Pergamon

Oral Oncol, Eur J Cancer, Vol. 31B, No. 5, pp. 310–314, 1995
Elsevier Science Ltd
Printed in Great Britain
0964–1955/95 $9.50+0.00

0964–1955(95)00042–9

Risk Factors Which Predict Persistent Cancer in the Abnormal Larynx Following Definitive Irradiation

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Laryngeal abnormalities following definitive irradiation for carcinoma of the larynx are common. The objective of this study was to identify risk factors for persistent cancer in such patients who were found to have abnormal larynges following definitive irradiation. A retrospective evaluation of 185 consecutive patients undergoing primary irradiation for a glottic or supraglottic laryngeal squamous carcinoma treated between 1976 and 1990 at the Affiliated Hospitals of the Medical College of Wisconsin was performed. From chart review, data concerning site, stage, intent of treatment, smoking history, treatment dose, fraction size, failure patterns, and outcome were obtained. In addition, worrisome signs and symptoms including ulceration, dysphasia, odynophagia, airway distress, aphonia, blood, pain, oedema, aspiration, and pneumonia were recorded. Univariate association with failure and a persistently abnormal laryngeal examination was assessed using the Mantel–Haenszel test. The odds ratio was used to estimate relative risk associated with dichotomous risk factors. Disease-free and overall survival were estimated using Kaplan–Meier methodology. The log rank test was used to compare survival as defined by the levels of various risk factors. Two-year disease-free survival was 83% (T_1=93%, T_2=72%, T_3/T_4=66%). Primary failure was associated with the presence of an abnormal examination (P=0.001), tracheotomy (P=0.001), symptom index (P=0.002), aphonia (P=0.003), advanced T stage (P=0.03), and lower total dose (P=0.03). Of 151 patients who survived 6 months disease-free with an intact larynx, an abnormal examination was seen in those with advanced T stage (P=0.002), supraglottic primary (P=0.003), symptom index (P=0.008), eventual failure at the primary site (P=0.008), continued smoking (P=0.01), and higher total dose (P=0.01). The symptom index (total signs and symptoms of airway distress, aphonia, ulceration, pain, oedema, dysphagia, blood production, aspiration, pneumonia, and odynophagia) was correlated with primary failure and continued smoking. Of 37 patients with continually normal examinations, only 1 (3%) failed at the primary site. Of 102 who survived 6 months but with an abnormal examination, 22 (22%) eventually developed a primary failure. Persistently abnormal larynges are common after radiation therapy, yet not all harbour cancer. Risk factors for persistent cancer include stage, airway, total dose, and symptom index. Patients whose larynges return to normal after radiation rarely fail at the primary site.

Keywords: laryngeal cancer, radiotherapy, prognostic factors, complications, locoregional control, survival

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INTRODUCTION

LARYNGEAL ABNORMALITIES following radiation therapy of laryngeal squamous cell carcinoma are common. Although many patients will have complete resolution of an initially abnormal examination, others will have oedema, voice disturbance, morphological distortion, and other signs and symptoms which may obscure a persistent cancer. A report recently summarised the literature regarding this clinical situation and recommended that oedema persisting beyond 6 months is an "indication for total laryngectomy, regardless of biopsy findings" [1]. However, it has been our observation that not all patients with a persistently abnormal larynx following irradiation develop a recurrence. In order to better understand the predictors of ultimate failure in patients with abnormal larynges, we reviewed a 15-year experience with laryngeal cancer patients treated with definitive radiation therapy, with particular attention to worrisome signs and symptoms recorded 6 months and beyond following completion of therapy.

METHODS

All patients with laryngeal squamous cell carcinoma who were treated with radiation therapy alone during the period

1976 to 1990 at two of the major teaching hospitals of the Medical College of Wisconsin were identified. The 185 patients in the cohort were characterised by reviewing hospital, radiation, and otolaryngology clinic records. From the charts, information about site, stage, intent of treatment, smoking history, treatment dose, fraction size, failure patterns, and outcome were recorded. Follow-up visits were specifically reviewed to identify worrisome or persistent signs and symptoms of laryngeal abnormality. These signs and symptoms included ulceration, dysphagia, odynophagia, airway distress, aphonia, blood, pain, edema, aspiration, and pneumonia.

