2015	1112 (11.64%)	87 (2.55%)	
2016	1174 (12.29%)	91 (2.67%)	
Laterality			0.159
Left	4477 (47.75%)	1561 (45.90%)	
Right	4890 (52.16%)	1836 (53.98%)	
Bilateral	8 (0.09%)	4 (0.12%)	
Cryptorchdism			0.759
No	203 (4.64%)	68 (4.45%)	
Yes	4174 (95.36%)	1461 (95.55%)	
CS (adjusted)			<0.001
I	6399 (67.01%)	2760 (81.01%)	
II	724 (7.58%)	351 (10.30%)	
III	679 (7.11%)	62 (1.82%)	

NA	1748 (18.30%)	234 (6.87%)	
Surgery			<0.001
none	283 (2.96%)	3 (0.09%)	
partial desection	15 (0.16%)	4 (0.12%)	
orchiectomy without cord	69 (0.72%)	17 (0.50%)	
orchectomy	9151 (95.82%)	3380 (99.21%)	
surgery(methods unknown)	18 (0.19%)	3 (0.09%)	
NA	14 (0.15%)	0 (0.00%)	
AFP pre-surgery			0.295
normal	1543 (92.51%)	1514 (94.15%)	
-1000	94 (5.64%)	69 (4.29%)	
1000-10000	24 (1.44%)	20 (1.24%)	
10000-	7 (0.42%)	5 (0.31%)	
hcG			<0.001
normal	1171 (72.51%)	1264 (79.30%)	
-5000	355 (21.98%)	266 (16.69%)	
5000-50000	70 (4.33%)	49 (3.07%)	
50000-	19 (1.18%)	15 (0.94%)	
LDH			<0.001
normal	691 (61.70%)	709 (70.76%)	
<1.5N	226 (20.18%)	189 (18.86%)	
1.5-10N	137 (12.23%)	76 (7.58%)	
>10N	66 (5.89%)	28 (2.79%)	
Persistence of Elevated Serum Tumor Markers			0.877
No	168 (94.92%)	102 (95.33%)	
Elevated	9 (5.08%)	5 (4.67%)	
Lymph-vascular Invasion			0.02
No	4464 (74.34%)	877 (71.13%)	
Identified	1541 (25.66%)	356 (28.87%)	
Tumor size			0.002
<4cm	3702 (47.82%)	1426 (44.56%)	
≥4cm	4040 (52.18%)	1774 (55.44%)	

normal value were significantly related with higher risk of CSM (p <0.05) (Table 2).

Subgroup analysis was also performed based on different CS: aging and elevated LDH value of 1.5-10 fold normal value were related with worse prognosis in CSI patients, no risk factors were observed in CSII and CSIII patients (Table 3).

Discussion

According to the results of our study, significant advantage was shown on the 5-year CSS of patients received PORT comparing with those not. Decreased risk of CSM was related with usage of PORT (HR=0.40, 95% CI=0.25-0.63, p <0.0001). However, things are different when taking clinical stage into account. No significant advance was found in risk of CSM in PORT patients compared

Table 2: Factors related with poor prognosis in PORT patients.

Exposure	Non-adjusted	Adjust
Age	1.07 (1.04, 1.11) <0.0001	1.07 (1.04, 1.11) <0.0001
hcG		
normal	1	1
-5000	0.00 (0.00, Inf) 0.9980	0.00 (0.00, Inf) 0.9979
5000-50000	5.65 (0.66, 48.37) 0.1142	6.41 (0.72, 57.22) 0.0960
50000-	19.17 (2.24, 164.25) 0.0070	24.74 (2.52, 243.21) 0.0059
LDH		
normal	1	1
<1.5N	7.65 (0.69, 84.41) 0.0966	7.81 (0.65, 94.06) 0.1055
1.5-10N	9.48 (0.59, 151.52) 0.1118	9.38 (0.55, 159.96) 0.1220
>10N	54.35 (4.93, 599.64) 0.0011	45.24 (3.23, 632.60) 0.0046

with those not in each CS. This result was controversial to the recommendation of utilization of radiotherapy in CSI and II patients. We can conclude from our analysis that PORT can be beneficial for prognosis of CSI patients (HR=0.61 95% CI=0.28-1.34 p=0.2184) and II patients (HR=0.40 95% CI=0.13-1.20 p=0.1010), but the result was not statistically significant. This may cause by the good prognosis of TS and insufficient number of censored patients in this study (a total of 160 died of this caner among 12957 patients, 38 died in 9159 CSI patients, 23 of 1075 CII patients and 86 of 741 CSIII patients).

