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High and low dose rate intraoperative radiotherapy for thoracic malignancies resected with close or positive margins

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Abstract

Purpose—Local recurrence is a significant problem after surgical resection of thoracic tumors. As intraoperative radiotherapy (IORT) can deliver radiation directly to the threatened margin, we have used this therapy in an attempt to reduce local recurrence, using high-dose-rate (HDR) as well as low-dose-rate (LDR) techniques.

Materials and Methods—We performed a retrospective review of patients undergoing LDR (I-125) mesh placement or HDR (Ir-192) afterloading therapy during lung tumor resection between 2001 and 2013 at our institution. Competing-risks methods were used to estimate the cumulative incidence of local failure. We also assessed possible predictive factors of local failure.

Results—Fifty-nine procedures (41 LDR, 18 HDR) were performed on fifty-eight patients. Median followup was 55.1 months. Cumulative incidence of local failure at 1, 2, and 3 years was 28.5%, 34.2%, and 34.2% respectively. Median overall survival was 39.9 months. There was no significant difference in local failure according to margin status, HDR vs. LDR, use of adjuvant EBRT, or metastatic vs. primary tumor. Two patients (3.4%) experienced grade 3+ toxicities likely related to brachytherapy. Additionally, 7 patients experienced grade 3+ postsurgical complications unlikely related to brachytherapy.

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Disclosures

The remaining authors have no conflicts to disclose.

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Conclusions—IORT is associated with good local control after resection of thoracic tumors otherwise at very high risk for local recurrence. There is a low incidence of severe toxicity attributable to brachytherapy. HDR-IORT appears to have equivalent outcomes to LDR-IORT. HDR or LDR-IORT can therefore be considered in situations where the oncologic completeness of thoracic tumor resection is in doubt.

Keywords

Intraoperative radiotherapy; high dose rate; thorax

Introduction

Thoracic tumors are generally managed surgically when the primary goal of treatment is durable local control. However, complete resection of the tumor is not always possible, and in cases where the surgical margin is known or presumed to be positive, adjuvant treatments are often prescribed in order to reduce the likelihood of local recurrence. Options for adjuvant treatment include systemic therapy and radiotherapy. If radiotherapy is used, external beam radiotherapy (EBRT) is the most common technique.

However, intraoperative radiotherapy (IORT) is an alternative to EBRT with unique practical and dosimetric benefits. Rapid dose fall-off allows for high dose to the threatened margin with minimal dose to additional normal tissue. Patients who have previously received a course of EBRT to the same or nearby site may not be candidates for more EBRT due to normal tissue tolerances, and brachytherapy may be the only option for adjuvant RT. Additionally, the difference in treatment length is substantial. Whereas a course of adjuvant EBRT may take four to six weeks to complete, IORT only requires that the operation be extended by one or two hours.

At our institution, IORT in the thorax has been performed either by low-dose rate (LDR) permanent implantation of a mesh containing iodine-125 seeds, or by high dose rate (HDR) temporary application of afterloaded iridium-192. In recent years HDR-IORT has become the more common method of thoracic IORT at our institution.

To date there is extremely limited data on the use of HDR-IORT in the thorax, with only one report consisting of 6 patients (1). Existing reports on the use of LDR-IORT in the lung have shown mixed results. A recent prospective trial comparing sublobar resection vs. sublobar resection with LDR I-125 implants for early-stage NSCLC found no significant increase in grade 3 adverse events, but also no significant benefit in local control (2,3). Published studies on intraoperative LDR implants in advanced thoracic malignancy have generally reported low incidence of toxicity with high rates of local control, and further investigation was therefore encouraged (4,5). Because of the paucity of contemporary literature regarding the safety and efficacy of thoracic IORT, in particular with HDR-IORT, we sought to review our institution's experience with these techniques to further elucidate their risks and benefits.

Materials / Methods

Patient Selection

Institutional review and privacy boards approved this study, and patient confidentiality was maintained as required by the Health Insurance Portability and Accountability Act. We performed a retrospective review of patients undergoing permanent LDR I-125 mesh placement or temporary HDR Ir-192 afterloading therapy during surgical resection of primary or metastatic lung tumors between 2001 and 2013. Patients were required to be at least 18 years of age at time of procedure to be included in the study. One patient underwent two separate LDR procedures one week apart, one to the anterior chest wall and the other to the posterior chest wall; each event was analyzed separately for local failure.

