

# High-dose radiation therapy alone by moderate hypofractionation for patients with thoracic esophageal squamous cell carcinoma

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## Abstract

We conducted retrospective analyses to investigate the clinical outcome of thoracic esophageal cancer patients who were treated with high-dose radiation therapy (RT) alone by moderate hypofractionation due to medical unfitness or refusal to receive either surgery or chemo-radiotherapy.

Between May 2003 and April 2013, 70 patients were treated with high-dose RT alone with curative aim. The planned total RT dose was 60Gy in daily 3.0Gy per fraction. We evaluated the survival outcome, toxicities, and prognostic factors affecting patients' survival.

At the time of analysis, 32 patients experienced disease progression. The 2-year overall survival (OS), cancer-specific survival (CSS) and local control (LC) rates were 52.1%, 57.8%, and 68.2%, respectively. Among them, 25 patients had superficial (cT1a-b) esophageal cancers, and the 2-year OS, CSS, and LC rates were 80.0%, 87.3%, and 81.6%, respectively. Multivariate analysis revealed that cT disease ( $P < 0.001$ ) and tumor location ( $P = 0.022$ ) were the significant factors for OS. The incidence of grade 3 or higher toxicities were 9.9%, including grade 3 esophagitis (2 patients, 2.8%) and grade 4 or 5 trachea-esophageal fistula (5 patients, 7.1%).

High-dose RT alone by moderate hypofractionation had led to reasonable clinical outcomes at acceptable toxicity risk in thoracic esophageal cancer patients who are medically unfit or refuse surgery or chemotherapy, especially for the patients having superficial lesion.

**Abbreviations:** AJCC = American Joint Committee on Cancer, CCRT = concurrent chemoradiotherapy, CSS = cancer-specific survival, CT = computed tomography, CTV = clinical target volume, EBRT = external beam radiation therapy, EMR = endoscopic mucosal resection, FDG-PET = <sup>18</sup>F-deoxy-glucose positron emission tomography, GTV = gross tumor volume, ILBT = intraluminal brachytherapy, JASTRO = Japanese Society of Therapeutic Radiology and Oncology, LC = local control, OAR = organs at risk, OS = overall survival, RT = radiation therapy, RTOG = Radiation Therapy Oncology Group, SCC = squamous cell carcinoma.

**Keywords:** esophageal cancer, esophageal squamous cell carcinoma, hypofractionation, radiation therapy

## 1. Introduction

Esophageal cancer is the eighth most common cancer worldwide and has generally a poor prognosis.<sup>[1]</sup> Squamous cell carcinoma (SCC) is a predominant histologic type in Asia, whereas adenocarcinoma is more common than SCC in Western

countries.<sup>[2,3]</sup> Complete resection has been the mainstay curative option for early stages, and it includes from endoscopic mucosal resection (EMR)<sup>[4-6]</sup> to esophagectomy with lymph node dissection. Multimodal approaches that combine surgery, radiation therapy (RT), and systemic chemotherapy are generally recommended for loco-regionally advanced stages.<sup>[7]</sup> Surgery or chemotherapy, however, is often limited because of patients' comorbidities, advanced age, or poor general conditions. EMR also cannot be suitable for submucosal tumors or larger mucosal tumors. In this clinical situation, definitive RT alone remains the only curative option. RT alone, however, has been usually associated with disappointing 5-year overall survival (OS) rates of 0% to 20% in loco-regionally advanced disease.<sup>[8-12]</sup> Although several authors have recently reported quite favorable outcomes with the local control rates of 70% to 80% level in the patients with clinical T1 stage esophageal cancer, the use of RT alone has no strong clinical support and clinical evidence as of yet.<sup>[13-15]</sup> Furthermore, the optimal RT dose and fractionation schedules in this setting have not yet been defined. High-dose definitive RT alone by hypofractionated schedule using daily 3.0 Gy has been applied to the patients with esophageal SCC who refuse surgery or chemotherapy or are medically unfit for aggressive approaches at the authors' institutes, and we would hereby report the clinical outcomes.

