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Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital Experience

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Abstract

Background and purpose: Radiotherapy for laryngeal carcinoma is conventionally given over a 6–7-week period. However, in a number of UK centres early lesions are treated over 3 weeks. We review recent results of this policy and discuss the reasons why short treatment times may be advantageous.

Materials and methods: Two hundred patients (100 from each centre) with T1 glottic invasive squamous cell carcinoma treated with definitive radiotherapy between 1989 and 1997 were analysed. The median age was 68 years. All patients received once daily fractionation, 5 days a week to a total tumour dose of 50.0–52.5 Gy in 16 fractions over 21 days; the fraction size ranged from 3.12 to 3.28 Gy. The median follow-up period was 5 years and 10 months.

Results: The 5-year local control rates with radiotherapy for the whole group was 93%; there were 14 recurrences of which seven were salvaged by laryngectomy giving an ultimate local control of 96%. The 5-year overall survival was 80% and cause specific survival at 5 years was 97%. Univariate analysis revealed that T1 substaging ($P = 0.82$) and anterior commissure involvement ($P = 0.47$) did not significantly influence local control. A severe late radiation complication was seen in only one patient who continued to smoke heavily after treatment. There were no severe acute complications.

Conclusions: Once daily radiotherapy over 3 weeks gives excellent local control in patients with T1 glottic squamous-cell carcinoma and has a low rate of severe complications. The short overall treatment time and large fraction size may be advantageous in radiotherapy of these well-differentiated tumours.

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1. Introduction

Radiotherapy is a widely used method of treatment for early laryngeal cancer. A policy of radical radiotherapy with surgery reserved for salvage of failures gives comparable survival rates to partial laryngeal surgery and gives better voice quality [34,50]. Laser surgery is increasing in popularity [47], but it is not yet clear whether the voice quality is as good as after successful radiotherapy, and there is a relatively high recurrence rate. Consequently radiotherapy remains the most popular method of treatment in many parts of the world including the United Kingdom.

Fractionation policy for early laryngeal cancer differs

between oncology centres in the UK. Some use the 2 Gy per day, 5 days per week, scheme for 6–7 weeks that has become regarded internationally as conventional treatment, while others use shorter overall times. The Christie Hospital developed a 3-week schedule during World War II when radiotherapy facilities were limited. Results were found to be no different from those previously seen with longer courses of treatment in the immediate pre-war period [37]. Accordingly the Christie and a number of other British centres adopted a 3-week treatment time as their standard for radiotherapy of laryngeal cancer.

In an attempt to resolve some of the issues regarding fractionation, a multi-centre trial was conducted in the UK by the British Institute of Radiology (BIR) in the 1970s. It compared ‘short’, i.e. 3 or 4 weeks, with ‘long’, i.e. 6-week

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treatment times. There was no significant difference in local control between the two arms of the study, but, surprisingly to some, the short treatment times gave significantly less severe late normal tissue radiation effects [52]. The Royal Marsden Hospital took part in the trial; when the results were known they adopted a 3-week treatment time for T1 glottic cancer.

The recent results of the 3-week schedule at the Christie and Royal Marsden Hospitals are presented here. Although there are differences in treatment technique and small differences in total dose and fraction size between the two centres, the aim of the study was to explore some of the issues applicable to this unconventional dose–time fractionation approach.

2. Material and methods

Case records of 200 patients with biopsy proven, previously untreated, T1 squamous cell carcinoma (SCC) of the true glottis and treated with definitive radiotherapy at the Christie and The Royal Marsden Hospitals (100 from each centre) were retrospectively analysed. The Royal Marsden series of 100 patients extended between 1989 and 1997; these were consecutive, non-selected patients except for exclusion of overseas patients for whom accurate follow-up was not available. The Christie series matched this number; it was consecutive and non-selected over a 2-year period between 1995 and 1997 to give the same minimum follow-up.

