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## ORIGINAL ARTICLE

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# Postoperative Radiotherapy for High-risk Laryngeal or Hypopharyngeal Squamous Cell Carcinoma

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### ABSTRACT

**Objectives:** To review the outcome of patients with positive / close margins and / or extracapsular extension (ECE) of lymph nodes who underwent radiotherapy (RT) with or without chemotherapy following radical surgery for laryngeal or hypopharyngeal squamous cell carcinoma, and to determine the factors associated with poor prognosis.

**Methods:** We retrospectively reviewed the records of patients with positive / close margins and / or ECE who underwent RT with or without chemotherapy following radical surgery for laryngeal or hypopharyngeal squamous cell carcinoma.

**Results:** In 70 men and 15 women aged 40 to 82 years, their primary lesions were graded as stage III (n = 6), IVA (n = 61), or IVB (n = 18). 73% of patients had either ECE (29%) or a high-risk margin (44%), and 27% of patients had both. The median RT dose was 64 (range, 54-76) Gy. The median follow-up periods for all patients and living patients were 2.5 and 4.0 years, respectively. The median times to locoregional failure and distant failure were 1.0 and 0.8 years, respectively. The 5-year rates for locoregional control, distant metastasis-free survival, disease-free survival, cause-specific survival, and overall survival were 72%, 69%, 47%, 52%, and 35%, respectively. These 5-year rates were poorer in patients with both ECE and positive / close margins than in those with one high-risk feature only (50% vs. 79%, 50% vs. 77%, 19% vs. 60%, 18% vs. 66%, and 16% vs. 42%, respectively). The presence of ECE consistently resulted in poorer 5-year outcomes. Patients with more pathologic features had poorer 5-year outcomes. 23 patients developed acute or late complications of grade 3 or higher. Two patients had grade-5 toxicity; one died during hospitalisation after surgery for an oesophageal perforation and the other had multiple organ failure.

**Conclusion:** In patients with positive / close margins and / or ECE, postoperative RT reduced the risk of recurrence. Patients with both high-risk pathologic features are at a higher risk of locoregional and distant failures and should undergo aggressive adjuvant or innovative treatment.

**Key Words:** Carcinoma, squamous cell; Head and neck neoplasms; Hypopharynx; Larynx; Radiotherapy

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## 中文摘要

### 術後放射治療高危喉癌和下嚥癌

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**目的：**回顧喉或下嚥鱗狀細胞癌患者接受根治手術治療後，放療（RT）加或不加化療治療切緣陽性 / 近和 / 或淋巴結包膜外侵（ECE）的療效，並確定預後不良因素。

**方法：**回顧性分析喉或下嚥鱗狀細胞癌患者接受根治手術治療後，RT加或不加化療治療切緣陽性 / 近和 / 或ECE的療效。

**結果：**70例男性15例女性年齡介於40至82歲其原發病變分期為III期（n = 6）、IVA期（n = 61）或IVB期（n = 18）。73%的患者有ECE（29%）或高危切緣（44%），27%的患者兩者皆有。中位RT劑量為64（範圍54-76）Gy。所有和仍活著患者的中位隨診時間分別為2.5和4.0年。局部區域失敗和遠處失敗的中位時間分別為1.0和0.8年。5年的局部區域控制率、遠處無轉移生存率、無病生存率、原因特異性存活率和總生存率依次為72%、69%、47%、52%和35%。有ECE和切緣陽性 / 近的患者比僅有一個高風險特徵的患者的以上提及的5年率更差（50%對79%、50%對77%、19%對60%、18%對66%、16%對42%）。有ECE導致較差的5年期結果。有較多病理特徵的患者5年期結果較差。23例患者出現3級以上急性或晚期併發症。兩名患者有5級毒性；一名因食管穿孔死亡，另一名因多器官衰竭死亡。