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## 2. Material and methods

### 2.1. Patients

Between May 2003 and Apr 2013, a total of 198 newly diagnosed and pathologically confirmed thoracic esophageal SCC patients were treated with RT with a curative aim at the authors' institutes. Among them, after excluding 128 patients who underwent chemoradiation therapy, 70 patients formed the basis of the retrospective study. The patients were treated by high-dose RT alone using 3.0 Gy per fraction due to either medical comorbidity or refusal of surgery or chemoradiation. The patients with T1a tumors who were not candidates for EMR due to large tumor size or circumferential extent were also included in the current study. The current study was approved by our institutional review board.

### 2.2. Staging procedures

The diagnostic procedures included a complete history-taking and physical examination, simple chest x-rays, endoscopic examination, computed tomography (CT) scans of the chest and abdomen, and routine blood test. Endoscopic ultrasonography was performed in the patients with apparently superficial lesions, and bronchoscopy was performed when tumor invasion into the tracheobronchial wall was suspected. <sup>18</sup>F-deoxy-glucose positron emission tomography (FDG-PET) or PET/CT was performed in nearly all patients (68 patients, 97.1%). The clinical stage was assigned according to the 7th American Joint Committee on Cancer (AJCC) staging system.

### 2.3. Radiation therapy

All patients underwent contrast-enhanced CT simulation in the supine position. The gross tumor volume (GTV) was delineated to include the grossly enlarged primary tumor and metastatic lymph nodes with the references to endoscopic findings, diagnostic CT, and FDG-PET/CT images. When no gross lesion was visible on these images, we requested endoscopist to place 1 or 2 metal clips at the superior and inferior edges of the primary tumor for GTV delineation. The clinical target volume (CTV) was delineated to include the known GTV of the primary tumor and lymph nodes plus a 2 to 3 cm margin in the caudal and cranial directions and a 5 to 10 mm margin in radial directions, considering the neighboring anatomic boundaries. The supraclavicular and/or celiac lymphatics, if not definitely enlarged, were not electively included in the CTV. The planning target volume (PTV) was determined by adding 5 to 10 mm to the CTV. The planned total dose was 54 to 60 Gy by daily 3.0 Gy per fraction over 3 to 4 consecutive weeks. Three or four 6 or 10-MV photon beams were arranged to adequately cover the PTV while minimizing the dose to the surrounding organs at risk (OARs) including the lungs, the spinal cord, the heart, and the bowels. The second plan during the RT course was done in 35 patients (50.0%) at 27 to 45 Gy range (median 30 Gy). The decision on second plan was individually made as per the physician's discretion not to exceed the tolerance limits of the OARs and to accommodate the possible changes in the CTV and OARs during the RT course.

### 2.4. Follow-up

The patients were evaluated at 1 month after RT. Thereafter, the patients were asked to visit our clinic at every 3 to 4 months'

interval for the first 2 years, and then at every 6 months' interval. Esophagogastroduodenoscopy or imaging study with either CT or whole-body PET/CT scans were performed on each follow-up visit. Local failure was defined as either persistent or progressive lesion within the CTV. The treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

### 2.5. Statistics

The duration of OS was calculated from the first day of RT to either the time of last follow-up or the time of death by any causes. The duration of cancer-specific survival (CSS) was calculated from the first day of RT to either the time of last follow-up or the time of death by esophageal cancer. The duration of local control (LC) was calculated from the first day of RT to either the time of last follow-up or the time of local failure. The survival rates were calculated using the Kaplan–Meier method, and the log-rank test and the Cox proportional-hazards regression model were employed for univariate and multivariate analysis, respectively. The distribution of categorical variables was analyzed using the chi-square test or Fisher exact test. A 2-sided *P*-value of 0.05 or less was considered statistically significant. SPSS 20.0 software was used for this analysis.

## 3. Results

### 3.1. Patient characteristics

The reasons to receive definitive RT alone instead of surgery were patients' refusal despite of physicians' recommendation in 9 patients (12.8%) and medically unfit patients' condition to undergo surgery and/or chemotherapy in 61 patients (87.2%), respectively. The patients' conditions included multiple primary cancer in 21 patients, old age in 18, poor performance status in 7, poor lung function in 7, heart problem in 4, and liver cirrhosis in 4, respectively. The patients' characteristics are summarized in Table 1. The vast majority of the patients were male (68, 97.1%), and the median age was 71 years (46–91 years). The mid-thoracic esophagus was the most common location of the primary tumor observed in 37 patients (52.9%), followed by upper and lower thoracic esophagus in 19 (27.1%) and in 14 (20.0%), respectively. About two-thirds of all patients had tumors with T2 or higher lesions (45, 64.3%), and three-fourths had no gross lymph node metastasis (53, 75.7%). The majority of patients (66, 94.3%) received 54 Gy or greater. The median radiation dose was 60 Gy (range 30–63 Gy). The median follow-up duration was 20 months (1–95 months) in all patients.

