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## Long-term Outcomes of Cervical Cancer Patients Treated with Definitive Chemoradiation following a Complete Metabolic Response

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### Abstract

**Aims:** A complete metabolic response (CMR) on early post-treatment <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET) is a positive prognostic factor for cervical cancer patients treated with definitive chemoradiation, but long-term outcomes of this group of patients are unknown. Patterns of failure and risk subgroups are identified.

**Materials and methods:** Patients who received curative-intent chemoradiation from 1998 to 2018 for International Federation of Gynecology and Obstetrics (FIGO) stage IB1–IVA cervical cancer and had a CMR on post-treatment FDG-PET within 5 months of treatment completion were included. Cox proportional hazards models determined factors associated with locoregional and distant failure. Kaplan–Meier estimates of freedom from any recurrence (FFR) of patient subgroups were compared with Log-rank tests.

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Conflicts of Interest

The authors report no conflicts of interest with this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clon.2021.01.010>.

**Results:** There were 402 patients with a CMR after chemoradiation on FDG-PET. Initial T stage was T1 (38%)/T2 (40%)/T3 (20%)/T4 (2%); initial FDG-avid nodal status was no nodes (50%)/pelvic lymph nodes (40%)/pelvic and para-aortic lymph nodes (10%). After a median follow-up of 6 years, 109 (27%) recurred. The pattern of recurrence was locoregional (27%), distant (61%) or both (12%). No factors were associated with locoregional failure. Distant recurrence was more likely in patients with T3–4 lesions (hazard ratio = 2.4, 95% confidence interval 1.5–3.8) and involvement of pelvic (hazard ratio = 1.6, 95% confidence interval 1.0–2.7) or para-aortic lymph nodes (hazard ratio = 2.7, 95% confidence interval 1.4–5.0) at diagnosis. The 5-year FFR rates for T1–2 patients with no nodes, pelvic nodes alone or para-aortic nodes at diagnosis were 85, 76 and 62%, respectively ( $P = 0.04$ , none versus para-aortic nodes). The 5-year FFR for T3–4 patients with no nodes, pelvic nodes alone or para-aortic nodes at diagnosis were 68, 56 and 25%, respectively ( $P = 0.09$ , none versus para-aortic nodes).

**Conclusions:** T3–4 tumours and para-aortic nodal involvement at diagnosis are poor prognostic factors, even after a CMR following chemoradiation.

### Keywords

Cervical cancer; chemoradiation; complete metabolic response; FDG-PET; prognosis; recurrence

### Introduction

Locally advanced cervical cancer is treated with definitive chemoradiation therapy. At initial staging,  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) is widely used to define metabolically active tissues, specifically the primary tumour and involved lymph nodes, which can then be targeted during treatment planning [1]. Following chemoradiation, the extent of residual FDG-uptake in the primary tumour and involved lymph nodes on post-treatment FDG-PET is highly prognostic of overall survival [2]. About 70% of patients will have a complete metabolic response (CMR), but 23% of these responders eventually experience cervical cancer recurrence [3].

Previous efforts to further define prognostic factors associated with recurrence in this subset of patients have shown mixed results. Beriwal *et al.* [4] reported on 112 cervical cancer patients with a CMR after chemoradiation, but only 11 (10%) had recurred after a short median follow-up of 15 months. Only initial tumour size was associated with local tumour recurrence [4]. Onal *et al.* [5] published on 122 patients with a CMR after chemoradiation and a median follow-up of 29 months. There were 25 (21%) recurrences, which were associated with tumour size  $\geq 5$  cm, International Federation of Gynecology and Obstetrics (FIGO) stage  $\geq$  IIB and pelvic and/or para-aortic nodal metastasis at diagnosis [5].

In this study, we examined the patterns of failure and risk factors for recurrence in a larger patient cohort with longer clinical follow-up than in the previous reports. Our goal was to define low-risk and high-risk subgroups of patients among those who had a CMR after curative chemoradiation, which could help to determine the necessity of subsequent follow-up imaging and/or identify patients who may benefit from additional adjuvant therapies.