Treatment

In general, for LDR I-125 brachytherapy, iodine seeds were sutured into a mesh at 1cm intervals to form a planar implant prescribed to deliver 85-150Gy to the minimum peripheral dose (MPD), which was then sutured onto the at-risk site. For HDR Ir-192 brachytherapy, a Harrison-Anderson-Mick (HAM) applicator was apposed to the at-risk site, then connected to the afterloader to deliver 7.5-16Gy to a depth of 0.5cm from the applicator surface. The prescription dose was at the radiation oncologist's discretion, based on factors such as size of treatment area, prior external beam radiotherapy, proximity to critical structures, and assessment of the probability or extent of residual disease. Representative dosimetry for HDR and LDR brachytherapy are shown in figures 1 and 2, respectively.

Data Collection

All patient charts were retrospectively reviewed to obtain patient, disease, and treatment factors at the time of brachytherapy procedure. Patient factors included age and gender. Disease factors included histology, site of origin, staging, treatment of primary vs. metastatic disease, first treatment vs. recurrence, and prior external beam radiation to the brachytherapy site. Treatment factors included site, size of resected tumor, frozen margin status, final margin status, technique (permanent LDR implants vs temporary HDR afterloading), prescription dose, prescription depth, area of implant, number of seeds and seed activity (LDR procedures), and number of channels utilized in the HAM applicator (HDR procedures).

We then assessed patient records for subsequent local failure and procedure-related complications. Local failure was defined as evidence of progression on CT or PET-CT imaging in the resected tumor bed. Intrathoracic failure that was judged to represent a new metastatic tumor, rather than a marginal recurrence of the resected and radiated tumor, was not counted as local failure. Complications were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Statistical Analysis

Local failure was analyzed using competing-risks methods on a per-procedure basis. The risk of local failure was estimated using a cumulative incidence function that accounted for death without local failure. Univariate analyses of disease and treatment factors with local

failure were evaluated using the Fine and Gray method. Kaplan-Meier analysis was used to estimate overall survival (OS), and patients who were still alive were censored at the date of last available follow-up. OS comparisons across subgroups were analyzed using the log-rank test. Local failure and OS were determined from the IORT procedure date. Statistical significance for all analyses was two-sided and used a 5% significance level ($p < 0.05$). Statistical analyses were performed using R (version 3.1.0; R Development Core Team) with the “survival” and “cmprsk” packages.

Results

Fifty-nine procedures (41 permanent, 18 temporary) were performed on 58 patients (median 56 years old, range 19-77). (See Table 1) The most common tumor histologies were NSCLC (n=22, with 68.2% having stage III or IV disease), sarcoma (n=18), thymic carcinoma (n=8), and mesothelioma (n=3). Treated sites included chest wall/paraspinal (n=31), lung (n=16), and mediastinum (n=12). Median OS was 39.9 months. OS at 1, 2, and 3 years was 81.8%, 72.0%, and 60.8% respectively (see Figure 3). Median followup was 55.1 months for patients alive at the time of analysis. The median size of the treated area was 27cm² (range: 4-152cm²). Thirty-four procedures were performed on patients who had previously received external beam RT to the area (range 30.6 – 67.0Gy, median 53.1 Gy). Final margins were microscopically negative in 25 cases (42.4%) and positive or not assessed in the remainder.

Cumulative incidence of local failure at 1, 2, and 3 years was 28.5%, 34.2%, and 34.2%, respectively (see Figure 4). No perioperative deaths occurred. There was no significant difference in local failure according to margin status, brachytherapy technique, use of additional adjuvant EBRT, or metastatic vs. primary tumor (See Table 2). Two patients (3.4%) experienced grade 3+ toxicities likely related to brachytherapy: one patient who also received preoperative EBRT developed grade 3 radiation pneumonitis; a second patient with prior EBRT for lymphoma died four years after IORT from complications of SVC syndrome likely induced by radiation fibrosis. An additional 7 patients experienced grade 3+ postsurgical complications less likely related to brachytherapy, consisting of 4 wound infections, bronchopleural fistula in a patient who underwent two IORT procedures over the course of two weeks, upper extremity DVT, and thoracic duct leak. Four patients experienced grade 2 neuropathy also unlikely related to brachytherapy. Overall grade 3+ complication rates were similar between LDR (9/40, 22.5%) and HDR (4/18, 22.2%) techniques. The rate of grade 3+ adverse events was similar between patients who had previously received EBRT (14.7%) and those who had not (16.7%).

