Title

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Journal

Annals of Surgical Oncology, 23(11)

ISSN

1068-9265

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Publication Date

2016-10-01

DOI

10.1245/s10434-016-5269-1

Peer reviewed

Published in final edited form as:

Ann Surg Oncol. 2016 October ; 23(11): 3541–3547. doi:10.1245/s10434-016-5269-1.

Local Control Modality and Outcome for Ewing Sarcoma of the Femur: A Report From the Children's Oncology Group

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICT OF INTEREST There are no conflicts of interest.

Abstract

Background—The choice of a local control (LC) modality for Ewing sarcoma (EWS) of the femur is controversial. This study aimed to determine the effect of LC modality on tumor LC and patient outcomes.

Methods—The study reviewed the treatment and outcomes for 115 patients who had EWS of the femur treated with similar chemotherapy in three cooperative group trials. Patient outcomes were analyzed according to the LC modality using the log-rank test and the cumulative incidence of local or distant failure using competing risks regression.

Results—The median age of the patients was 13 years. The most common tumor location was the proximal femur followed by the mid femur. For 55 patients with available data, the tumor was larger than 8 cm in 29 patients and 8 cm or smaller in 26 patients. For 84 patients (73 %), surgery only was performed, whereas 17 patients (15 %) had surgery plus radiation, and 14 patients (12 %) had radiation only. The 5-year event-free survival (EFS) rate was 65 % (95 % confidence interval [CI], 55–73 %), and the 5-year overall survival (OS) rate was 70 % (95 % CI, 61–78 %). Patient outcomes did not differ significantly according to tumor location within the femur (proximal, mid or distal) or tumor size (<8 vs ≥8 cm). The findings showed no statistically significant differences in EFS, OS, cumulative incidence of local failure, or cumulative incidence of distant failure according to LC modality (surgery, surgery plus radiation, or radiation).

Conclusions—The LC modality did not significantly affect disease outcome for EWS of the femur. Further study of treatment complications and functional outcome may help to define the optimal LC modality.

Ewing sarcoma (EWS) is the second most common malignant bone tumor in children after osteosarcoma. Modern therapy for EWS includes a combination of multi agent chemotherapy and local treatment. Three successive randomized trials conducted by the Children's Oncology Group (COG) have shown the positive impact of adding ifosfamide and etoposide (IE) to a chemotherapy regimen containing vincristine, doxorubicin, and cyclophosphamide (VDC) and of intensifying chemotherapy through interval compression but not through dose escalation of alkylating agents on the outcome of patients with localized disease.[1–3] Surgery, radiation, or both are used for local tumor control. The choice of local treatment modality is influenced by multiple factors including age, tumor location, tumor size, metastatic pattern, response to chemotherapy, patient preference, physician preference, and institutional practice.[4,5]

The femur is the most commonly involved bone in EWS, followed by the ilium and the rib.[1,6] Because of their anatomic location, femoral tumors present significant challenges in terms of local treatment, and the most appropriate treatment modality for this site has been debated. In addition, the femur has important structural significance. It is a weight-bearing bone, and forces across its proximal aspect can exceed six to eight times the body weight with every step.[7,8] Hence, EWS arising at this site presents some therapeutic challenges. The local control (LC) modality may have an impact not only on the rate of local recurrence and treatment complications,[9,10] but also on patient survival.[11]

Although our previous analysis of Ewing sarcoma of all bones showed no significant correlation between the LC modality and patient survival, but an increased risk of local failure with radiation versus surgery, it is worth conducting a site-specific analysis of LC because the choice of LC may be influenced by the anatomic site.[4] For these reasons, we conducted a detailed analysis of the treatment and outcomes for all patients with EWS of the femur who received similar chemotherapy in the three successive EWS trials. Our study aimed to evaluate the effect of LC modality on LC and patient outcome and to identify factors that may correlate with the choice of LC modality.

METHODS

Study Population

The study included eligible patients with non-metastatic EWS of the femur who were enrolled in three cooperative group trials (INT-0091, INT-0154, and AEWS0031).[1–3,4] To ensure homogeneity of the systemic therapy received by the study population, we included only patients who received VDC alternating with IE (VDC/IE) every 3 weeks and local therapy after neoadjuvant chemotherapy. We excluded all patients treated in the standard arm of INT-0091 without IE and in the intensive arms of INT-0154 and AEWS0031. We also excluded 16 patients for whom data on the LC modality and date were missing.