## Materials and Methods

### Patients and Initial Treatment

Cervical cancer patients treated at a tertiary academic medical centre by definitive external beam radiation with brachytherapy boost and concurrent chemotherapy were identified in a prospectively maintained database (by a single physician, author PWG) from March 1998 to November 2018. All patients had a complete pre-treatment work-up, including history and physical examination, examination under anaesthesia, cervical tumour biopsy, pelvic computed tomography (CT) or magnetic resonance imaging (MRI) and FDG-PET. Patients were treated with external beam radiation to the pelvis to 50.4 Gy in 28 daily fractions and received either low or high dose rate brachytherapy boost to the cervix, as previously described [6]. Para-aortic nodal regions up to the renal veins were treated if para-aortic nodes were involved on staging FDG-PET. Concurrent weekly cisplatin 40 mg/m<sup>2</sup> was prescribed to all patients. Patients who did not complete radiation treatment or did not have FDG-PET staging and follow-up scans were excluded.

### Follow-up and Outcomes

Patients were followed with clinical examinations about every 2 months for the first 6 months, every 3 months for the next 2 years and then every 6 months. FDG-PET was typically ordered 3 months after the completion of treatment and then as indicated by clinical examination or symptoms. Patients had a CMR if pre-treatment FDG-avid disease had post-treatment FDG uptake that was less than or equal to blood pool activity and there were no new sites of disease. Patients whose disease subsequently recurred were restaged at that time with another FDG-PET. Locoregional failure was defined as within the initial radiation field, and distant failure was outside the initial radiation field. The time to event was determined from each patient's pre-treatment PET scan. This retrospective analysis was approved by our institutional Human Research Protection Office with waiver of informed consent (IRB# 201911195).

### Statistical Analysis

Fisher's exact test was used to compare categorical data and the non-parametric Mann–Whitney *U* test was used for continuous variables. Freedom from any recurrence (FFR) was shown with Kaplan–Meier analyses. Statistical significance was calculated by Log-rank test. Cox regression analysis was carried out for both univariable and multivariable modelling of locoregional and distant failure. Factors significant on univariable analysis ( $P < 0.1$ ) were entered in a backward-conditional multivariable model. Final significance was defined as  $P < 0.05$ , and all tests were two-tailed. Statistical analyses were carried out in SPSS, version 23 (IBM, Armonk, NY, USA).

## Results

The median time from the completion of therapy to post-treatment FDG-PET was 2.9 months (range 1.0–5.0). Of a total of 542 patients completing curative chemoradiation, there were 402 (74%) with a CMR after chemoradiation on FDG-PET (16% imaged with PET alone and 84% PET/CT). Table 1 shows the baseline clinical characteristics of these patients.

The median age was 49 years (23–86 years); initial T stage was T1 (38%)/T2 (40%)/T3 (20%)/T4 (2%); the median cervical metabolic tumour volume [7] was 31 ml (1–347 ml); initial FDG-avid nodal status was involvement of no nodes (50%)/pelvic lymph nodes (40%)/pelvic and para-aortic lymph nodes (10%); and histology was squamous (84%)/non-squamous (16%). The median treatment length was 48 days (range 35–97).

After a median follow-up of 6 years (range 0.5–20), 109 (27%) patients had cancer recurrence. The pattern of first recurrence was locoregional (27%), distant (61%) or both (12%). All cervix recurrences were biopsy-proven. There were 37 (34%) patients with recurrences diagnosed by clinical examination and imaging alone. Table 2 shows the patterns of recurrence by initial FDG-avid nodal status. The predominant risk of recurrence in patients with initial pelvic or para-aortic nodes was distant failure outside the radiation field. Isolated para-aortic failure in patients irradiated to the pelvis alone was rare (2%). No baseline or treatment factors were significantly associated with cervix or pelvic failure (see Supplementary Tables S1 and S2). Table 3 shows that distant recurrence was more likely in patients with T3–4 lesions (hazard ratio = 2.4, 95% confidence interval 1.5–3.8) and involvement of pelvic (hazard ratio = 1.6, 95% confidence interval 1.0–2.7) or para-aortic lymph nodes (hazard ratio = 2.7, 95% confidence interval 1.4–5.0) at diagnosis. Similar results were found in the Cox model for any recurrence (Table 4).