Discussion

There is limited data on the safety and efficacy of thoracic intraoperative IORT, particularly the use of HDR-IORT. The recently reported ACOSOG Z0432 trial investigated the use of IORT in the context of sublobar resection for early-stage NSCLC, and did not demonstrate a significant benefit. However, those results are not generalizable to our patient population, which mostly comprised advanced-stage or metastatic tumors for which oncologically complete resection was felt to be difficult or impossible to achieve. This fundamental difference in oncologic scenarios is reflected by the significantly higher rate of two-year

local recurrence observed in our study (34.2%) vs. 9.3% in the brachytherapy arm of the Z0432 trial. When the baseline risk of local failure is higher, as in our cohort, interventions to reduce that risk are more likely to be clinically meaningful.

Our results show a favorable safety profile for thoracic IORT, with only 3.4% of patients developing grade 3+ toxicities that were likely radiotherapy-related. There is inherent difficulty in determining whether other observed post-surgical complications were due to surgery alone, or may have been potentiated by IORT. However, the nature and incidence of those complications led us to conclude that they were not related to IORT. For example, our observed rate of chronic post-surgical pain (6.8%) compares favorably to a recent study reporting the incidence following thoracic surgery as high as 24.9% (6). We also observed a 6.8% (4/58) incidence of grade 3 wound infections, which is not significantly greater than reported rates of deep chest infections after cardiothoracic surgeries on the order of 5.0% (7). The additional grade 3 complications of bronchopleural fistula, upper extremity DVT, and thoracic duct leak all occurred in the immediate postoperative setting and are therefore presumed complications of surgery. In total, 9/58 (15.5%) patients experienced grade 3+ toxicity, which closely matches the Harvard report on I-125 mesh implants reporting a 12% incidence of grade 3+ toxicity at one year (4).

The Harvard experience with I-125 permanent implants showed a 1-year local control rate of 80.1%. Our study utilized a competing-risk regression to evaluate local failure, which should be a more precise analysis since it takes into account the significant competing risk of death without failure. Our finding that the cumulative incidence of local failure was 28.5% at one year supports the idea that most patients achieve initial local control with IORT. Because our observed incidence of local failure was not significantly greater at two and three years, it appears that most local failures occur within the first year and thereafter, local control is durable with IORT. Additionally, we did not find a significant difference in local failure between patients with positive vs. negative margins, which suggests that IORT may have been effective in equalizing local failures among patients who otherwise would have been expected to have higher risk.

Our study also adds to the literature by presenting data on the use of HDR-IORT in addition to LDR-IORT. HDR-IORT has certain practical advantages over LDR brachytherapy: no foreign objects or residual radioactivity are left in the patient, there is no need to order radioactive seeds in advance, and centers that already have the capability to perform HDR afterloading therapy can relatively easily adapt their existing equipment to deliver intrathoracic IORT. Additionally, changes in anatomy and implant configuration after surgery can result in discrepancies between the prescribed and delivered dose with permanent LDR implants, as opposed to HDR treatment where the entire treatment is both planned and completed during the operation itself. Due to these advantages, HDR-IORT has become increasingly popular in the past few decades for use in multiple body sites, particularly in rectal and breast cancers (8). To our knowledge there exists only one prior report on HDR-IORT in the thorax, and this report included only six patients receiving HDR brachytherapy (1). Our report therefore presents the first substantive and contemporary data showing that HDR-IORT can be safely done in the thorax and appears to yield comparable results to permanent LDR implants.