Huge advances have been made in the therapeutic regimens of through years, outcome of TS patients has been continuously improved [1,5,6]. Advanced multi-modal management of TS brought benefit not only to patients' prognosis, but to patients' long term survival [1,5,6]. Radiotherapy has been a predominant adjuvant/salvage therapeutic option for decades, however, considering its adverse effects and improvements of medical technology, the dose and fields of radiotherapy had been reduced over the past 20 years [5].

Although PORT could reduce the risk of CSM in all TS patients [1,4,9-11], performance of PORT should be comprehensively considered according to its severe adverse effects. Taking CS into consideration, PORT showed no advantage in reducing the risk of CSM in each CS. Based on previous studies and improvement of multi-modal management regimens, current utilization of radiotherapy may have come to a crossroad, adjustment has become a challenge for urologists and oncologists [7].

Although PORT can be beneficial in improving prognosis of TS patients, its severe side effects should not be underestimated. Utilization of radiotherapy resulted in multi adverse events such as sexual dysfunction, Secondary Malignant Neoplasms (SMN) and cardio-vascular diseases etc [5,6,12]. Evidences of these effects had been widely reported.

Sex played an important role in men's life, however, as reported by Wrotel et al. [13] in 2015, 45% patients suffered adverse effects on sexual life after orchiectomy and PORT especially in younger patients. Bandak et al. demonstrated that erectile dysfunction and orgasmic dysfunction was associated with radiotherapy in their study in 2018 [14].

Alexandra et al. had reported a 3.7-fold (95% CI, 2.2- to 6.2-fold)

Table 3: Prognostic factors of patients in each clinical stage.

Exposure	CS (adjusted)=I	CS (adjusted)=II	CS (adjusted)=III
Age	1.08 (1.02, 1.14) 0.0055	1.06 (0.95, 1.18) 0.2814	1.08 (0.99, 1.19) 0.0862
AFP Pre-Surgery			
normal	1	1	1
-1000	0.00 (0.00, Inf) 0.9995	0.39 (0.00, Inf) 1.0000	266.62 (0.00, Inf) 1.0000
1000-10000	0.00 (0.00, Inf) 0.9999	1	0.37 (0.00, Inf) 1.0000
10000-	0.24 (0.00, Inf) 1.0000	1	1
Hcg			
normal	1	1	1
-5000	0.00 (0.00, Inf) 0.9992	0.00 (0.00, Inf) 0.9996	38822.81 (0.00, Inf) 1.0000
5000-50000	0.00 (0.00, Inf) 0.9998	1	inf. (0.00, Inf) 0.9996
50000-	0.00 (0.00, Inf) 1.0000	1	inf. (0.00, Inf) 0.9998
Ldh			
normal	1	1	1
<1.5N	0.00 (0.00, Inf) 0.9854	inf. (0.00, Inf) 0.9984	0.00 (0.00, Inf) 1.0000
1.5-10N	55.01 (1.73, 1751.02) 0.0232	1	3.50 (0.00, Inf) 1.0000
>10N	0.08 (0.00, inf.) 0.9325	1	3.50 (0.00, Inf) 1.0000
Persistence Of Elevated Serum Tumor Markers			
none	1	1	1
elevated	1	1	1
Lymph-Vascular Invasion			
none	1	1	1
identified	2.43 (0.40, 14.89) 0.3377	1.06 (0.00, inf.) 0.9992	0.00 (0.00, Inf) 0.9994
Tumor Size			
<4cm	1	1	1
>=4cm	3.34 (0.68, 16.29) 0.1364	0.94 (0.07, 11.81) 0.9615	2.13 (0.12, 38.43) 0.6091