Figure 1 shows that the 5-year FFR rates for T1–2 patients with no nodes, pelvic nodes alone or para-aortic nodes at diagnosis were 85, 76 and 62%, respectively ( $P=0.04$  between no nodes and para-aortic nodes). The 5-year FFR rates for T3–4 patients with no nodes, pelvic nodes alone or para-aortic nodes at diagnosis were 68, 56 and 25%, respectively ( $P=0.09$  between no nodes and para-aortic nodes).

## Discussion

The National Comprehensive Cancer Network guidelines recommend a 3–6 month post-treatment surveillance FDG-PET after definitive chemoradiation for cervical cancer. Patients who have a CMR after definitive radiation on early post-treatment FDG-PET have a good prognosis compared with patients who have only a partial metabolic response or progressive disease [8]. However, the crude recurrence rate still approaches 30% in this large series of over 400 patients with a CMR, indicating that the predictive power of FDG-PET may be limited by its insensitivity for detection of microscopic disease. Pre-treatment T-stage and metabolically active pelvic and/or para-aortic lymph nodes were independently associated with risk of recurrence after a CMR, ranging from 15 to 75% in different subsets of patients. The pattern of failure was mostly distant, and no factors tested predicted locoregional failure. This study identified high-risk patients with a CMR who might benefit from either adjuvant therapy or more intensive surveillance, both of which are active areas of research.

In contrast to prior studies [4,5], we did not show initial tumour volume or the maximum standardised uptake value to predict local failure in patients with a CMR. Notably, 88% of the patients in our series received 6 weekly fractions of HDR intracavitary brachytherapy, starting usually within 2 weeks of treatment interdigitated with external beam radiation. The dose delivered to at least 90% of the primary tumour was often over 100 Gy (equivalent

dose in 2 Gy fractions) [9], which is an ablative dose. This differs from the previous studies in which external beam radiation was given upfront and then followed by a brachytherapy boost, which was prescribed to a lower dose. Tumour volume changes after external beam radiation but prior to brachytherapy have been shown to predict tumour sensitivity to radiation [10]. In the Pittsburgh cohort [4], interstitial brachytherapy was used if patients had a poor response to external beam radiation (about 25% of their patients), which could also change the patterns of recurrence.

Tumour histology also did not impact the prognosis after a CMR in this cohort. Onal *et al.* [5] found that patients with squamous histology had a worse overall survival compared with those with adenocarcinoma after a CMR, but this was not significant after accounting for tumour size and stage. The negative predictive value of FDG-PET for detecting lymph node metastasis in early stage cervical cancer is only 78% for squamous versus 92% for adenocarcinoma histology [11]. A CMR theoretically could be more predictive of lower recurrence risk for adenocarcinoma histology, but a larger cohort may be needed to discover this effect.

The 5-year risk of any recurrence after a CMR in this study was stratified from 15 to 75%, depending on the pre-treatment T and N stage. These results could help to select only high-risk patients for future studies testing adjuvant therapy. Adjuvant gemcitabine and cisplatin after concurrent chemoradiation improved overall survival over concurrent chemoradiation alone for locally advanced cervical cancer patients in a prospective randomised trial [12], but utilisation in standard practice has been limited because of concerns of overtreatment and toxicity. Another recently reported trial testing three cycles of adjuvant carboplatin and paclitaxel failed to accrue and was thus underpowered to show any survival differences [13]. The OUTBACK trial ([Clinicaltrials.gov ID: NCT01414608](https://clinicaltrials.gov/ct2/show/study/NCT01414608)) tested four cycles of adjuvant carboplatin and paclitaxel and we await early results to be reported. In contrast to cytotoxic chemotherapy, adjuvant immunotherapy after chemoradiation in locally advanced cervical cancer patients seemed to be tolerable in a phase I study [14]. Response rates in metastatic cervical cancer have been low when given in a non-selected patient population, yet most patients with an immune response against tumours have had sustained progression-free survival [15]. Identifying both imaging and immune biomarkers for patients who benefit from immunotherapy is a secondary objective of an ongoing randomised phase II multi-institutional trial of concurrent or adjuvant pembrolizumab for locally advanced cervical cancer ([NCT02635360](https://clinicaltrials.gov/ct2/show/study/NCT02635360)).