The patients were treated primarily at COG centers in the United States and Canada. The treatment protocols were approved by the institutional review board of each participating center, and appropriate informed consent was obtained for all the enrolled patients.

Statistical Analyses

The patients were grouped into three groups according to the LC modality used for their treatment: surgery only, surgery plus radiation, or radiation only. The three groups were compared using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. The variables of comparison included patients' demographics, the trial in which patients were enrolled, year of enrollment, tumor location within the femur (distal, mid, or proximal), and tumor size (≤8 or>8 cm in greatest dimension). Tumor size data were not collected in AEWS0031, and data on surgical resection margins were not available. The patients who had missing data for a given characteristic were not included in the statistical tests for differences among groups.

Event-free survival (EFS) was defined as the interval from the date of LC to the date of disease relapse/progression, diagnosis of a second malignant neoplasm, or death or to the date of the last patient contact for patients without events. The date of LC was defined as the date of the first LC intervention the patient underwent after initial neoadjuvant chemotherapy. For the patients who experienced disease relapse or progression, in whom a second malignant neoplasm was diagnosed, and those who died were considered to have experienced an EFS event. Otherwise, the patient was considered as censored at the last contact.

Overall survival (OS) was defined as the interval from the date of LC to the date of death or last patient contact for survivors. The patients who died were considered to have experienced

an OS event regardless of the cause of death. Otherwise, the patient was considered as censored at the last contact.

The method of Kaplan and Meier was used to estimate EFS and OS as a function of time since the start of LC.[12] The log-rank test was used to evaluate differences in EFS and OS according to the LC modality.[13]

The EFS events were classified as identification of a new disease at the primary site (local recurrence) regardless whether disease was identified at any other site, identification of disease at a site not present at enrollment but not at the primary site (distant recurrence), or any other EFS event as defined earlier. The cumulative incidence of local and distant recurrences as a function of time since LC was estimated by the method of Gray.[14] Tests for significant differences in cumulative incidence rates among LC modalities were calculated by competing risks regression using the method of Fine and Gray.[15]

RESULTS

Patient Characteristics and Treatment

The criteria for inclusion in the study were met by 131 patients with non-metastatic EWS of the femur. The patient characteristics and treatment are summarized in Table 1. The median age at study enrollment was 13 years (range, 1–33 years). The most common tumor location was the proximal femur followed by the mid and distal femurs.

For 29 (53 %) of 55 patients who had available data on tumor size, the tumor was more than 8 cm in the largest dimension. The modality of LC was surgery for only 84 patients (73 %), surgery plus radiation for 17 patients (15 %), and radiation only for 14 patients (12 %). The majority of the 101 patients who underwent surgery had reconstruction using a prosthesis or an allograft prosthetic composite ($n = 35$) or an allograft ($n = 37$). A small proportion had a vascularized autograft ($n = 7$), rotationplasty ($n = 2$), or amputation ($n = 5$). The type of reconstruction was unknown for 15 patients.

We compared the three groups of patients with the different LC modalities in terms of clinical characteristics and treatment protocol (Table 1). The three groups did not differ significantly in terms of age, gender, race, tumor location within the femur, or tumor size. Significant differences were found by treatment protocol and year of enrollment. More patients enrolled in INT-0091 between 1989 and 1992 had radiation only ($p = 0.0129$).

Patient Outcomes

Of the 115 patients in this study, 34 had a disease relapse, 2 had a second malignant neoplasm, and 5 experienced death as a first event. For these 115 patients, the estimated 5-year EFS was 65 % (95 % confidence interval [CI] 55–73 %), and the estimated 5-year OS was 70 % (95 % CI 61–78 %) (Fig. 1). Patient outcomes did not differ significantly with respect to age, gender, race, tumor location within the femur (proximal, mid, or distal), tumor size (<8 vs ≥8 cm), treatment protocol, or year of enrollment (Table 2).

