Radiotherapy for laryngeal cancer—technical aspects and alternate fractionation

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Received February 24, 2017; Revised March 25, 2017; Editorial Decision April 3, 2017

Abstract

Early laryngeal, especially glottic, cancer is a good candidate for radiotherapy because obvious early symptoms (e.g. hoarseness) make earlier treatment possible and with highly successful localized control. This type of cancer is also a good model for exploring the basic principles of radiation oncology and several key findings (e.g. dose, fractionation, field size, patient fixation, and overall treatment time) have been noted. For example, unintended poor outcomes have been reported during transition from 60Cobalt to linear accelerator installation in the 1960s, with usage of higher energy photons causing poor dose distribution. In addition, shell fixation made precise dose delivery possible, but simultaneously elevated toxicity if a larger treatment field was necessary. Of particular interest to the radiation therapy community was altered fractionation gain as a way to improve local tumor control and survival rate. Unfortunately, this interest ceased with advancements in chemotherapeutic agents because alternate fractionation could not improve outcomes in chemoradiotherapy settings. At present, no form of acceleration can potentially compensate fully for the lack of concurrent chemotherapy. In addition, the substantial workload associated with this technique made it difficult to add extra fractionation routinely in busy clinical hospitals. Hypofractionation, on the other hand, uses a larger single fractionation dose (2–3 Gy), making it a reasonable and attractive option for T1–T2 early glottic cancer because it can improve local control without the additional workload. Recently, Japan Clinical Oncology Group study 0701 reprised its role in early T1–T2 glottic cancer research, demonstrating that this strategy could be an optional standard therapy. Herein, we review radiotherapy history from 60Cobalt to modern linear accelerator, with special focus on the role of alternate fractionation.

Keywords: laryngeal cancer, glottic cancer, radiotherapy, alternated fractionation

Introduction

Early laryngeal cancer, especially of the glottis, is primarily a local disease, and radiotherapy is the main treatment used to preserve the larynx. This type of cancer is a good model for testing basic radiotherapeutic hypotheses associated with optimal dose, fractionation, field size, overall treatment time (OTT), and wedge factor usage [1, 2]. With the advent of radiotherapy machines, higher photon energy has enabled us to treat deep-seated tumors. However, higher energy photons worsen dose distribution for shallow-seated tumors, such as in glottic cancer, resulting in poor outcomes [3]. Moreover, precise dose delivery cannot be performed with irresponsible patient fixation, and elevating the dose to the normal tissue worsens the toxicity [4].

The efficacy of radiotherapy is related to several biological factors, including intrinsic cellular radiosensitivity and proliferation during treatment. For instance, accelerated tumor repopulation has been described in head and neck cancer after initiation of radiotherapy [2]. Non-conventional fractionated radiotherapy (alternate fractionation) is an attractive option, as the treatment dose intensity...
can be increased either by increasing the total dose using a smaller, single fraction (hyperfractionation, HF) or by reducing the OTT (acceleration). Reduced OTT is expected to counteract the tumor growth induced by accelerated fractionation (AF), and thereby improve locoregional control [1, 2]. Such shorter OTT without a dose reduction can be achieved either by applying an accelerated higher dose/fraction (fr) or more fractions per week. In either situation, there is a risk of increased toxicity. Many publications have presented both positive and negative opinions for alternate fractionation, and a summary of the important studies is reviewed below.

FROM COBALT TO LINEAR ACCELERATION: PHOTON ENERGY, FIELD SIZE, SHELL FIXATION, AND WEDGE FACTOR

Increasing X-ray energy did not always improve outcome

The history of external radiotherapy of laryngeal carcinoma can be divided into two periods, characterized by the machines used for external beam radiotherapy. From the 1950s, a 60Co external beam was employed, and from the 1960s, linear accelerator (Linac) machines were installed to expand the utility of radiotherapy for deep-seated tumors using higher energy photon beams (8 or 10 MV). Izuno et al. reported an unexpectedly lower local control rate using 10-MV X-rays for T1N0M0 glottic carcinoma [3]. A daily dose of 1.8 or 2 Gy at the midplane was administered in 5 fr/week. The mean total dose was 63.3 Gy (range, 50–70 Gy) in the 60Co group and 65.9 Gy (50–80 Gy) in the 8/10-MV group. The 5-year local control was 88% (15/17 patients) in the 60Co group compared with only 60% (15/25 patients) in the 8/10-MV group (P = 0.05). This phenomenon may have occurred by ionization build-up and -down effects of photon irradiation, with a decrease in the radiation dose at the interior surface layer of the larynx. This effect can be enhanced in beams with higher photon energies, such as 10-MV X-rays, resulting in poorer local control. Even 6-MV photon beams sometimes resulted in poor dose distribution for anteriorly located tumors that required placing a bolus on the skin surface to compensate for dose distribution [5].