Post-treatment circulating blood biomarkers, such as squamous cell carcinoma antigen [16,17], the circulating neutrophil-to-lymphocyte ratio [18] and circulating tumour cells [19] or human papillomavirus (HPV) DNA [20], are prognostic of disease-free survival in cervical cancer patients. In addition to detecting residual microscopic disease in patients with a CMR, these liquid biopsies could also give an early readout of whether adjuvant systemic therapy is going to be effective. For example, detectable circulating tumour DNA (ctDNA) after definitive chemoradiation was predictive of response to adjuvant immunotherapy in locally advanced lung cancer [21]. Recurrence rates were low in patients who had no detectable ctDNA whether they received adjuvant immunotherapy or not. If detectable ctDNA increased early during adjuvant immunotherapy, recurrence rates were

higher than if ctDNA levels decreased. These blood biomarkers need to be evaluated in a prospective trial, which would be costly if tested in every locally advanced cervical cancer patient. The positive predictive value of these tests could be enriched by only evaluating patients with an intermediate-to-high risk of recurrence, such as those identified in this study.

Finally, the role of continued surveillance FDG-PET after a CMR is controversial because of the cost of scans. We and others have shown that surveillance FDG-PET scans detect asymptomatic metastasis early, which has translated to increased overall survival in retrospective series [22,23]. The efficacy of radical local therapy, such as surgery or ablative radiation, to extend survival in oligometastatic disease has been shown prospectively [24]. However, this study proves that 3-month post-treatment FDG-PET alone cannot be used to direct surveillance intensity or give cervical cancer patients confidence in their prognosis. Therefore, alternative strategies for surveillance should be explored in prospective randomised studies. For example, our group recently showed that something as simple as post-treatment HPV DNA clearance from a vaginal swab sample was independently associated with better recurrence-free and overall survival [25]. Distant recurrence is the most common pattern of failure in this subset of patients, but continued FDG-PET surveillance may not necessarily be the only option. Future prospective work could focus on the cost-effectiveness of obtaining surveillance FDG-PET versus CT or MRI in patients with high risk of progression after a CMR, based on this study.

In conclusion, this retrospective study's strengths are that nearly all cervical cancer patients at our institution received an early post-treatment FDG-PET in the study period and we had adequate follow-up time to capture recurrences after a CMR. However, some clinics outside of the USA and in much of the developing world do not routinely carry out FDG-PET scans due to constrained resources, which limits the generalisability of this study. Most recurrences occurred outside the radiation field, indicating that better systemic therapies are needed. Patients with either T3–4 disease or FDG-avid para-aortic lymph nodes pre-treatment are at high risk of recurrence even with a CMR. Both imaging and circulating biomarkers of initial treatment response will probably be important for current and future studies of adjuvant therapy. Our results indicate that continued clinical follow-up is necessary despite a CMR after definitive chemoradiation therapy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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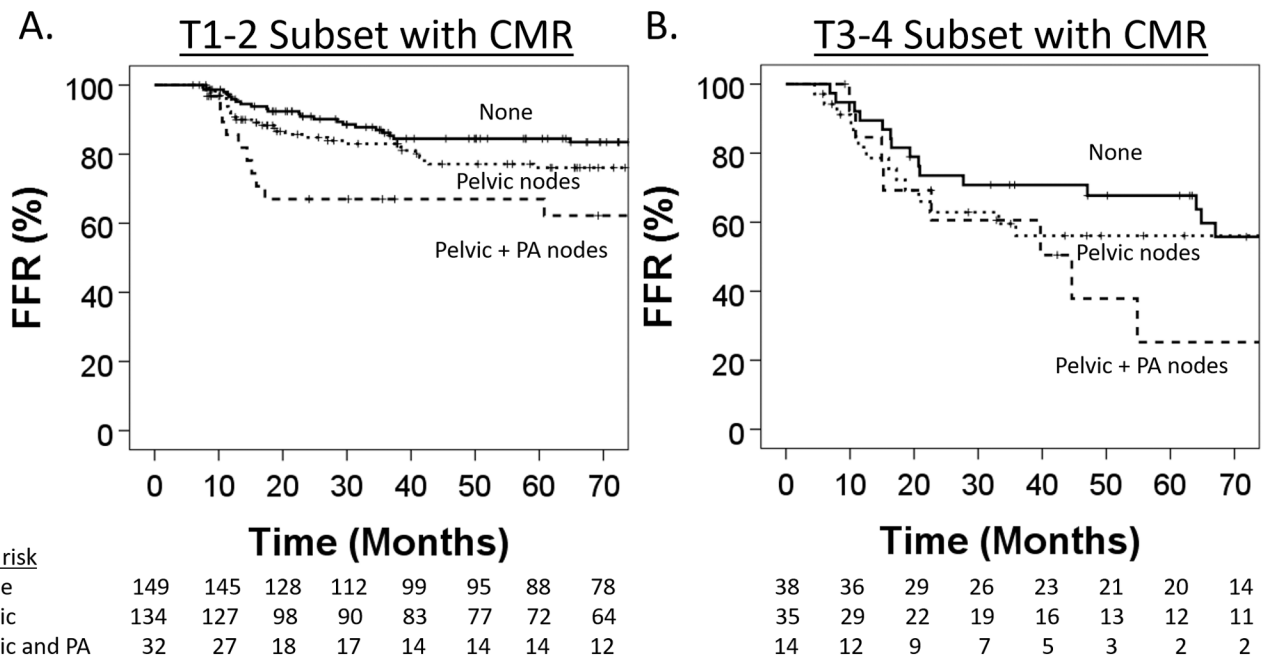
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**Highlights:**