Local Control Modality and Patient Outcomes

Of the 84 patients in the surgery-only group, 24 had a disease relapse or death as the first event compared with 8 of 17 patients in the surgery-plus-radiation group and 7 of 14 patients in the radiation-only group. The two patients who experienced a second malignant neoplasm were in the surgery-only group. The estimated 5-year EFS rates were 69 % (95 % CI 57–78 %) for the patients who had surgery only, 53 % (95 % CI 28–73 %) for those who had surgery plus radiation, and 57 % (95 % CI 28–78 %) for those who had radiation only. The estimated 5-year OS rates were 74 % (95 % CI 62–82 %) for the patients who had surgery only, 59 % (95 % CI 33–78 %) for those who had surgery plus radiation, and 64 % (95 % CI 34–83 %) for those who had radiation only. No statistically significant differences in EFS ($p = 0.32$) or OS ($p = 0.43$) according to the LC modality (surgery only, surgery plus radiation, or radiation only; Fig. 2a and b) were observed.

Local Control Modality and Cumulative Incidence of Local Failure

The sites of failure included 17 distant-only, 2 local-only, and 4 concurrent local plus distant locations. The cumulative incidence of local recurrence was 5.3 % 2 years after the LC procedure, and no local recurrences were detected after that time. The cumulative incidence of distant recurrence was 16 % 7 years after the LC procedure, and no distant recurrences were detected after that time. No statistically significant differences in the cumulative incidence of local failure ($p = 0.93$) or the cumulative incidence of distant failure ($p = 0.16$) according to LC modality (surgery only, surgery plus radiation, or radiation only; Fig. 3a, b) were observed.

DISCUSSION

This study included the largest series of patients with localized EWS of the femur. To control extraneous variation that could arise from different chemotherapies, the study included only patients treated with VDC/IE every 3 weeks ($n = 115$). The tumors arose most commonly in the proximal aspect of the femur, and the majority of the patients underwent surgery for LC. The estimated 5-year EFS of 65 % (95 % CI 55–73 %) appeared similar to that for patients with EWS of all sites treated with VDC/IE every 3 weeks.[3] Importantly, we found that the LC modality did not significantly affect the cumulative incidence of local failure, EFS, or OS.

The current COG strategy for LC in EWS favors surgical resection when possible and the use of radiotherapy when surgical resection would result in significant or unacceptable morbidity. In a recent comparative evaluation of LC modality for 465 patients with localized EWS of all bones, the choice of LC did not significantly correlate with EFS or OS, but the risk of local failure was higher with radiation than with surgery.[4]

In the current study investigating EWS of the femur, the choice of LC also did not correlate with EFS or OS, but we did not find a statistically significant increased risk of local failure with radiation alone. These findings may be related in part to the small number of patients in this site-specific study and to a bias for performing surgery for LC of extremity tumors.

In our study, the choice of LC did not correlate with clinical characteristics including age, tumor location within the femur, and tumor size. However, we found a tendency for using less definitive radiotherapy for LC in the two most recent trials conducted after 1995. This tendency could be related to better ability to perform surgery due to improvements in imaging, surgical, and reconstructive techniques over time and to an increased awareness of the potential risk for radiation-induced secondary malignancies.

Small tumor size (<8 cm) and imaging response to induction chemotherapy have been associated with LC in patients who received radiation only.[16] In addition, tumor location within the femur is thought to be of prognostic significance. Patients with tumors of the distal femur have a survival advantage over those with proximal and mid-femoral tumors.[9] Similar to the Cooperative Ewing's Sarcoma Studies (CESS) group study, our study did not show a significant correlation between tumor size or tumor location within the femur and patient outcome.[11]

The 5-year EFS of the patients with localized EWS of the femur in our study (65 %) was similar to that for patients with EWS of all sites treated with similar chemotherapy (65 %),[3] and at least as good as that for 91 patients with localized EWS of the femur treated at the Istituto Ortopedico Rizzoli (56 %).[10] The EFS also was comparable with the 10-year relapse-free survival rate of 55 patients with localized EWS of the femur treated in CESS 86 and CESS 91P (65 %).[11] Although age, gender, and tumor size have been associated with EFS of patients with EWS of bone,[6,17–19] these factors did not show statistically significant correlation with patient outcomes in our cohort who had EWS of the femur.