The median age of these patients was 68 years (range 27–90). There were 173 males (86.0%) and 27 females (14.0%). The median follow-up was 5 years and 10 months; the minimum was 2 years and 10 months; 95% had more than 4 years of follow-up.

Tumours were staged using the 1987 TNM staging. Tumour characteristics are shown in Table 1.

2.1. Radiotherapy details

The patients were treated with a continuous course of radiotherapy using megavoltage photons. They received once-daily fractionation for 5 days per week to a total tumour dose of 50–52.5 Gy in 16 fractions. The treatment

time was 21 days in 69% of cases, with a range of 21–26 days. The Christie Hospital patients were all treated with 4-MV photons; the Royal Marsden patients were treated with either 5- or 6-MV photons. The dose specified at the ICRU reference point was 52.5 Gy at the Christie Hospital and 50 Gy at the Royal Marsden; the fraction sizes were 3.28 and 3.12 Gy, respectively.

The patients were treated supine in an immobilisation shell. At the Christie Hospital the beam arrangement was a pair of anterior oblique fields 5×5 cm. A bolus 4-mm-thick was applied routinely over the midline anterior neck (Fig. 1); the rest of the shell was cut out. The Royal Marsden technique was to use parallel opposed lateral fields, except in patients with a short neck, when anterior oblique fields were used; field sizes were chosen individually to treat a target volume 4 cm long covering the whole length of the vocal cords. The shell was left uncut over the anterior half of the fields, but bolus was used only in thin patients with anterior commissure (AC) involvement.

Following completion of treatment, patients were followed up regularly every month for the first year, 2-monthly for the second year, 3-monthly for the third year and then 6-monthly. At each visit history and clinical examination, including laryngoscopy, were performed.

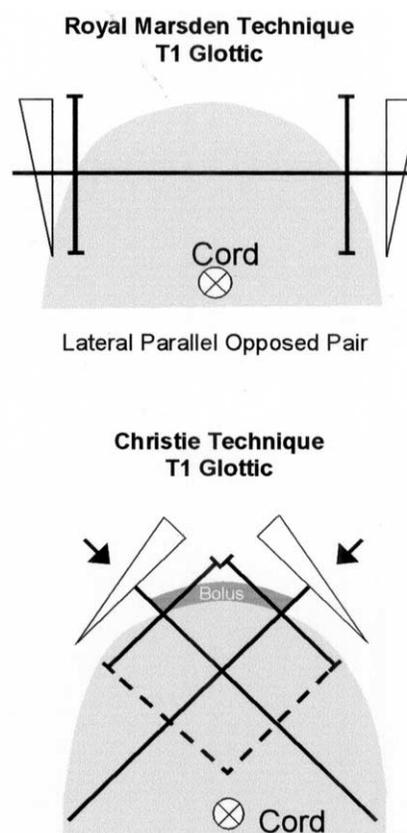


Fig. 1. Comparison of treatment techniques at the Royal Marsden and the Christie Hospitals.

Table 1
Tumour characteristics of the study population

Parameter	No of patients	Percentage
Stage		
T1A	168	84
T1B	32	16
Anterior commissure involvement		
No	150	75
Yes	50	25

An acute complication was defined as severe if an unplanned treatment break was necessary. A late complication was defined as severe if it necessitated a surgical procedure.

2.2. Statistical analysis

The endpoints analysed were local control, ultimate local control, overall survival and cause specific survival. They were calculated from the date of start of radiotherapy. Ultimate local control was defined as local control after surgical salvage. Overall survival included deaths from any cause. Cause specific survival included deaths due to laryngeal cancer and deaths from any cause within 3 months of start of radiotherapy; other causes were censored at the point of death. Kaplan–Meier estimates were used to calculate survival curves and the log rank test to compare groups. All 200 patients were included in the analysis.