increased risk in patients received radiotherapy compared with surgery alone using the data of 2,512 5-year survivors of testicular cancer [3]. In a study of 990 men with unilateral testicular cancer conducted by Haugnes et al. [15], the risk of cardio-vascular diseases in patients received radiotherapy was 2.3-fold than surgery only, which showed a similar result as described previously. The mechanism of radiation-induced cardio-vascular disease is unclear, it may come from the direct vascular injury of radiation [16]. And it was also reported that a potential reason for radiation-induced cardio-vascular diseases was that ionizing radiation can result in a rise in reactive oxygen species triggering lipid oxidation, damage of the endothelium and activation of nuclear factor (NF)-κB, a transcriptional factor involved in the local inflammatory responses [17].

Secondary malignancies played an important role in the adverse effect on long term survival associated with radiotherapy. As described in the study of Maroto et al. [18], the risk of secondary malignant neoplasms doubled after radiotherapy or chemotherapy. Alexandra et al. [3] also reported a 2.6 fold (95% CI, 1.7- to 4.0-fold) risk of secondary malignant neoplasms in patients received PORT compared with surveillance. Similarly, Stephanie A et al. [19] reviewed that the risk of secondary malignant neoplasms after radiotherapy was significantly higher than those who did not, and the risk was dose related. In another study conduct by Mazonakis et al. [20], Para-aortic radiotherapy in a low dose of 20Gy may lead to a very small probability for the appearance of prostate, lung, or thyroid cancer, however, para-aortic radiotherapy may result in a substantial increase of the baseline risk for the induction of bladder or esophageal cancer.

As shown in our study, the risk of CSM in patients received PORT was 0.40 fold of those who did not (HR=0.40, 95% CI=0.25-0.63, p<0.0001) which demonstrated a significant benefit in patients' survival. In patients of CSI and II TS, the risk of CSM in PORT patients was lower than those not (CSI: HR=0.61, 95% CI=0.28-1.31, p=0.2184) (CSII: HR=0.40, 95% CI=0.13-1.20, p=0.1010), however, these results were of no statistical significance. In patients with advanced disease (CSIII TSs), radiotherapy brought adverse impact on patients' survival, which showed 1.49-fold risk of CSM in PORT patients compared with those did not (HR=1.49, 95% CI=0.74-3.00, p=0.2592), still not statistically significant. These results was parallel with the opinion in the EAU and NCCN guidelines that radiotherapy could be used in CSI and II patients but not recommended in CSIII patients. And the reason why our results were of no statistical significance maybe caused by the relatively low probability of CSM in TS patients.

Analyzing the factors may effect the survive of PORT patients, we found that elevated tumor markers (hcG and LDH) were related with higher risk of CSM. Elevation of hcG value was not usually seen in TS, it may indicate mixture of non-seminomatous germ cell tumor elements, these subtypes often presented a poorer prognosis than TS and not sensitive to radiotherapy. LDH was not a specific tumor marker for TS, its elevation often related with higher tumor burden, which demonstrates the tumor was underestimated and thus led to a higher risk of CSM. Aging is also found to be related with worse prognosis in PORT patients. Elder people always have worse baseline conditions, considering the severe side effects that radiotherapy brought, utilization of PORT in elder people should be very cautious.

The present study has several limitations. First, not all clinical data (information of chemotherapy, dose and field of radiotherapy, end points other than death, etc.) were collected in SEER database. This could not be avoided due to its retrospective nature. Secondly, the timeframe of this study is relatively short, with an observation period of ten years, considering the optimal prognosis of TS patients, the observation time may not be long enough. Thirdly, side effects and complications related with therapy was not provided.

Conclusion

According to the results of our study, PORT can be beneficial to the long term survival in TS patients, however, it did not show significant advantage in patients of each CS. Elevation of hcG and LDH and elder age can lead to higher risk of CSM in PORT patients. Regarding our results and previous evidence on adverse effects of radiotherapy, utilization of PORT in the management of TS should be considered comprehensively. Adjustment for radiotherapy in TS management has become a must in clinical practice.

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