### 3.2. Treatment outcomes

At the time of analysis, 32 patients experienced disease progression and 42 had died. As the first site of recurrence, local failure developed in 20 patients, and the 2 and 5-year LC rates were 68.2% and 61.3%, respectively (Fig. 1). Eight patients died of nonesophageal cancer: hypopharyngeal cancer in 2, hepatobiliary cancer in 2, nonsmall cell lung cancer in 1, oral cavity cancer in 1, heart disease in 1, and liver cirrhosis in 1, respectively. Metachronous esophageal cancer outside of the initial CTV developed in 4 patients (5.7%). The 2 and 5-year OS and CSS rates were 52.1% and 38.8%, and 57.8% and 46.6%, respectively (Fig. 1). The median durations of OS and CSS were 36 and 51 months, respectively.

Table 1	
Patient characteristics.	
Characteristics	Number of patients (%)
Sex	
Male	68 (97.1%)
Female	2 (2.9%)
Age, y	
<70	32 (45.7%)
≥70	38 (54.3%)
Performance status	
ECOG 1	47 (67.1%)
ECOG 2	23 (32.9%)
Tumor location	
Upper thoracic	19 (27.1%)
Mid-thoracic	37 (52.9%)
Lower thoracic	14 (20.0%)
cT disease	
T1a	8 (11.4%)
T1b	17 (24.3%)
T2	21 (30.0%)
T3	22 (31.4%)
T4	2 (2.9%)
cN disease	
N0	53 (75.7%)
N1	11 (15.7%)
N2	6 (8.6%)
Grade	
Well	6 (8.6%)
Moderate	49 (70.0%)
Poor	3 (4.3%)
X	12 (17.1%)
AJCC stage 7th	
IA	5 (7.1%)
IB	20 (28.6%)
IIA	15 (21.4%)
IIB	15 (21.4%)
IIIA	7 (10.0%)
IIIB	6 (8.6%)
IIIC	2 (2.9%)

AJCC=American Joint Committee on Cancer, ECOG=Eastern Cooperative Oncology Group.

### 3.3. Superficial esophageal cancer (cT1a to T1b)

Among 25 patients who initially had cT1a-bN0 disease, 10 (40.0%) experienced disease progression: local progression in 4, regional recurrence outside of the CTV in 2, distant metastasis in 2, combined local and regional failures in 1, and combined regional and distant failure in 1, respectively (Table 2). In these patients, the 2-year OS, CSS, and LC rates were 80.0%, 87.3%, and 81.6%, respectively (Fig. 2).

### 3.4. Prognostic factors

In univariate analyses, poor prognostic factors for OS were poor performance status ( $P=0.022$ ), upper or mid-thoracic tumor location ( $P=0.017$ ), cT3-4 disease ( $P<0.001$ ), the presence of lymph node involvement ( $P<0.001$ ), and lower RT dose ( $P=0.030$ ). Other factors including reasons for receiving RT alone ( $P=0.194$ ), sex ( $P=0.864$ ), age ( $P=0.251$ ), and tumor grade ( $P=0.361$ ) were not significant for OS (Table 3). Multivariate analysis revealed that cT disease ( $P<0.001$ ) and tumor location ( $P=0.022$ ) were significant factors for OS (Table 4).

### 3.5. Toxicities

Acute toxicities were observed in 7 patients. Two patients (2.8%) developed grade 3 esophagitis during the RT course. Five patients (7.1%) developed grade 4 to 5 toxicities after RT: 3 died of aspiration pneumonia due to trachea-esophageal fistula in 1 to 3 months, 1 died of tumor bleeding in 3 months, and 1 was hospitalized for trachea-esophageal fistula in 3 months. All these patients initially had advanced cT disease: cT3 in 4 and cT4 in 1. Late toxicity included 1 patient (1.4%) who experienced grade 2 esophageal stricture, and there was none who developed grade 3 or higher late event.