Role of field size, wedge factor, and shell fixation

The standard radiation therapy for T1 glottic carcinoma is 60–66 Gy, with field sizes ranging from 4 × 4 cm to 6 × 6 cm [1]. Harwood et al. reported that field size was the most important factor affecting local control of T1 glottic carcinoma in a free set-up situation [6]. By increasing the treatment field size with the same dose (5500 rad in 5 weeks), local control at 5 years for 160 patients treated with a field size of ≤25 cm^2 was 82% and for 171 patients treated with a field size of 26 cm^2 was 91% (P = 0.034). This indicates an underdosed tumor lesion (geographic miss) when using a small field size. Chatani et al. cited the importance of shell fixation using an adequate wedge filter [4]. They compared outcomes between Group A (Styrofoam head holder and band used to ensure immobilization) and Group B (shell fixing device used with wedge filter). The total radiation dose administered was 50–70 Gy over 5–7 weeks. The 5-year progression-free survival (PFS) for Groups A and B was 85 and 90%, respectively. However, in patients with large T1a lesions (total length of one vocal cord) in Groups A and B, the 5-year relapse-free survival rates were 62% and 88% (P = 0.003), respectively. Based on these results, they conducted a randomized controlled trial (RCT) to compare the influence of field width between small-field (5 × 5 cm) and wide-field (6 × 6 cm) sizes in T1N0M0 glottic cancer patients with 60 Gy/30 fr over 6 weeks (Table 2) [4]. Minor chronic complications, such as persistent arytenoid edema lasting more than 6 months or benign polypoid lesion of the vocal cords, was more frequently observed in the wide-field group (23%) than in the small-field group (17%; P = 0.038), while there were no significant differences in acute mucosal and skin reactions. The 5-year PFS was the same in both groups (88%). They concluded that a small field with an appropriately angled wedge filter and shell fixing device is recommended to avoid adverse effects and keep local control [7]. In general, the local control of Tis, T1, T2, T3 and T4 glottic carcinoma treated with radiation alone was reported to be 92–98%, 77–94%, 67–88%, 42–67% and 20–82% (Table 1).

ALTERNATE FRACTIONATION: INFLUENCE OF OTT AND FRACTION SIZE

Alternate fractionation can be generally explained in terms of strategy. First, in HF regimens, two to three fractions are delivered each day, with a reduced dose/fr equal to 1.1–1.6 Gy. The reduction of the dose/fr might reduce the risk of late toxicity, despite an increased total dose. These regimens were designed to increase the dose intensity by delivering a higher total dose in the same amount of time. Next, reducing the total treatment time (i.e. accelerating the treatment) should reduce the repopulation of tumor cells between sessions, resulting in improved locoregional control (AF). Those two alternated schedules can be combined, particularly for regimens in which OTT is reduced (accelerated hyperfractionation, AHF). Therefore, it is difficult to clearly differentiate between HF and AF because many trials have used mixed strategies.

There are many publications related to alternate fractionation, and it can generally improve radiotherapy outcomes, as shown in retrospective analyses (Table 1) and multiple RCTs (Table 2). Of these, large variations in the OTT have been reported, from 1 week of reduction (moderate acceleration) to >3 weeks of reduction (considerable acceleration). For comparison of outcomes, the biological equivalent dose (BED) was calculated using $\alpha/\beta = 10$ Gy for tumor and early reaction, and $\alpha/\beta = 3$ for chronic reaction:

$$\text{BED} = (\text{total dose}) \times \left(1 + \frac{\text{fraction dose} \times \alpha/\beta}{2}\right)$$

In addition, the corrected BED for OTT (cBED) was determined by:

$$\text{cBED} = (\text{BED}_2 \times 0.6) \times (\text{OTT} - T_{lag})$$

where $T_{lag}$ is the assumed lag period of 28 d for a burst of accelerated repopulation of tumor clonogenic cells to occur, 0.6 is the rate of dosage loss in 2-Gy fractions, and:

$$\text{BED}_2 = (\text{number of fractions}) \times \left(\frac{\text{fraction doses}}{\alpha/\beta + 2}\right).$$
Table 1. Retrospective radiotherapy outcome for glottic cancer according to T category