The 5-year survival rate for the patients in our cohort (70 %) was comparable with that for the patients treated at the Istituto Ortopedico Rizzoli (64 %).[10] In the latter study, the 5-year OS for the patients who underwent surgery with or without radiotherapy was 64 % compared with 57 % for those who received radiotherapy only.[10] In comparison, the survival of the patients treated in three CESS studies (CESS 81, CESS 86, and CESS 91P) was worse after radiotherapy alone than after surgery with or without radiotherapy. However, this finding may be related to a high local or combined relapse rate due to a high local failure rate when radiotherapy was used for LC in patients treated in CESS 81 with a four-drug chemotherapy regimen (vincristine, actinomycin-D, cyclophosphamide, and doxorubicin without ifosfamide or etoposide).[11] Our study of patients who received VDC/IE did not show any significant difference in EFS or OS according to LC modality.

Our study was limited by its retrospective nature, the limited number of patients with a site-specific rare cancer, and the long span of study enrollment (1989–2005), which may have had an impact on treatment decisions. The unavailability of certain data elements such as tumor response to chemotherapy, extent of surgery/resection margins, complications after local treatment including rate of fracture or amputation, and functional outcome did not allow investigation of these important factors relevant to LC. Surgery has been advocated for treatment of EWS in bones for which reliable, functionally enabling reconstructions are anticipated. The femur in most cases is such a bone. Although the feasibility of resection and reconstruction must be evaluated for each individual patient, the durability of the

construction, the best choice of reconstructive procedure, and the rate of complications are not clearly defined.

Radiation offers an alternative to surgery for this radiosensitive tumor but has its own advantages and disadvantages. Although radiation provides the advantage of maintaining the patient's joint/bone, it may increase the risk for fractures, limb length/alignment discrepancies in skeletally immature patients, local induration, joint stiffness, and secondary malignancy.[20–23] A recent report of long-term functional outcomes for patients with EWS of all sites suggests that quality of life and musculoskeletal outcomes are similar for patients treated with surgery and those managed with radiotherapy.[24]

In summary, we found that the prognosis for EWS of the femur is similar to that for EWS of all sites. Although the risk of local failure is increased with the use of radiation alone for local treatment of EWS of all bones,[4] our site-specific analyses of femoral tumors did not detect a significant correlation between LC modality and disease outcome. Feasibility of reconstruction and its durability in addition to potential risks associated with radiation should be considered in the decision making about local treatment. Further study of treatment complications and functional outcome of the limb may help to elucidate the best LC modality. Prioritizing such research in the cooperative group setting to ensure adequate patient numbers is critical to answering these important questions. Our findings from the current study further highlight the need for conducting national and international multi-institutional studies to help address controversies regarding the management of a rare cancer such as Ewing sarcoma.

Acknowledgments

This study was supported by National Institute of Health/National Cancer Institute grant 1K23CA154530 and by U10CA180886 (NCTN Operations Center Grant) and U10CA180899 (NCTN Statistics & Data Center Grant), as well as by U10CA98543 (Chair's Grant) and U10CA98413 (Statistics & Data Center Grant) grants from the National Cancer Institute. Additional support for research was provided by a grant from the WWWW (QuadW) Foundation, Inc. (www.QuadW.org).

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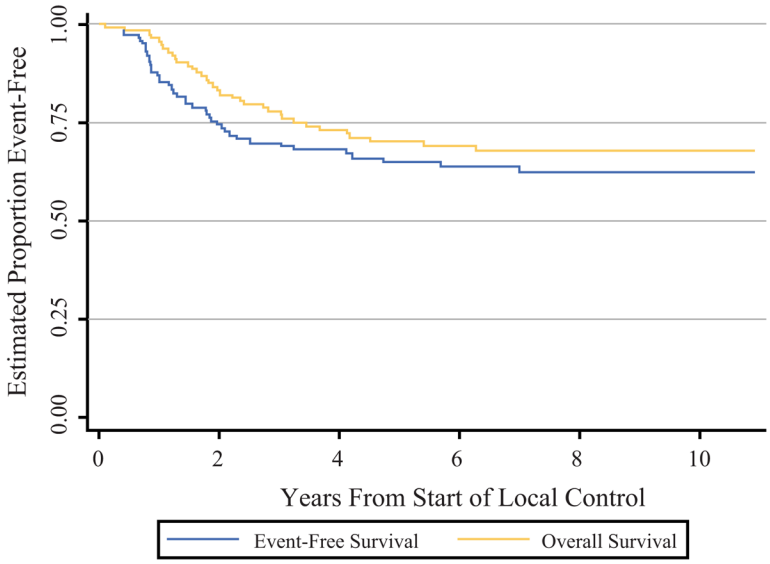

FIG. 1.