## 4. Discussion

Optimal management of localized esophageal cancer in the patients who are medically unfit for aggressive modality remains a controversial and challenging issue. Though definitive RT alone used to play an important role before the era of concurrent chemoradiotherapy (CCRT), however, the outcomes after RT alone were generally poor with the 5-year OS rate of 0% to 20%, ranging according to the stages.<sup>[8-10]</sup> In the Radiation Therapy Oncology Group (RTOG) 85-01 study, which compared RT alone with CCRT, the RT-alone group showed a 3-year OS rate of 0% in cT1-3N0-1M0 esophageal cancer.<sup>[16]</sup> Thus, RT alone without concurrent chemotherapy has been considered mainly a palliative tool rather than a curative option for esophageal cancer patients. Thereafter, no evident treatment strategy has emerged in managing these medically unfit patients.

The Japanese Society of Therapeutic Radiology and Oncology (JASTRO) evaluated the effectiveness of RT in 141 patients with superficial esophageal cancer (cT1a-bN0 stage), who were treated by external beam RT (EBRT) with or without chemotherapy through a multi-institutional study.<sup>[13]</sup> Most patients received 60 to 70 Gy by conventional fractionation RT alone. The rates of OS and LC at 3 years for cT1a and cT1b stages were 90% and 70%, and 80% and 70%, respectively. There was no statistically significant difference in clinical outcomes between the patients treated by RT alone or RT with chemotherapy. They concluded that RT alone could lead to much

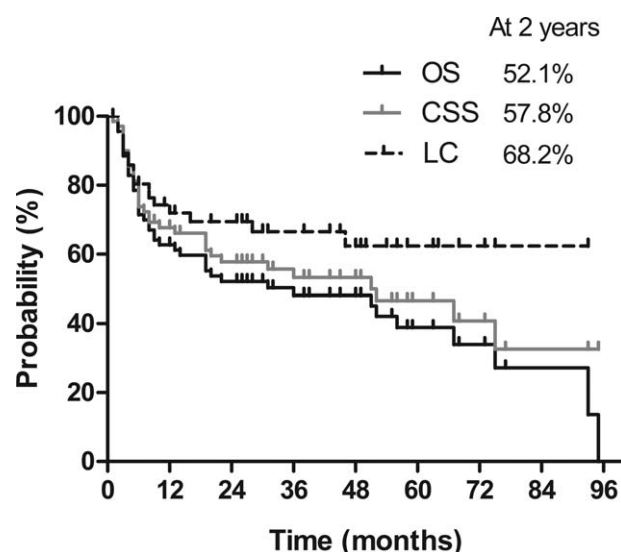


Figure 1. Overall survival (OS), cancer-specific survival (CSS), and local control (LC) rates in all patients.

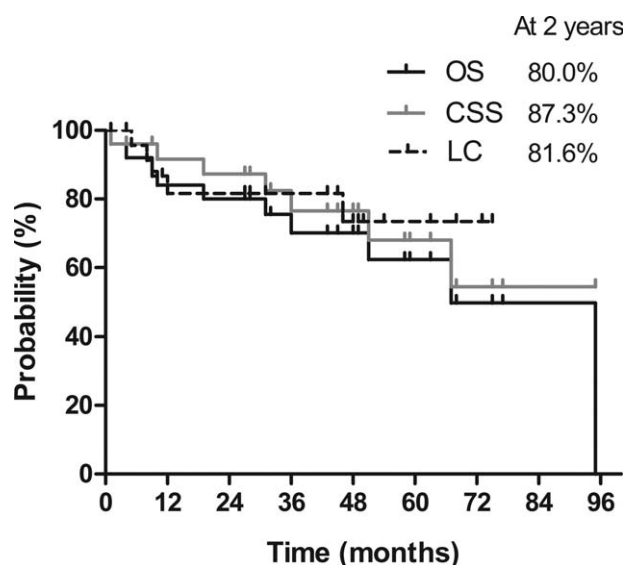
**Table 2****Patients that experienced disease recurrence in 25 patients with cT1a-1bN0 superficial esophageal cancer.**