- Complete metabolic response (CMR) on 3-month PET has non-homogeneous cervical cancer control rates
- Distant recurrence is the most common pattern of failure
- Initial T and N stage independently stratify risk of distant recurrence after CMR



**Fig 1.** (A) Kaplan–Meier estimates of freedom from recurrence (FFR) in the subset of T1–2 patients with a complete metabolic response (CMR) after curative chemoradiation stratified by pre-treatment fluorodeoxyglucose (FDG)-avid lymph nodes. (B) FFR in the subset of T3–4 patients with a CMR after curative chemoradiation stratified by pre-treatment FDG-avid lymph nodes.

**Table 1:**

Baseline clinical and initial treatment characteristics of patients that had a complete metabolic response on early post-treatment FDG-PET, stratified by those that subsequently had disease recurrence.

Baseline factors	Any Recurrence n=109	No Recurrence n=293	P value
Median Age	47 (26–77)	49 (23–86)	0.27
<u>Race</u>			0.32
Caucasian	76 (26%)	214 (74%)	
African American	32 (32%)	69 (68%)	
Asian	0 (0%)	6 (100%)	
Hispanic	1 (20%)	4 (80%)	
<u>Histology</u>			0.52
Squamous	93 (27%)	246 (73%)	
Adenosquamous	3 (43%)	4 (57%)	
Adenocarcinoma	13 (23%)	43 (77%)	
<u>FIGO 2009 (T stage)</u>			<b>0.03</b>
IB1	8 (17%)	38 (83%)	
IB2	24 (22%)	85 (78%)	
IIA1	1 (33%)	2 (67%)	
IIA2	0 (0%)	1 (100%)	
IIB	39 (25%)	117 (75%)	
IIIA	3 (60%)	2 (40%)	
IIIB	31 (41%)	45 (59%)	
IVA	3 (50%)	3 (50%)	
Median metabolic tumor volume (mL) *	37 (1–198)	30 (2–346)	0.10
Cervix SUVmax **	12 (3.4–50)	13 (2.1–60)	0.20
<u>PET Lymph Nodes</u>			0.10
None	44 (24%)	143 (76%)	
Pelvic	47 (28%)	122 (72%)	
Pelvic and Para-aortic	18 (39%)	28 (61%)	
<u>Brachytherapy</u>			0.80
LDR	12 (26%)	35 (74%)	
HDR	97 (27%)	258 (73%)	
<u>EBRT planning</u>			<b>0.002</b>
2D	49 (37%)	83 (63%)	
IMRT	60 (22%)	210 (78%)	
Median Treatment Days	50 (39–90)	48 (35–97)	<b>0.008</b>

Abbreviations: FIGO-International Federation of Gynecology and Obstetrics; PET- positron emission tomography; LDR- low dose rate; HDR- high dose rate; EBRT- external beam radiation therapy; 2D- 2 dimensional; IMRT- intensity modulated radiation therapy

\* Calculated from the FDG-avid cervical tumor primary, with 40% maximum standard uptake value as the volume threshold. Data incomplete. 293 pts with PET volume data.