Event-free survival (EFS) and overall survival (OS) for 115 patients with Ewing sarcoma of the femur treated with vincristine, doxorubicin, and cyclophosphamide (VDC) plus ifosfamide and etoposide (IE) every 3 weeks

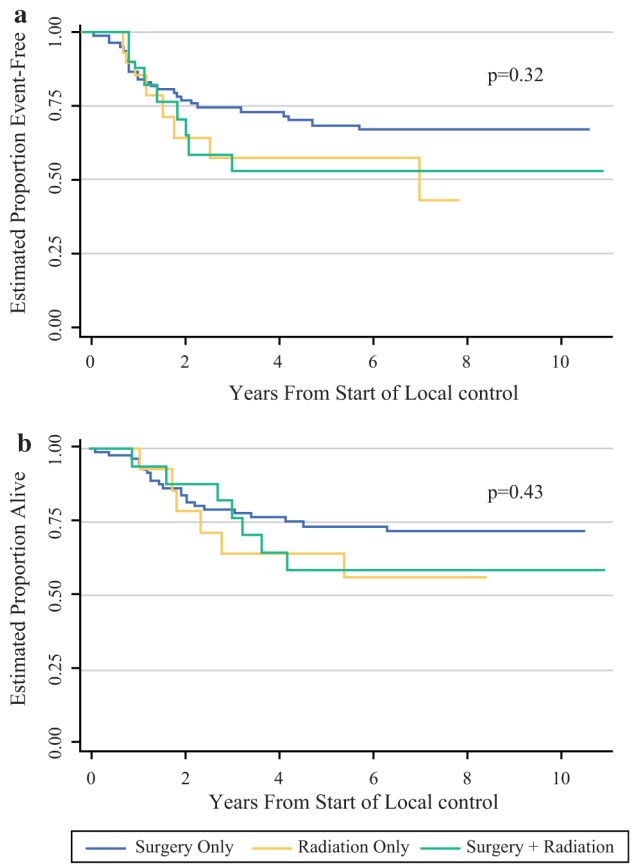

FIG. 2.

a Event-free survival (EFS) and **b** overall survival (OS) for patients with Ewing sarcoma of the femur according to the local control modality

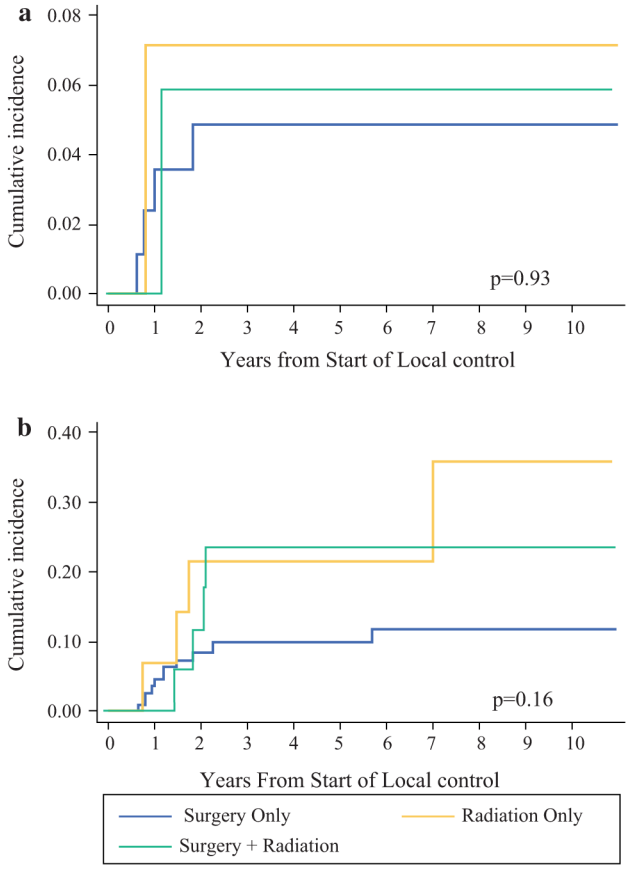

FIG. 3.