3. Results

3.1. Local control

Local control after radiotherapy is depicted in Fig. 2. The 5-year local control rates were as follows: T1A, 93.1%; T1B, 89.1%; overall, 92.6%. The difference between the sub-stage local control rates was not statistically significant ($P = 0.82$). Those with AC involvement had a local control of 89%, compared to 94% when the AC was not involved ($P = 0.47$).

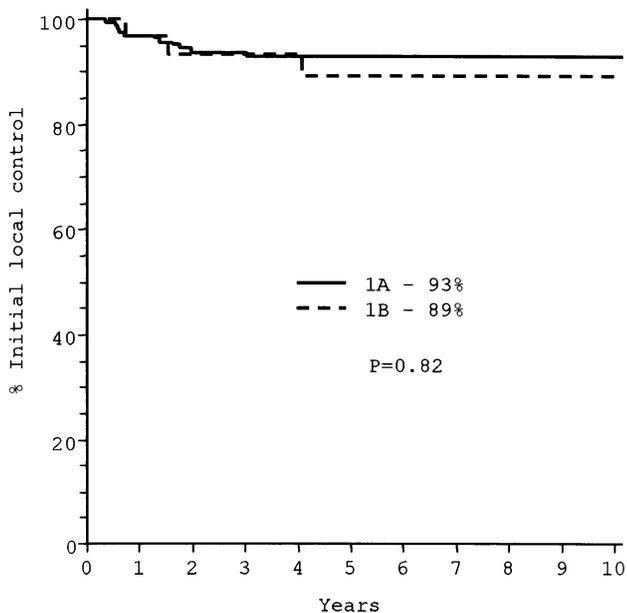


Fig. 2. Local control by radiotherapy. Five-year percentages are shown on the right.

3.2. Ultimate local control

Fourteen patients in the whole group developed local recurrence. Seven of these were salvaged with surgery, giving an ultimate 5-year local control rate of 96.3% for the whole group. The 5-year ultimate local control for T1A was 96.2%, and for T1B 96.6% ($P = 0.67$). In those with AC involvement the 5-year ultimate local control rate was 95%, compared with 97% for those without AC involvement ($P = 0.88$).

3.3. Overall survival and cause specific survival (CSS)

The 5-year overall survival for the whole group was 80% (T1A 81% and T1B 72% $P = 0.26$). CSS in the whole group was 97.2% (T1A = 96.7% and T1B = 100%; $P = 0.74$). Five-year actuarial CSS in males was 97.3% and in females was 96.3%, with six male and one female laryngeal cancer related deaths.

3.4. Complications

There were no severe acute complications. One patient had a severe complication related to the treatment. This patient had to undergo a laryngectomy because of 5 months of persistent pain in the throat after radiotherapy—the patient continued to smoke up to 40 cigarettes/day after completion of radiotherapy. The laryngectomy specimen showed extensive chondronecrosis with no evidence of malignancy. There was one anaesthetic-related death in an 80-year-old female patient who was admitted for a biopsy of recurrence 6 months after treatment of the primary.

3.5. Second primary cancers

Eighteen of the 200 patients developed second primary cancers (Table 2). There were no cancers diagnosed synchronously with glottic cancer. The 5-year actuarial incidence was 9.3%. Lung was the most common site of second primary cancers accounting for 27% of the cases, followed by gastrointestinal tract and prostate cancers.

Table 2
Incidence of secondary cancers in the study group

Site	Number	Percentage
Head and neck	2	11
Lung	5	27
Bowel	3	16
Stomach	3	16
Pancreas	1	5
Prostate	4	22

4. Discussion

This is the first joint analysis of radiotherapy outcome by the Royal Marsden and Christie hospitals, two of the largest cancer centres in England. A 3-week radiotherapy schedule gave results comparable to those of other major cancer centres internationally.