\*\* Calculated from the FDG-avid cervical tumor primary. Data incomplete. 318 patients with cervix SUVmax data.

**Table 2:**

Sites of failure in patients with CMR stratified by initial FDG-avid lymph node status

<b>Pre-treatment FDG-avid lymph nodes</b>	<b>Failure in cervix alone</b>	<b>Failure in pelvic lymph nodes alone</b>	<b>Failure in para-aortic nodes alone</b>	<b>Locoregional failure inside radiation field alone *</b>	<b>Distant failure outside radiation field alone</b>	<b>Both locoregional and distant failure</b>
None (n =187)	13 (7%)	3 (2%)	3 (2%)	16 (9%)	21 (11%)	7 (4%)
Pelvic only (n=169)	6 (4%)	4 (2%)	3 (2%)	10 (6%)	33 (20%)	4 (2%)
Pelvic and para-aortic (n=46)	0 (0%)	2 (4%)	0 (0%)	3 (7%)	13 (28%)	2 (4%)

\* Radiation field included the pelvis for all patients. The para-aortic region was only irradiated in patients with pre-treatment FDG-avid para-aortic lymph nodes.

**Table 3:**

Univariable and multivariable Cox proportional hazard models for distant failure after CMR on early post-treatment FDG-PET.

Baseline factors	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Age	1.00 (0.98–1.01)	0.57		
<u>T stage</u>				
I-II	Ref		Ref	
III-IVA	2.53 (1.61–3.97)	<b>&lt;0.001</b>	2.42 (1.53–3.82)	<b>&lt;0.001</b>
MTV*	1.00 (0.99–1.01)	0.93		
Cervix SUVmax**	1.00 (0.97–1.03)	0.86		
<u>PET lymph nodes</u>				
None	Ref		Ref	
Pelvic	1.61 (0.98–2.62)	0.06	1.63 (1.00–2.66)	<b>0.05</b>
Pelvic and PA	2.93 (1.57–5.50)	<b>0.001</b>	2.65 (1.41–4.98)	<b>&lt;0.001</b>
<u>Histology</u>				
Squamous	Ref			
Non-squamous	0.85 (0.44–1.65)	0.63		
<u>Brachytherapy</u>				
HDR	Ref			
LDR	0.73 (0.36–1.47)	0.37		
<u>EBRT planning</u>				
IMRT	Ref			
2D EBRT	1.41 (0.90–2.21)	0.13		
<u>Treatment length</u>	1.03 (1.003–1.05)	<b>0.02</b>	NS, removed from model	

Abbreviations: as in Table 1; MTV- metabolic tumor volume; Ref- reference value; HR- hazard ratio; CI- confidence interval; NS- not statistically significant

**Table 4:**

Univariable and multivariable Cox proportional hazard models for any failure after CMR on early post-treatment FDG-PET.

Baseline factors	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Age	0.99 (0.98–1.01)	0.40		
<u>T stage</u>				
I-II	Ref		Ref	
III-IVA	2.16 (1.46–3.22)	<b>&lt;0.001</b>	2.09 (1.40–3.11)	<b>&lt;0.001</b>
MTV*	1.00 (0.99–1.01)	0.94		
Cervix SUVmax**	1.00 (0.97–1.02)	0.70		
<u>PET lymph nodes</u>				
None	Ref		Ref	
Pelvic	1.28 (0.85–1.93)	0.24	1.29 (0.86–1.95)	0.22
Pelvic and PA	2.21 (1.28–3.83)	0.005	2.03 (1.17–3.52)	<b>0.01</b>
<u>Histology</u>				
Squamous	Ref			
Non-squamous	1.04 (0.61–1.76)	0.90		
<u>Brachytherapy</u>				
HDR	Ref			
LDR	0.67 (0.36–1.23)	0.20		
<u>EBRT planning</u>				
IMRT	Ref			
2D EBRT	1.29 (0.87–1.90)	0.21		
<u>Treatment length</u>	1.03 (1.005–1.05)	<b>0.01</b>	NS, removed from model	

Abbreviations: as in Tables 1–2