a Cumulative incidence of any local failure (isolated or in combination with distant failure) and **b** distant failure only according to the local control modality

TABLE 1

Clinical characteristics of 115 patients with Ewing sarcoma of the femur according to local control modality

Characteristic	Total no. of patients (*n* = 115)	Surgery only (*n* = 84)	Surgery plus radiation (*n* = 17)	Radiation only (*n* = 14)	*p* Value[a]
Median age: years (range)	13 (1–33)	13 (1–33)	14 (3–27)	12 (2–23)	0.929[b]
Age (years)					
≤13	63	46	8	9	0.625
>13	52	38	9	5	
Gender					
Male	69	53	9	7	0.528
Female	46	31	8	7	
Race					
White	98	73	13	12	0.629
Black	4	2	1	1	
Hispanic	10	7	2	1	
Other	1	1	0	0	
Not available	2	1	1	0	
Location in femur					
Proximal	49	39	6	4	0.956
Mid	26	19	4	3	
Distal	19	15	2	2	
Not available	21	11	5	5	
Median tumor size: cm (range)		11 (5–35)	11 (4–18)	10 (7–22)	0.879[b]
Tumor size (cm)					
≤8	26	18	4	4	0.923
>8	29	18	5	6	
Not available	60	48	8	4	
Treatment regimen					
INT-0091 experimental arm	33	19	4	10	0.013
INT-0154 standard arm	50	39	8	3	
AEWS0031 standard arm	32	26	5	1	
Year of enrollment in study					

Ann Surg Oncol. Author manuscript; available in PMC 2016 December 04.

Characteristic	Total no. of patients (n = 115)	Surgery only (n = 84)	Surgery plus radiation (n = 17)	Radiation only (n = 14)	p Value[a]
1989–1992	33	19	4	10	0.013
1995–1998	50	39	8	3	
2001–2005	32	26	5	1	

[a] p Value calculated using Fisher's exact test except for continuous variable.

[b] p Value calculated using the Wilcoxon test

TABLE 2

Analyses of event-free survival (EFS) and overall survival (OS) according to clinical characteristics

Variable	EFS		OS	
	Relative HR (95 % CI)	*p* Value[a]	Relative HR (95 % CI)	*p* Value[a]
Age (years)				
≤13	1.0	0.575	1.0	0.635
>13	1.19 (0.65–2.20)		1.17 (0.60–2.28)	
Gender				
Male	1.0	0.672	1.0	0.783
Female	1.14 (0.62–2.12)		1.10 (0.56–2.15)	
Race				
White	1.0	0.814	1.0	0.875
Not white	0.89 (0.35–2.28)		1.08 (0.42–2.78)	
Location in femur				
Proximal	1.0	0.508	1.0	0.317
Mid	1.30 (0.58–2.90)		1.63 (0.67–3.93)	
Distal	1.64 (0.69–3.88)		1.96 (0.76–5.06)	
Tumor size (cm)				
≤8	1.0	0.671	1.0	0.815
>8	1.22 (0.48–3.10)		1.12 (0.43–2.91)	
Treatment regimen				
INT-0091 experimental arm	1.0	0.339	1.0	0.125
INT-0154 standard arm	0.68 (0.32–1.43)		0.53 (0.23–1.19)	
AEWS0031 standard arm	1.16 (0.53–2.51)		1.17 (0.52–2.61)	
Surgery/reconstruction				
Amputation	0.54 (0.07–4.12)	0.824	0.59 (0.08–4.55)	0.803
Prosthesis/allograft prosthesis composite	0.96 (0.42–2.17)		0.88 (0.36–2.13)	
Allograft	1.0		1.0	
Rotationplasty	2.13 (0.28–16.45)		2.07 (0.27–16.11)	
Vascularized autograft	1.35 (0.38–4.80)		0.43 (0.06–3.32)	
Local control modality				
Surgery only	1.0	0.320	1.0	0.431
Surgery plus radiation	1.56 (0.70–3.44)		1.50 (0.64–3.52)	
Radiation only	1.69 (0.73–3.90)		1.64 (0.66–4.04)	

HR hazard ratio

[a] *p* Values calculated using the log-rank test