The major limitation of this study is its retrospective nature. Though we made efforts to adjust for clinical and treatment factors that could confound the analysis of predictive factors, it is impossible to account for every potential factor, especially when the individual patient scenarios are so diverse. A randomized trial would be necessary to prove that the rates of local recurrence are lower with IORT than without. However, such a trial is very unlikely to be done in this patient population. Obviously, in our retrospective series it is impossible to know how much higher the local recurrence rates would have been without IORT, if at all. However, given that IORT was only used for select cases that were clinically judged to be at very high risk for local recurrence, we believe that the relatively low rates of local recurrence we observed suggest that IORT has a valuable role to play in these scenarios, particularly since IORT also appears to have a low risk of causing significant toxicity.

Conclusions

This is one of the largest published experiences with thoracic IORT and the first substantive report on the outcomes of HDR-IORT for lung tumors. Our results support the conclusions that thoracic IORT, including HDR-IORT, is safe, and is associated with relatively low rates of local recurrence in situations where, due to positive or threatened margin status, the risk of local failure is thought to be very high.

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Glossary

IORT	intraoperative radiotherapy
HDR	high dose rate
LDR	low dose rate
EBRT	external beam radiation
MPD	minimum peripheral dose
HAM	Harrison-Anderson-Mick
CTCAE	Common Terminology Criteria for Adverse Events

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Figure 1.

HDR dosimetry. A 6×5cm (7 channels × 11 dwell positions) implant is shown. Source channels are depicted in red and prescription plane points are shown in blue. 12Gy were prescribed using an Atlas based plan to 1cm from the source (5mm from the surface of the HAM applicator). Panel A shows the treatment geometry, and panels B, C show the sagittal, axial isodose through the center of the applicator, panel D shows the isodose distribution in the coronal prescription plane (5 mm from the surface of the applicator).

Figure 2.
LDR dosimetry

Figure 3.
Overall Survival

Figure 4.
Cumulative incidence of local failure (competing-risks regression)

Table 1

Patient, disease, and treatment factors, with outcomes

Pt.	Histology	EBRT	Metastatic at surgery	IORT Technique	Dose (Gy)	Site of IORT	Follow up (months)	Final margin status	Local Failure	Time to LF (months)	Death	OS (months)	Cause of Death	Toxicity
1	Chondrosarcoma	No	Yes	HDR	15	Chest wall	6.50	Negative	No	6.50	Yes	6.57	Other	
2	Desmoid tumor	No	No	HDR	10	Chest wall	72.90	Positive	Yes	24.16	No	74.16		Chronic pain over incision and arm
3	Ewing's sarcoma	55.8Gy prior, 30Gy adjuvant	No	HDR	8	Chest wall	21.05	Not assessed	No	21.05	No	23.04		
4	Fibrolamellar HCC	No	Yes	HDR	10	Mediastinum	10.31	Not assessed	No	10.31	Yes	10.56	Intrathoracic progression	
5	Leiomyosarcoma	44Gy prior, 40Gy adjuvant	No	HDR	12	Mediastinum	52.66	Positive	No	52.66	Yes	52.66	Treatment-related	SVC syndrome
6	Liposarcoma	No	Yes	HDR	15	Chest wall	8.04	Not assessed	No	8.04	No	8.04		
7	Mesothelioma	50.4Gy prior	No	HDR	Two overlapping RT fields: 11Gy to periphery of tumor, 16Gy to center	Chest wall	6.15	Negative	Yes	6.15	Yes	7.59	Extrathoracic progression	
8	Myxoid fibrosarcoma	67Gy prior	Yes	HDR	15	Chest wall	41.36	Positive	Yes	6.57	Yes	41.36	Intrathoracic progression	
9	NSCLC	63Gy prior	No	HDR	15	Chest wall	58.53	Negative	No	58.53	No	58.53		Chronic pain over incision
10	NSCLC	66Gy prior	Yes	HDR	15	Chest wall	12.90	Positive	Yes	5.14	No	12.90		
11	NSCLC	62Gy prior	Yes	HDR	12	Chest wall	18.95	Negative	No	18.95	No	19.41		
12	Synovial sarcoma	65Gy prior	No	HDR	15	Chest wall	163.18	Negative	No	163.18	No	165.42		
13	Synovial sarcoma	No	No	HDR	15	Chest wall	36.89	Positive	Yes	1.54	No	36.89		
14	Thymic carcinoma	45Gy adjuvant	Yes	HDR	15	Mediastinum	5.14	Positive	No	5.14	Yes	25.91	Intrathoracic progression	Wound infection
15	Thymic carcinoma	No	No	HDR	7.5	Mediastinum	59.41	Positive	No	59.41	No	59.41		
16	Thymic carcinoma	54Gy prior	No	HDR	15	Chest wall	78.85	Negative	Yes	57.52	No	79.13		