Laryngeal radiation techniques were generally consistent throughout the period of the study. Glottic tumours stage T_1 or T_2 were treated with field sizes between 4×4 cm and 6×6 cm with daily fractionation between 180 and 220 cGy. Larger fraction sizes were used more commonly in the later years. Glottic tumours stage T_3 were treated with larger fields to cover the first echelon of draining lymph nodes. Supraglottic tumours were treated more widely with bilateral fields extending from 1 cm on the mandible down to the cricoid. Supraclavicular nodes were treated bilaterally. The total dose for the vast majority of patients fell between 65 and 70 Gy regardless of site and stage. Clinically involved nodal disease received doses similar to the primary tumour, typically 65–70 Gy.

Univariate associations with failure and persistent abnormal laryngeal examination were assessed using the Mantel–Haenszel test. The odds ratio was used to estimate the magnitude of the relative risk associated with dichotomous risk factors. Disease-free survival and overall survival curves were constructed using the Kaplan–Meier (actuarial) method. The log rank test under the assumption of proportional hazards was used to compare survival curves defined by the levels of various risk factors.

Predictors of outcome were assessed for both the entire population (185 patients) and for those who survived failure-free for 6 months (151 patients).

RESULTS

Of the 185 patients studied, 34 either died, underwent a salvage laryngectomy, or were lost to follow-up within 6 months of completion of treatment. Of the 151 surviving failure-free with a larynx at 6 months, 37 had consistent records of completely normal examinations and no potentially worrisome symptoms. 12 had inadequate documentation of signs and symptoms, and 102 had at least one documented entry of a worrisome, persistent, or developing sign or symptom. Patient characteristics are shown in Table 1. Of the 37 without worrisome signs or symptoms at 6 months, only 1 (3%) eventually developed a primary failure. Of the 102 with worrisome characteristics, 22 (22%) developed a primary failure. Of the 43 patients undergoing a salvage procedure in this series at any point after completion of radiation, 3 (7%) had no cancer in the specimen.

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Received 4 Dec. 1994; provisionally accepted 14 Dec. 1994; revised manuscript received 3 July 1995.

Table 1. Patient characteristics (185 patients)

Sex	
Male	164
Female	21
Site	
Glottic larynx	127
Supraglottic larynx	58
Stage	
Stage I	98
Stage II	46
Stage III	24
Stage IV	17
Total radiation dose (curative intent without interruption only)	
< 50 Gy	2
50–60 Gy	3
60–65 Gy	14
65–70 Gy	116
> 70 Gy	22
Unknown	1
Tobacco use	
Never smoked	6
< 1 pack per day	19
1–2 packs per day	94
2–3 packs per day	31
> 3 packs per day	9
Amount not recorded	26
Smoking cessation	
Never smoked	6
Quit < 1 year before diagnosis	6
Quit 1–5 years before diagnosis	15
Quit > 5 years before diagnosis	22
Quit—interval not recorded	3
Smoked until diagnosis	25
Smoked past diagnosis	65
Smoked—not otherwise recorded	43

Table 2. Two-year survival

	n	Absolute survival (%)	Disease-free survival (%)
Stage I	98	95	93
Stage II	46	60	72
Stage III/IV	41	59	66
Overall	185	79	83

Survival data derived from the Kaplan–Meier curves are shown in Table 2. The median survival by T stage for the entire population was 8.1, 3.9 and 3.0 years for T_1, T_2, and T_3/T_4 patients, respectively.

Factors associated with primary failure in the entire study cohort are shown in Table 3. Patients with an abnormal examination were more likely to fail than those with a normal examination ($P = 0.001$, odds ratio = 13.8). Other factors associated with primary failure included the need for a tracheotomy at some point after therapy, an increasing number of signs and symptoms, the development of aphonia or severe voice loss, increasing T stage at presentation, and a

Table 3. Factors associated with primary failure in the entire population (185 patients)

Factors associated with primary failure	Factors analysed	Significance (*P*)
Abnormal examination	Abnormal versus normal examination	0.001
Need for tracheotomy	Tracheotomy versus no tracheotomy	0.001
Symptom index	Increasing number of signs and symptoms	0.002
Aphonia	Aphonia versus no aphonia	0.003
Advanced T stage	T_1 versus T_2 versus T_3/T_4	0.03
Lower total dose	<65 Gy versus 65–70 Gy versus >70 Gy	0.03
Fraction size	<2 Gy/fraction versus >2 Gy/fraction	0.09 (n.s.)
Continued smoking	Quit before versus quit at versus smoked after Dx	0.21 (n.s.)
Site	Supraglottic versus glottic	0.52 (n.s.)
Treatment intent	Curative versus palliative	0.60 (n.s.)

n.s. = not significant.