**結論：**對於切緣陽性 / 近和 / 或ECE的患者，術後RT可降低復發的風險。有高風險病理特徵的患者有較高局部區域和遠處失敗的風險，故應進行積極的輔助或創新治療。

## INTRODUCTION

Stage-III or -IV laryngeal and hypopharyngeal squamous cell carcinoma is primarily treated with surgery when organ preservation is not an option. Postoperative radiotherapy (RT) with or without chemotherapy is the standard of care to minimise the risk of recurrence due to residual disease such as extracapsular extension (ECE) of lymph nodes, inadequate surgical margin, primary T4 disease, N2 or N3 nodal disease, lymphovascular space invasion, and / or perineural invasion.<sup>1</sup> The toxicity of adjuvant therapy is high and its potential benefit is limited in patients with head and neck cancer arising from multiple sites.<sup>1,2</sup> Adjuvant therapy mostly benefits patients at risk of local and regional failure such as inadequate margin or ECE.<sup>3,4</sup> Conversely, the benefit of adjuvant therapy is mitigated by an increased risk of distant metastasis in very high-risk patients. This study reviewed the outcome of patients with positive / close margins and / or ECE who underwent RT with or without chemotherapy following radical surgery for laryngeal or hypopharyngeal squamous cell carcinoma, and to determine the factors associated with poor prognosis.

## METHODS

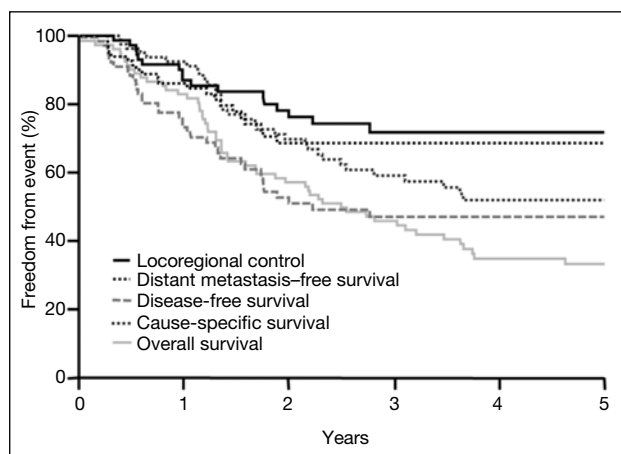
This study was conducted in accordance with an Institutional Review Board-approved protocol and the Health Insurance Portability and Accountability Act. We retrospectively reviewed the records of patients with positive / close margins and / or ECE who underwent RT with or without chemotherapy following radical surgery for laryngeal or hypopharyngeal squamous cell carcinoma at the University of Florida between May 1991 and June 2012. Patients were excluded if they had received prior radiotherapy or brachytherapy to the head and neck or had gross disease or prior head and neck cancer (except for cutaneous basal cell carcinoma).

The primary lesions were classified according to the 2009 American Joint Committee on Cancer staging system.<sup>5</sup> Toxicity was graded according to the Common Terminology Criteria for Adverse Events.<sup>6</sup> Locoregional recurrence was defined as recurrence above the level of the clavicles. Distant failure was defined as recurrence elsewhere. The Kaplan-Meier product limit method<sup>7</sup> was used to estimate the rates of locoregional control, distant metastasis-free survival, disease-free survival,

**Table 1.** Patient characteristics and treatment details.

Variable	Value*
Age (years)	60.5 (40-82)
No. of males:females	70:15
Tumour classification	
T1	0 (0)
T2	3 (4)
T3	20 (24)
T4	62 (73)
Nodal classification	
N0	19 (22)
N1	10 (12)
N2	37 (44)
N3	19 (22)
High-risk pathologic features	
Positive margin	15 (18)
Close margin	45 (53)
Extracapsular extension	48 (56)
Other pathologic features	
Perineural invasion	32 (38)
Lymphovascular space invasion	34 (40)
Multiple positive nodes	55 (65)
Radiotherapy	
Conventional radiotherapy	65 (76)
Intensity-modulated radiotherapy	20 (24)
Fractionation	
1.8-2 Gy once daily	62 (73)
1.2 Gy twice daily	9 (11)
2 Gy once daily with 6 weekly fractions with simultaneous integrated boost	7 (8)
1.8 Gy once daily with a PM boost (1.65 Gy) during the last 12 days	7 (8)
Dose to high-risk planning target volume (Gy)	64 (54-76)
Chemotherapy	13 (15)
Cisplatin weekly	10 (12)
Cetuximab weekly	1 (1)
Carboplatin weekly	1 (1)
Paclitaxel followed by concurrent paclitaxel and cisplatin	1 (1)

\* Data are presented as median (range) or No. (%) of patients.



**Figure.** The 5-year rates for locoregional control, distant metastasis-free survival, disease-free survival, cause-specific survival, and overall survival.

cause-specific survival, and overall survival. The log-rank test was used to determine factors associated with poor prognosis.