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Pt.	Histology	EBRT	Metastatic at surgery	IORT Technique	Dose (Gy)	Site of IORT	Follow up (months)	Final margin status	Local Failure	Time to LF (months)	Death	OS (months)	Cause of Death	Toxicity
17	Thymoma	No	Yes	HDR	12	Chest wall	12.06	Not assessed	Yes	11.47	No	12.20		
18	Thyroid carcinoma	63Gy prior	No	HDR	15	Chest wall	85.28	Negative	Yes	5.73	No	86.78		
19	Colorectal	No	Yes	LDR	225	Chest wall	6.05	Positive	No	6.05	Yes	9.16	Intrathoracic progression	
20	Desmoid tumor	No	No	LDR	100	Chest wall	164.23	Positive	No	164.23	No	164.23		Empyema
21	Desmoid tumor	46.8Gy prior	No	LDR	150	Mediastinum	104.83	Positive	Yes	11.08	No	107.83		
22	Leiomyosarcoma	50Gy prior	No	LDR	150	Chest wall	105.77	Negative	No	105.77	No	105.77		
23	Leiomyosarcoma	No	Yes	LDR	150	Chest wall	39.86	Not assessed	No	39.86	Yes	40.07	Extrathoracic progression	
24	Leiomyosarcoma	No	Yes	LDR	150	Lung Parenchyma	24.93	Positive	No	24.93	No	24.93		
25	Mesothelioma	50.4Gy prior	No	LDR	150	Chest wall	47.69	Negative	No	47.69	Yes	51.71	Extrathoracic progression	Empyema
26	Mesothelioma	44Gy adjuvant	No	LDR	175	Chest wall	3.88	Positive	Yes	2.31	Yes	5.35	Extrathoracic progression	
27	Neuroendocrine	No	Yes	LDR	100	Mediastinum	24.16	Positive	No	24.16	No	24.16		
28	Neurofibrosarcoma	No	Yes	LDR	85	Mediastinum	63.43	Negative	No	63.43	Yes	64.06	Extrathoracic progression	
29	NSCLC	45Gy prior	No	LDR	150	Lung Parenchyma	37.45	Negative	No	37.45	Yes	38.88	Other	Radiation pneumo-nitis
30	NSCLC	45Gy prior	No	LDR	120	Lung Parenchyma	100.17	Positive	No	100.17	No	100.17		Chronic arm pain, weakness
31	NSCLC	45Gy prior	No	LDR	150	Lung Parenchyma	5.63	Negative	No	5.63	Yes	7.20	Extrathoracic progression	Thoracic duct leak
32	NSCLC	50.4Gy prior	No	LDR	150	Lung Parenchyma	62.66	Negative	No	62.66	No	62.66		
33	NSCLC	30.6Gy prior	No	LDR	150	Lung Parenchyma	9.86	Positive	Yes	7.10	Yes	18.74	Extrathoracic progression	
34	NSCLC	45Gy prior	Yes	LDR	95	Lung Parenchyma	20.52	Positive	Yes	16.68	Yes	22.55	Extrathoracic progression	
35	NSCLC	No	No	LDR	250	Lung Parenchyma	5.87	Positive	No	5.87	Yes	8.43	Other	