Reported local control rates for T1 glottic cancer treated with definitive radiotherapy vary between 80 and 95% [1, 20,24,42,46] with surgical salvage increasing local control to 90–100%. The reasons for this wide variation have been attributed to a range of patient, tumour and treatment related factors; these are summarised in Table 3. Some of the radiation failures were probably understaged at the initial assessment, as the pattern of local recurrence is not always in keeping with that of a T1 tumour [25].

Sub-stage is a factor in many, but not all reported series, T1A tumours doing better than T1B [28]. Our series did not show any significant difference in local control or survival between the T1 sub-stages: the local control was only marginally lower in T1b.

Anterior commissure involvement has often been regarded as an indication for surgery rather than radiotherapy, because of allegedly poor results of the latter [2,26,

35]. However, our experience showed no significant difference in local control related to AC involvement—those without AC involvement showing a local control of 94% and those with involvement 89%.

Treatment related parameters that may have an effect on end results include overall treatment time (OTT) [6,16,27, 33,40,41,42,49,51], fraction size [20,22,29,43,54], beam energy [1,11,17] and biological effective dose (BED).

Many series have shown that prolonging OTT in T1 glottic cancers has an adverse impact on local control. Rudoltz et al. in their study of 91 patients with T1N0 glottic cancers reported LC rates of 100% if treatment was completed within 42 days, 91% for 43–46 days, 74% for 47–50 days, 65% for 51–54 days and 50% for 55–66 days ($P = 0.0001$) [42]. Even with surgical salvage, the group of patients whose treatment was most prolonged had an increased risk of death from loco-regional progression of disease. Disease-specific survival was 97% when treatment was completed within 54 days, versus 80% for 55–66 days ($P = 0.02$). Wang and Efirid reported 5-year LC rates of 95% for patients with T1 glottic tumours whose OTT was <60 days, compared with 60% when OTT was >60 days ($P = 0.0056$) [51]. Hayakawa et al. reported significantly inferior LC in patients treated >50 days (73%) compared to

Table 3
Patient, tumour and treatment related parameters that may be prognostic in T1 glottic cancers

	Comments from literature	References
Patient		
Sex	Females do better	Mendenhall et al. [28]
Smoking	Continued smoking, worse control, also increase risk complications	van der Voet et al. [49]
Pre-treatment haemoglobin	Low Hb, worse control	Fein et al. [10]
Tumour		
Bulky vs. non-bulky	Bulky tumours do worse	Reddy et al. [38]
Verrucous histology	High recurrence rate	O'Sullivan et al. [36]
T1A vs. T1B	T1A do better	Kirchner et al. [21]
Anterior commissure involved	AC involvement has inferior LC	Olszewski et al. [35] Mantravadi et al. [26] Amornarn et al. [3]
Histological differentiation	Well differentiated do better	Johansen et al. [18]
Treatment		Lund et al. [23]
Overall treatment time (OTT)	Prolonging OTT, inferior LC	Mendenhall et al. [29] Rudoltz et al. [43] Nishumura et al. [33] Fein et al. [11]
Uncompensated gaps	Inferior LC	Duncan et al. [6] Robertson et al. [41]
Energy	>6 MV, inferior	Foote et al. [12] Izuno et al. [17]
Fraction size	≥2.25, is superior to <2 Gy	Schwaibold et al. [43] Yu et al. [54]
Field size	≤25 cm ² , better LC, >36 cm ² , more complications	Mendenhall et al. [29] Fein et al. [9]
BED (total dose for given treatment time)	e.g. 55 Gy/5 weeks do worse than 60 Gy/5 weeks	Teshima et al. [48] Harwood et al. [15] van der Voet et al. [49]

AC, anterior commissure; Hb, haemoglobin; LC, local control; RT, radiotherapy; OTT, overall treatment time.

those treated <45 days (87%) [16]. van der Voet et al. in their report of 383 T1N0 glottic cancer patients found that 5-year LC decreased from 95% for patients treated within 22–29 days to 79% for treatment time >40 days [49]. Gaps in treatment have a similar adverse effect [41]. It is now our policy to avoid gaps resulting from national holidays either by treating over the holiday period or delaying the start of treatment.