## RESULTS

In 70 men and 15 women aged 40 to 82 years, their primary lesions were classified as stage III (n = 6), IVA (n = 61), or IVB (n = 18). 73% of patients had either ECE (29%) or a high-risk margin (44%), and 27% of patients had both (Table 1).

After a median of 41 (range, 12-115) days from surgery, 65 patients underwent conventional RT and 20 underwent intensity-modulated RT (IMRT), with fractionation of 1.8 to 2 Gy once daily (n = 62), 1.2 Gy twice daily (n = 9), 2 Gy once daily with 6 weekly fractions with simultaneous integrated boost (n = 7), or 1.8 Gy once daily with a PM boost (1.65 Gy) during the last 12 days (n = 7). The median RT dose was 64 (range, 54-76) Gy.

13 patients received concurrent chemotherapy of cisplatin (30 mg/m<sup>2</sup>) weekly (n = 10), cetuximab weekly (n = 1), carboplatin weekly (n = 1), or paclitaxel followed by concurrent paclitaxel and cisplatin (n = 1).

The median follow-up periods for all patients and living patients were 2.5 (range, 0.1-21.1) years and 4.0 (range, 0.3-21.1) years, respectively. The median times to locoregional failure and distant failure were 1.0 (range, 0.3-2.8) years and 0.8 (range, 0.3-1.9) years, respectively. The 5-year rates for locoregional control, distant metastasis-free survival, disease-free survival, cause-specific survival, and overall survival were 72%, 69%, 47%, 52%, and 35%, respectively (Figure). These 5-year rates were poorer in patients with both ECE and positive / close margins than in those with one high-risk feature only (50% vs. 79%, 50% vs. 77%, 19% vs. 60%, 18% vs. 66%, and 16% vs. 42%, respectively; Table 2). The presence of ECE consistently resulted in poorer 5-year outcomes. Patients with more pathologic features had poorer 5-year outcomes.

23 patients developed acute or late complications of grade 3 or higher (Table 3). Two patients had grade-5 toxicity; one died during hospitalisation after surgery for an oesophageal perforation and the other had multiple organ failure. The oesophageal toxicities included oesophageal stenosis, tracheoesophageal fistula, and oesophageal perforation. Additional toxicities included pharyngocutaneous fistula, pharyngeal stricture, tracheal

**Table 2.** 5-year outcomes of patients stratified by pathologic features.

Comparison of groups	5-year locoregional control	5-year distant metastasis-free survival	5-year disease-free survival	5-year cause-specific survival	5-year overall survival
Overall (n = 85)	72%	69%	47%	52%	35%
Either close / positive margins or extracapsular extension (n = 62)	79%	77%	60%	66%	42%
Both close / positive margins and extracapsular extension (n = 23)	50%	50%	19%	18%	16%
<b>p Value</b>	<b>0.16</b>	<b>0.02</b>	<b>0.01</b>	<b>&lt;0.01</b>	<b>0.06</b>
Extracapsular extension present (n = 48)	55%	55%	29%	31%	25%
Extracapsular extension absent (n = 37)	92%	86%	77%	81%	53%
<b>p Value</b>	<b>&lt;0.01</b>	<b>0.04</b>	<b>&lt;0.01</b>	<b>&lt;0.01</b>	<b>0.01</b>
Positive margin (n = 15)	60%	69%	40%	41%	8%
Close margin (n = 45)	81%	73%	56%	60%	46%
Negative margin (n = 25)	60%	59%	38%	43%	32%
<b>p Value</b>	<b>0.18</b>	<b>0.93</b>	<b>0.44</b>	<b>0.11</b>	<b>0.13</b>
Tumour stage IV (n = 79)	74%	67%	48%	52%	34%
Tumour stages I-III (n = 6)	68%	72%	47%	52%	38%
<b>p Value</b>	<b>0.47</b>	<b>0.54</b>	<b>0.88</b>	<b>0.56</b>	<b>0.85</b>
Perineural invasion present (n = 32)	71%	64%	40%	43%	32%
Perineural invasion absent (n = 53)	77%	71%	58%	67%	40%
<b>p Value</b>	<b>0.65</b>	<b>0.49</b>	<b>0.20</b>	<b>0.23</b>	<b>0.53</b>
Lymphovascular space invasion present (n = 34)	64%	54%	30%	34%	27%
Lymphovascular space invasion absent (n = 51)	88%	80%	68%	75%	59%
<b>p Value</b>	<b>0.11</b>	<b>0.12</b>	<b>0.04</b>	<b>0.01</b>	<b>0.10</b>
Multiple lymph nodes present (n = 55)	75%	54%	40%	42%	29%
Multiple lymph nodes absent (n = 30)	69%	96%	61%	72%	42%
<b>p Value</b>	<b>0.83</b>	<b>&lt;0.01</b>	<b>0.04</b>	<b>&lt;0.01</b>	<b>0.08</b>
No. of pathologic features					
1 (n = 8)	79%	100%	78.8%	88%	52%
2 (n = 12)	73%	78%	56.9%	70%	43%
3 (n = 29)	81.6%	70%	55.7%	54%	36%
4+ (n = 36)	53.8%	40%	16.0%	16%	15%
<b>p Value</b>	<b>0.33</b>	<b>0.01</b>	<b>&lt;0.01</b>	<b>0.06</b>	<b>&lt;0.01</b>