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Pt.	Histology	EBRT	Metastatic at surgery	IORT Technique	Dose (Gy)	Site of IORT	Follow up (months)	Final margin status	Local Failure	Time to LF (months)	Death	OS (months)	Cause of Death	Toxicity
36	NSCLC	66Gy prior	No	LDR	150	Lung Parenchyma	15.35	Negative	No	15.35	Yes	33.15	Unknown	
37	NSCLC	45Gy prior	No	LDR	150	Lung Parenchyma	22.34	Negative	No	22.34	Yes	22.34	Other	
38	NSCLC	66Gy prior	No	LDR	140	Chest wall	10.03	Positive	No	10.03	Yes	18.18	Extrathoracic progression	
39	NSCLC	50.4Gy prior	No	LDR	150	Chest wall	1.26	Positive	No	1.26	Yes	5.42	Unknown	
40	NSCLC	52.2Gy prior	No	LDR	130	Lung Parenchyma	0.38	Negative	No	0.38	No	0.38		
41	NSCLC	45Gy prior	no	LDR	150	Lung Parenchyma	41.19	Negative	Yes	8.08	Yes	42.45	Intrathoracic progression	
42	NSCLC	64.8Gy prior	Yes	LDR	150	Lung Parenchyma	21.33	Positive	Yes	11.89	Yes	30.84	Intrathoracic progression	
43	NSCLC	63Gy prior	No	LDR	150	Chest wall	5.28	Positive	No	5.28	Yes	6.50	Extrathoracic progression	
44	NSCLC	50.4Gy prior	No	LDR	120	Lung Parenchyma	7.41	Positive	No	7.41	No	7.41		
45	NSCLC	45Gy prior	No	LDR	150	Chest wall	58.04	Positive	No	58.04	Yes	58.32	Other	
46	NSCLC	45Gy prior	No	LDR	150	Lung Parenchyma	2.59	Negative	No	2.59	No	2.59		
47	NSCLC	No	No	LDR	110	Lung Parenchyma	25.66	Negative	Yes	3.67	Yes	46.22	Unknown	
48	Renal cell carcinoma	No	Yes	LDR	150	Mediastinum	38.46	Negative	No	38.46	Yes	40.91	Intrathoracic progression	
49	Rhabdomyosarcoma	54Gy prior	No	LDR	130	Mediastinum	10.63	Positive	Yes	4.20	Yes	10.63	Intrathoracic progression	
50	Spindle cell carcinoma	No	No	LDR	150	Chest wall	16.43	Negative	Yes	1.75	Yes	16.75	Intrathoracic progression	
51	Synovial sarcoma	No	No	LDR	150	Mediastinum	66.89	Negative	No	66.89	Yes	83.15	Extrathoracic progression	
52	Synovial sarcoma	No	No	LDR	132	Chest wall	45.24	Negative	Yes	8.81	Yes	47.48	Intrathoracic progression	Empyema
53	Synovial sarcoma	No	Yes	LDR	150	Chest wall	106.01	Negative	Yes	65.87	No	106.36		
54	Thymic carcinoma	54Gy adjuvant	No	LDR	150	Mediastinum	28.53	Positive	No	28.53	Yes	33.57	Extrathoracic progression	Upper extremity DVT

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Pt.	Histology	EBRT	Metastatic at surgery	IORT Technique	Dose (Gy)	Site of IORT	Follow up (months)	Final margin status	Local Failure	Time to LF (months)	Death	OS (months)	Cause of Death	Toxicity
55	Thymic carcinoma	54Gy prior	Yes	LDR	130	Chest wall	43.29	Negative	Yes	38.71	Yes	46.36	Intrathoracic progression	Broncho- pleural fistula
55	Thymic carcinoma	54Gy prior	Yes	LDR	150	Chest wall	43.60	Positive	Yes	39.02	Yes	46.68	Intrathoracic progression	Broncho- pleural fistula
56	Thymic carcinoma	66Gy prior	No	LDR	110	Chest wall	13.29	Positive	Yes	10.52	Yes	32.03	Extrathoracic progression	
57	Thymic carcinoma	No	Yes	LDR	150	Mediastinum	122.48	Positive	No	122.48	No	124.13		Hoarseness 2/2 nerve injury
58	Thymic carcinoma	45Gy adjuvant	Yes	LDR	105	Chest wall	27.52	Positive	Yes	13.57	No	27.52		

Table 2

Local failure analysis by subgroups

	Hazard Ratio	95% CI	P-value
Adjuvant EBRT (yes vs. no)	0.80	0.18 – 3.51	0.77
Margin Status (R0 vs. other)	0.86	0.38 – 1.95	0.71
Metastatic vs. Primary tumor	0.75	0.31 – 1.83	0.53
Technique (HDR vs LDR)	1.35	0.58 – 3.16	0.48