The benefit of a short overall treatment time may be explained by the fact that most (approx. 90%) early glottic carcinomas are of the well- or moderately-differentiated squamous type [18,49]. Well-differentiated squamous cell carcinoma has a shorter potential doubling time and a greater propensity for accelerated repopulation during radiotherapy than most other tumour types [53]. The experiences of the CHART and the DAHANCA studies tend to confirm the benefit of short overall treatment times for well differentiated compared with poorly differentiated squamous cell carcinomas [5,14]. Slevin et al. have commented on the potential value of combining information on histological grade and cell kinetics when choosing fractionation schedules [44].

Many studies have demonstrated fraction size to be an important factor in the LC of glottic cancers. Million et al. [30] noted a trend towards improved LC in all groups of laryngeal cancer patients treated with higher daily fraction sizes and shorter OTT. There are data that show that fractionation schedules using doses >2 Gy are superior to those using 1.8 Gy per fraction [20,27,43,54]. Schwaibold et al. in their retrospective analysis of 58 patients found a 3-year LC of 75% in patients treated with 1.8-Gy fractions, compared with 100% in those treated with 2 Gy or above [43]. Kim in their study of 85 patients with T1 glottic cancer reported a 2-year LC of 79% in patients treated with 1.8 Gy compared to 96% in those who received 2 Gy [20]. Mendenhall et al. in a larger study reported 100% LC in carefully selected tumours limited to one vocal cord measuring 5–15 mm treated with 2.25 Gy, compared to 80% for patients treated with 2–2.2 Gy fractions [20]. Yu et al. in their study of 126 patients showed a 84% LC rate for those treated with >2 Gy (2.25–2.5) compared to 65.6% for those treated with 2-Gy fractions, with no increased toxicity [54].

Squamous cell carcinoma is generally thought to have low fractionation sensitivity, i.e. a high alpha–beta ratio, so that small fraction sizes are advised. By contrast, late-responding normal tissues and less radiosensitive tumours such as prostatic carcinoma and melanoma have low alpha–beta ratios [3]. It is possible that since T1 glottic tumours are well-/moderately-differentiated and slow growing in the majority of cases they may contain a low proportion of dividing cells, with a consequent relatively low alpha–beta ratio. The effect of fraction size per se in the above studies is difficult to assess, as in nearly all cases those patients who received larger fractions were also treated over shorter times, making it difficult to disentangle fraction size from

OTT for a given radiotherapy schedule. Nevertheless, the multivariate analysis by Le et al. [22] suggested that OTT and fraction size were both independent prognostic variables for local control. Whatever fractionation schedule is used, the biological effective dose (BED), the total dose in a given time, is an important factor in determining success of radiotherapy. For example, Harwood et al. [15] in their series reported an inferior local control of 86% using 55 Gy over 5 weeks compared to van der Voet et al. [49] who observed 91% local control rates treating with 60 Gy over 5 weeks.

Many radiation oncologists are concerned that using large doses per fraction may lead to an increase in late normal tissue morbidity. However, the opposite was found in the BIR trial [52]. In our series, using fraction sizes ranging from 3.12 to 3.28 Gy, there was only one late serious complication, a patient who underwent laryngectomy for persistent pain and histology showed chondronecrosis. This patient, however, continued to smoke heavily after completion of radiotherapy, and it is known that smoking increases the risk of complications [49]. It is possible that the reduction in total dose is sufficient to compensate for any possible adverse effect of increased fraction size, while the shorter overall time maintains tumour control.