No.	Sex	Age, y	Tumor location	T stage	Site of failure	Time to progression, mos	Treatment after recurrence	Survival duration, mos	Status at last follow-up
1	Male	67	Lower thoracic	T1a	Regional (mediastinal node), distant (liver, lung)	55	Systemic chemotherapy	68	Dead
2	Male	61	Mid-thoracic	T1b	Distant (liver, para-aortic node)	50	Best supportive care	52	Dead
3	Male	77	Upper thoracic	T1b	Local	8	Best supportive care	36	Dead
4	Male	67	Upper thoracic	T1b	Local, regional (supraclavicular node)	12	Radiation therapy	19	Dead
5	Male	63	Upper thoracic	T1a	Local	47	Best supportive care	58	Alive with disease
6	Male	67	Upper thoracic	T1b	Local	5	Best supportive care	31	Alive with disease
7	Male	59	Lower thoracic	T1b	Local	9	Esophagectomy	59	Alive with no disease
8	Male	72	Mid-thoracic	T1b	Regional (upper mediastinal node)	9	Radiation therapy	10	Dead
9	Male	60	Lower thoracic	T1b	Distant (lung, single)	11	Stereotactic body radiation therapy	32	Alive with no disease
10	Male	67	Mid-thoracic	T1b	Regional (supraclavicular node)	12	Radiation therapy	32	Alive with no disease

better clinical outcomes in treating superficial lesions than advanced-stage lesions, and the addition of concurrent chemotherapy to RT did not improve survival. Recently, Ishikawa et al<sup>[17]</sup> reported that combining intraluminal brachytherapy (ILBT) with EBRT was more effective than EBRT alone in patients with medically inoperable T1b esophageal cancer, with the higher 5-year CSS rate in the ILBT group (86% vs 62%;  $P = 0.04$ ). Sai et al<sup>[18]</sup> also reported the 5-year CSS rate of 80.0% and LC rate of 68.4% after EBRT ± ILBT in 34 patients with stage I esophageal cancer. In their study, the LC rate of the EBRT + ILBT group was superior to that of the EBRT-alone group, although the difference was not statistically significant. The current study also showed comparable results confined to the patients having cT1a-bN0 stage to the above-mentioned Japanese data. In the current study, the 2-year OS, CSS, and LC rates were 80.0%, 87.3%, and 81.6%, respectively. These findings indicate that high-dose RT alone by moderate hypofractionation in treating medically unfit patients with superficial esophageal cancer is quite effective, and could be a reasonable alternative curative option.

Several studies explored nonconventional, altered fractionated RT schemes in an effort to improve the treatment outcomes of esophageal cancer patients. There are a few studies that tested accelerated hyperfractionation schedules.<sup>[19]</sup> For medically unfit patients, a Norwegian group tested split-course hyperfractionation, delivering a total of 63 Gy (35 Gy at 1.75 Gy twice daily, 2 weeks' break, and 28 Gy at 1.75 Gy twice daily).<sup>[20]</sup> Although this hyperfractionation regimen was well-tolerated by the patients with favorable symptom relief, the 3-year OS was unsatisfactory at 11%. Zhao et al<sup>[21]</sup> tested delayed accelerated hyperfractionation in 201 cT1-4N0-1 esophageal cancer patients, who received a total of 68.4 Gy in 41 fractions over 44 days (41.4 Gy at 1.8 Gy once daily during the first 4 and half weeks, followed by 27 Gy at 1.5 Gy twice daily). They reported that the 5-year LC and OS rates were 56% and 26%, respectively, which were comparable with those of the CCRT group in the RTOG 85-01 study. Very similar dose scheme was tested by Sun et al,<sup>[22]</sup> who delivered a total dose of 68.4 to 71.0 Gy over 8 weeks by modern RT techniques (50–50.4 Gy at 1.8 Gy or 2.0 Gy

once daily during the first 5–6 weeks, followed by 18–21 Gy at 1.5 Gy twice daily thereafter). They compared the RT-alone group with the surgery group, and found that the 3 and 5-year OS rates after RT alone did not differ statistically from those after surgery (61% and 37%, vs 56% and 35%, respectively). Hypofractionation regimen is considered a convenient strategy with the merits of reduced overall treatment duration and cost, especially in medically unfit patients, and deserves attention if the consequent clinical outcomes are not suboptimal. Ma et al<sup>[23]</sup> compared hypofractionation with conventional fractionation in the patients with cT2-4N0-1 stage esophageal cancer. The hypofractionation regimen was to deliver a total dose of 54 to 60 Gy at 3.0 Gy daily fraction, whereas the conventional fractionation was a total dose of 60 Gy at 2.0 Gy daily fraction, where intravenous paclitaxel (60 mg/m<sup>2</sup>) was administered concurrently

**Figure 2.** Overall survival (OS), cancer-specific survival (CSS), and local control (LC) rates in cT1 stage esophageal cancer.