**Table 3.** Complications of grade 3 or higher.

Complication	No. of patients		
	Grade 3	Grade 4	Grade 5
Oesophageal	14	-	1
Respiratory / thoracic (including tracheal stenosis and fistula)	6	2	-
Musculoskeletal / soft tissue	2	-	-
Multi-organ failure	-	-	1
<b>Total</b>	<b>22</b>	<b>2</b>	<b>2</b>

stenosis, tracheoesophageal fistula, osteoradionecrosis, and soft-tissue necrosis.

## DISCUSSION

The rate of local recurrence after resection of primary head and neck cancer can be as high as 80% in those with positive / close margins and 15% to 32% in those with a negative margin.<sup>8,9</sup> Patients with a positive

margin have a significantly decreased 5-year overall survival.<sup>10</sup> The presence of ECE of lymph nodes is associated with decreased disease-free survival and overall survival even when resection is complete.<sup>11</sup> Patients with extranodal spread have a higher incidence of distant metastasis. In a study of 511 patients who underwent resection for head and neck squamous cell carcinoma, 19% and 7% of patients with and without ECE, respectively, developed distant metastasis within 5 years.<sup>12</sup> In our series, 47% of the patients were disease-free at 5 years despite having at least one high-risk pathologic feature. However, the disease-free survival was only 19% when both ECE and positive / close margins were present.

In one study, the rate of primary failure is higher in patients with a total radiation dose of  $\leq 54$  Gy, compared with  $>57.6$  Gy.<sup>13</sup> In patients with ECE of lymph nodes, the rate of recurrence is higher in those with total radiation dose of  $<57.6$  Gy, compared with  $\geq 63$  Gy.<sup>13</sup>

In our patients, almost all locoregional and distant failures occurred within 2 years of completion of RT and there was no failure after 3 years. Thus, frequent follow-up with physical examination and imaging in the first 3 years is important. The high rate of distant metastasis (31%) after a median of 0.8 year indicated that some patients did not benefit from adjuvant therapy because the benefit of improved locoregional control is offset by rapid metastasis and subsequent death. Furthermore, few patients who have recurrence after radical surgery and adjuvant radiation are eligible for curative-intent salvage therapy such as re-irradiation or surgical resection owing to high toxicity and limited potential benefit.<sup>14,15</sup> Thus, upfront aggressive locoregional management is justified in nearly all patients. In our series, the cause-specific survival and overall survival at 5 years differed significantly (52% vs. 35%) because the general health of the patients was poor and many of them died from non-disease-related causes. Thus, this should be discussed with patients and adjuvant treatment should be weighed against the anticipated toxicity.

One limitation to the study is its retrospective nature. There may have been advancements in surgical techniques and diagnostic imaging during the study period that might have improved treatment outcome or salvage option. Chemotherapy is now used more commonly and IMRT is routinely implemented and may have improved locoregional and distant disease control. Only 15% of patients received chemotherapy with a non-standardised regimen. Concurrent platinum-based chemotherapy improves outcomes.<sup>1,2</sup>

## CONCLUSION

In patients with positive / close margins and / or ECE, postoperative RT reduces the risk of recurrence. Patients with both high-risk pathologic features are at a higher risk of locoregional and distant failures and should undergo aggressive adjuvant or innovative treatment.

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