Beam energy has been implicated as a factor influencing local control of T1 glottic carcinoma. It has been suggested that ^{60}Co or 4-MV photons are optimal [30]. Izuno in their study of T1 glottic tumours observed a significantly inferior 5-year local control when these patients were treated with 8/10-MV photons compared to ^{60}Co (60% vs. 88%) [17]. This has been attributed to the longer distance required for secondary electrons to attain an electronic equilibrium in comparison with photons of lower energies [7]. Inadequate build-up of electrons may be found beneath the skin of the neck as the anterior commissure is only 1 cm from the skin, and also on the surface of the air cavity in the interior of the larynx resulting in underdosing of these regions. This effect can be enhanced in beams with higher photon energies such as 10-MV photons, resulting in inferior local control. Reports from phantom dosimetric studies showed that the dose absorbed at the anterior commissure may be decreased by 12% with 6-MV photons and by 18% with 10-MV photons when compared with ^{60}Co [12]. Sombeck and associates have reported underdosing of between 16% and 35% at the skin surface and for a point 3 mm below the anterior neck surface with 6-MV photons compared to ^{60}Co [45]. However, doses measured along the vocal cord and AC were essentially identical. The only difference was several millimetres below the skin of the anterior neck, where 6-MV photons delivered a lower dose than ^{60}Co , which would not be an issue for T1 stage patients. There are limited clinical data for 6-MV photons in T1 glottic cancers. Foote et al. in their retrospective analysis compared ^{60}Co , 4- and 6-MV photons in T1–T3 glottic cancers [12]. They reported local tumour control rates similar in all the energy groups. Akine

et al. in their series of T1 glottic cancer patients reported an 81% local control for 27 patients with AC involvement compared with 91% LC for 127 patients without AC involvement which was of borderline significance ($P = 0.06$) [1]. As the analysis did not control for other treatment factors it is a moot point whether the increased failure rate with AC involvement was in fact the result of underdosing at the AC. A review of 2200 T1 vocal cord cancer treated with ^{60}Co showed no increase in local failure with AC involvement [30]. The authors suggested using bolus in patients with a very thin anterior neck or AC involvement when using 6-MV photons. We used appropriate build-up where indicated, so underdosing is unlikely to have been a cause of failure in our series.

Mortality from T1 glottic carcinoma is low, as recurrences can usually be successfully salvaged by surgery. Only seven of our 200 patients died from their glottic cancer. Subsequent unrelated primary neoplasms are a more frequent cause of death. It has been recognized that second primary tumours are a major cause of death in patients who present with early-stage disease [4]. Most of them occur in patients who present with small-volume primary tumours because of their better survival. Reports from literature quote annual risk of 3–5% and a 5-year cumulative risk of 15–40% [13,19,32,39]. The most common sites of second primary tumours are the lung, prostate and colon. The amount of cigarette smoking has been shown to be an independent prognostic factor for appearance of second primary tumours [39]. Cessation of smoking, close follow-up and chemoprevention have been suggested to alleviate this problem [32]. Our results, which are comparable to the series reported in the literature, showed a 5-year actuarial incidence of 9.3%.

The treatment methods most widely employed for T1 glottic carcinoma are radiotherapy and laser excision [41]. The latter is becoming more popular: it is more convenient for the patient than radiotherapy, but seems to be associated with a higher recurrence rate and poorer voice quality [8]. A study of voice quality after 3-week radiotherapy showed that voice quality was satisfactory in the majority of patients [31]. In comparison with laser treatment, a short treatment schedule mitigates the disadvantage of radiotherapy in terms of convenience, while not adversely affecting recurrence rate or voice quality.

5. Conclusion

Three weeks radiotherapy is a safe and effective treatment for T1 glottic carcinoma and is comparable to longer fractionation schemes in terms of local control, function, and morbidity. The potential attractions of this shorter fractionation regimen are (a) convenience and logistics benefit; b) from the literature, shorter overall treatment time may be advantageous for well/moderately differentiated squamous carcinomas; (c) higher fraction size

could be beneficial in T1 glottic cancers (a background of prolonged hoarseness may indicate slow growth in some cases); and (d) prospective voice quality analysis demonstrates satisfactory outcomes in the majority of patients [31].

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