Table 4. 151 patients failure-free 6 months after irradiation: factors associated with a persistently abnormal examination

Factors associated with abnormal examination	Factors analysed	Significance (*P*)
Advanced T stage	T_1 versus T_2 versus T_3/T_4	0.002
Supraglottic primary	Supraglottic versus glottic	0.003
Symptom index	Increasing number of signs and symptoms	0.008
Eventual failure	Failure versus no failure	0.008
Continued smoking	Quit before versus quit at versus smoked after Dx	0.01
Higher total dose	<65 Gy versus 65–70 Gy versus >70 Gy	0.01

lower total dose. Factors not associated with failure included fraction size, continued smoking after diagnosis, site of primary tumour, or intent of treatment (7 of the 13 patients treated palliatively had control of their primary tumours).

Factors associated with improved overall survival in the entire population included stage (early stage > advanced stage, $P=0.001$), and site (glottic > supraglottic, $P=0.001$). When stratified by T stage, only higher total dose was significantly associated with improved survival ($P=0.02$).

Factors associated with a persistently abnormal laryngeal examination in patients who were failure-free 6 months after completion of radiation therapy are shown in Table 4. For example, patients who presented with advanced stage primaries were more likely to have an abnormal larynx when examined 6 months after treatment than patients who presented with early stage primaries ($P=0.002$). Similarly, patients who went on to eventually develop a primary failure were more likely to have an abnormal examination at 6 months ($P=0.008$; odds ratio = 10.2). Other factors which were significantly associated with a persistently abnormal examination in failure-free patients were a supraglottic primary, the total number of laryngeal signs and symptoms, continued smoking after cancer diagnosis, and a higher total radiation dose.

The "symptom index" is a reflection of the number of signs and symptoms recorded in the clinical record. Although few of the individual symptoms were significantly associated with primary failure (Table 5), the cumulative benefit of the index was significant ($P=0.002$). Patients who had symptom index scores of "0" or "1" had a 10% incidence of primary failure while patients with scores of "4" or greater had a 40% incidence. The symptom index was also higher in patients who continued to smoke after diagnosis ($P=0.03$). An increase in the probability of recurrence was observed with increasing symptom index score for both glottic and supraglottic sites. For patients with glottic tumours, 13% of patients with a symptom index score of "$\leqslant 1$" developed a recurrence as compared to 32% of patients with a symptom index score of ">2" ($P=0.033$). For supraglottic tumours, a similar trend was identified although the difference did not reach statistical

Table 5. "Symptom index" association with primary failure in the entire population (185 patients)

Increasing total number of symptoms			$P=0.002$
Individual symptoms			
Airway distress			$P=0.003$
Aphonia			$P=0.003$
Ulceration			$P=0.09$
Pain			$P=0.22$
Oedema			$P=0.42$
Dysphagia			$P=0.52$
Blood production			$P=0.73$
Pneumonia			$P=0.89$
Aspiration			$P=0.90$
Symptom index score	*% with primary failure*		
	Glottic ($n=127$)	Supraglottic ($n=54$)	Total
0 or 1	13	0	10
2	24	21	24
3	32	44	38
4 or greater	39	41	40

significance. No patients with a symptom index score of "$\leqslant 1$" developed a recurrence compared to 44% of those patients with a symptom index score of ">2" in the supraglottic cohort ($P=0.07$).

DISCUSSION

The reported incidence of postirradiation laryngeal oedema and other architectural abnormalities is variable. Several series have described oedema and perichondritis in 13–22% of patients receiving radiation therapy for laryngeal carcinoma [2–7]. One series of 43 patients with oedema 6 months following radiation therapy yielded 23 persistent cancers (53%), with only 6 of these cases successfully salvaged [8]. Even with clinical vigilance, evaluation and histological confirmation of recurrence in an oedematous irradiated larynx is difficult. The presence of oedema itself can obscure the tumour. Concern that persistent oedema reflects diffuse submucosal failure is supported by salvage laryngectomy, whole-organ sectioning [9]. However, this concern of recurrence associated with oedema often prompts a biopsy of the irradiated larynx which in itself can cause mischief. Decreased vascularity and reduced lymphatic flow make the irradiated larynx more susceptible to infection following biopsy. Post-biopsy chondritis and worsened oedema can precipitate dramatic airway obstruction. As a result, laryngectomy may be necessary in the absence of a proven recurrence [1, 8, 10]. For these reasons, others have proceeded to laryngectomy based on clinical suspicion without benefit nor the potential risk of a prelaryngectomy biopsy [11].