**Table 3**  
**Prognostic factors by univariate analysis for overall survival (OS).**

Characteristics	2-year OS rate	P
Sex		
Male (n=68)	52.3%	0.864
Female (n=2)	50.0%	
Age, y		
<70 (n=32)	62.1%	0.251
≥70 (n=38)	44.0%	
Performance status		
ECOG 1 (n=47)	59.1%	<b>0.022</b>
ECOG 2 (n=23)	37.1%	
Reason for RT alone		
Medically unfit (n=47)	49.9%	0.194
Refusal to other modalities (n=23)	66.7%	
Tumor location		
Upper to mid-thoracic (n=56)	45.6%	<b>0.017</b>
Lower thoracic (n=14)	77.9%	
cT disease		
T1–2 (n=46)	76.1%	<b>&lt;0.001</b>
T3–4 (n=24)	0%	
cN disease		
N0 (n=53)	66.0%	<b>&lt;0.001</b>
N1–2 (n=17)	0%	
Grade		
Well and X (n=18)	44.4%	0.361
Moderate and poor (n=52)	54.9%	
RT dose, Gy		
<60 (n=23)	39.1%	<b>0.030</b>
≥60 (n=47)	58.7%	

AJCC=American Joint Committee on Cancer, ECOG=Eastern Cooperative Oncology Group.  
 Bold value indicates a statistically significant difference with a P value less than 0.005.

with RT once a week in all the patients. The 3 and 5-year LC rates were higher in the hypofractionation group (81.4% and 50.0% vs 71.8% and 44.1%;  $P=0.02$ , respectively), whereas the 3 and 5-year OS rates were not different between the groups (43.2% and 38.8% vs 38.2% and 28.0%;  $P=0.268$ , respectively). In addition, the incidence of grade 3 or higher toxicity was not different between the groups (acute toxicities 66.3% vs 50.0%, late toxicities 27.0% vs 22.4%, respectively). In the current study, the treatment outcomes were favorable in regard to the OS and LC rates at 2 years, which were 52.1% and 68.2%, respectively, although a direct comparison between the studies is impossible. Furthermore, the incidence of RT-related grade 3 or greater esophagitis was 2.6%, which seemed, more or less, in the acceptable range. There are a few possible explanations on the favorable outcome profiles following the current regimen: use of relatively small RT target volume which was based on accurate diagnostic images; generous application of individualized adaptive re-plan during the RT course; and inclusion of the patients with superficial esophageal cancer (35.7%). The treatment outcomes of the patients with cT3–4 tumor, however, still remained poor, where the 2-year OS rate was 0%. Thus, RT alone might have mainly palliative role in patients with advanced T disease.

This study has a limitation of retrospective analysis with a small number of patients. However, it is difficult to perform a prospective study with large numbers of patients who are medically unfit or who declined to receive surgery or chemotherapy. Prospective registry study with many institutions would be an alternative design for this group of patients. In conclusion, high-dose RT alone by moderate hypofractionation using 3.0 Gy per fraction in the medically unfit patients had led to reasonable

**Table 4**  
**Prognostic factors by multivariate analysis for overall survival (OS).**

Characteristics	HR (95% CI)	P
Age (<70 vs ≥70 y)	0.942 (0.470–1.889)	0.942
Performance status (ECOG 1 vs 2)	0.801 (0.376–1.704)	0.801
Reason of RT (medically unfit vs refusal)	1.037 (0.270–3.982)	0.958
Tumor location (upper to mid vs lower)	3.339 (1.187–9.397)	<b>0.022</b>
cT disease (cT1–2 vs cT3–4)	0.153 (0.054–0.430)	<b>&lt;0.001</b>
cN disease (cN0 vs cN1–2)	0.812 (0.299–2.203)	0.812
Grade (well and X vs moderate to poor)	1.053 (0.483–2.295)	0.897
RT dose (<60 vs ≥60 Gy)	1.702 (0.874–3.313)	0.118

CI=confidence interval, HR=hazard ratio, RT=radiation therapy.

clinical outcomes at acceptable toxicity risk, especially for the patients having superficial lesions.

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