With the hope of maximal organ preservation, as well as the observation that not all patients with the persistently abnormal larynx following irradiation ultimately fail, we sought to identify risk factors in patients with the persistently abnormal larynx which may predict for ultimate failure. Using a retrospective chart review, we reviewed diagrams and descriptions of abnormalities, confirming that 102 of 151 patients (68%) were alive and free of disease 6 months following radiation therapy and had at least one worrisome laryngeal sign or symptom.

Our review demonstrated several factors correlating with primary failure. Not surprisingly, laryngeal distortion, airway compromise, loss of voice, advanced initial stage, and lower total radiation dose all predicted primary failure. Additionally, the greater the number of signs and symptoms recorded, the higher the likelihood of primary failure. As noted above, oedema has been used in the literature as a benchmark predicting imminent failure. Oedema was a component of the symptom index which we developed, but was not, by itself, a significant predictor of recurrence. When combined with other signs and symptoms of laryngeal oedema listed in Table 5, the symptom index was a significant predictor of primary failure. Of note is that patients who continued to smoke after diagnosis were more likely to have a higher symptom index ($P=0.03$).

Although persistent cancer was significantly correlated with an abnormal examination 6 months after completion of radiation, it was not the only factor. Other associations included advanced T stage at presentation, supraglottic primary, and a high symptom index. Patients who continued to smoke after diagnosis and those receiving a higher total radiation dose were also more likely to have an abnormal examination. Several factors besides persistent cancer are responsible for prolonged laryngeal abnormalities following radiation therapy. Tumour dose and field size are associated with oedema when patients receive more than 70 Gy in field sizes of greater than 6×6 cm [2, 12]. Some patients may exhibit unusually brisk soft tissue reactions to the radiation which can lead to fibrosis, scarring and distortion. Local tissue trauma and continued smoking may contribute in some patients with a persistently abnormal examination. These factors reflect increased normal tissue destruction by the cancer, increased sensitivity to the therapy, and the continuing local trauma.

The management of patients with an abnormal laryngeal examination following radiation therapy poses a real dilemma for the clinician. Routine examination with indirect or flexible laryngoscopy with a careful recording of laryngeal findings and symptoms provides the starting point for decision making. Periodic videostroboscopy detects early changes and provides a record of laryngeal appearance [13]. In some patients, imaging studies may provide earlier detection of failure following radiation therapy. However, computerised tomography (CT) and magnetic resonance imaging (MRI) have only a limited ability to distinguish oedema/necrosis from persistent tumour [14, 15]. A higher level of suspicion is maintained for patients with airway compromise, advanced initial T stage, and multiple signs and symptoms.

The decision regarding biopsies in a radiated larynx is not always clear cut. Resolving or stable laryngeal oedema and distortion is expected in a significant number of patients and does not warrant routine biopsy. Progressive airway distress, loss of voice, development of a new ulceration, persistent pain, and progressive laryngeal oedema are ominous signs which suggest the need for laryngeal biopsy, particularly if several of them occur and progress simultaneously. Salvage laryngectomy is reserved for patients with histologically-proven carcinoma and the rare patient with a nonfunctional larynx due to radionecrosis. Based on our data, we give strong consideration to biopsies in patients who have a system index score of ">2" as this was associated with a $>30\%$ instance of recurrence for both glottic and supraglottic sites. Patients with a system index score of "<2" are carefully followed although not routinely biopsied.

Laryngeal preservation treatment schemes will encourage the management of large tumours with high-dose radiation therapy, possibly using altered fractionation schemes and chemotherapy. These patients will frequently develop persistent laryngeal abnormalities. Physicians involved in the management of laryngeal cancer will increasingly find themselves in situations where a significantly distorted larynx might harbour persistent cancer. Evaluation of risk factors, the use of the symptom index described in this manuscript, and the regular recording of laryngeal appearance may help to appropriately preserve distorted, but cancer-free, larynges.

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