| T category | Institution/Author | PY  | PT No. subcategory | Tx Fractionation (Gy) | 5 year LC |
|------------|--------------------|-----|--------------------|-----------------------|-----------|
| Tis        |                    |     |                    |                       |           |
| PMH/Spayne [8] | 2001      | 67  | AF                | 2.55 51               | 98%       |
| MGH/Wang [9]  | 1997       | 60  | SF                | 2 Not available       | 92%       |
| T1N0       |                    |     |                    |                       |           |
| MGH/Wang [9]  | 1997       | 665 | SF                | 2 65–66               | 93%       |
| PMH/Walde [10] | 1998     | 403 | T1a                | AF ~2.5 ~50           | 91%       |
|             |           | 46  | T1b                | AF ~2.5 ~50           | 82%       |
| Italia/Cellai [11] | 2005 | 831 | SF-AF             | 2–2.4 60–65           | 84%       |
| Tohoku U/Nomiya [12] | 2008 | 115 | T1a                | SF 2 64               | 92%       |
|             |           | 48  | T1b                | SF 2 66               | 85%       |
| UF/Chera [13] | 2010     | 253 | T1a mainly AF     | 2.25 63               | 94%       |
|             |           | 72  | T1b mainly AF     | 2.25 63               | 93%       |
| T2N0       |                    |     |                    |                       |           |
| MGH/Wang [9]  | 1997       | 69  | T2a                | SF 2 66–70            | 70%       |
|             |           | 31  | T2b                | SF 2 66–70            | 67%       |
|             |           | 76  | T2a                | AHF 1.6 BID 70        | 83%       |
|             |           | 61  | T2b                | AHF 1.6 BID 70        | 72%       |
| PMH/Walde [10] | 1998     | 286 | AF                | ~2.5 ~50              | 69%       |
| UF/Chera [13] | 2010     | 165 | T2a mainly HF     | 1.2BID 74.4           | 80%       |
|             |           | 95  | T2b mainly HF     | 1.2BID 74.4           | 70%       |
| MDAC/Garden [14] | 2003 | 81  | HF                | 1.1–1.2BID 74–80      | *79%      |
|             |           | 89  | SF                | 2 32–75               | 68%       |
|             |           | 57  | AF                | 2.06–2.23 66–70       | *82%      |
| ChH/Slevin [15] | 1993   | 242 | AF                | 3.3–3.4 50–55         | 85%       |
| Italia/Cellai [16] | 2005  | 256 | SF-AF             | 2–2.4 60–65           | 73%       |
| T3         |                    |     |                    |                       |           |
| MGH/Wang [9]  | 1997       | 24  | SF                | 2 70                  | 42%       |
|             |           | 41  | AHF               | 1.6BID 70             | *67%      |
| PMH/Harwood [17] | 1980   | 112 | AF                | ~2.2–2.5 50–55        | 51% (3Y)  |
| ChH/Wylie [18] | 1999     | 114 | AF                | 3.3–3.4 50–55         | 68%       |
| Vancouver/Jackson [19] | 2001 | 70  | AF                | 2.4 60               | 65%       |

Continued
after 3 years (AF: 81%; SF: 76%; AF and SF groups showed a 5% difference in locoregional control. M0, glottic, or supraglottic laryngeal cancers were randomized. The and they had World Health Organization Grade 0

Four months after treatment, all types of toxicity symptoms, except reactions than those treated with SF. Eight weeks after treatment, 395 T1pared with sequential fractionation (SF; 66 Gy/33 fr over 45 d) in moderate AF (66 Gy/33 fr over 38 d; 2 fr every Thursday) com-

| Institution/Author | PY  | PT No. subcategory | Tx     | Fractionation (Gy) | 5 year LC |
|--------------------|-----|--------------------|--------|-------------------|-----------|
| T4                 |     |                    |        |                   |           |
| PMH/Harwood [21]   | 1981| 39                 | AF     | ~2.2–2.5          | 56%       |
| UF/Hinerman [20]   | 2007| 22                 | HF     | 1.2BID-2          | 81%       |

PMH = Princess Margaret Hospital, MGH = Massachusetts’s General Hospital, UF = University of Florida, MDAC = MD Anderson Cancer Center, ChH = Christie Hospital Holt Radium Institute, PY = publication year, SF = standard fractionation, AF = accelerated fractionation, HF = hyperfractionation, AHF = accelerated hyperfractionation, BID = twice a day, Tx = treatment, LC = local control rate. *Statistically significant (vs SF).

We hypothesized that radiotherapy started on Monday with no holidays during the radiotherapy period, except for Sunday and Saturday, if elapsed days were not described in the literature.

Randomized controlled trials examining alternate fractionation for laryngeal cancer

Table 2 shows the major RCTs. A Polish trial studied the effect of moderate AF (66 Gy/33 fr over 38 d; 2 fr every Thursday) compared with sequential fractionation (SF; 66 Gy/33 fr over 45 d) in 395 T1–T3 glottic cancer patients. Patients’ ages were ≤75 years, and they had World Health Organization Grade 0–1 T1–T3, N0, M0, glottic, or supraglottic laryngeal cancers were randomized. The AF and SF groups showed a 5% difference in locoregional control after 3 years (AF: 81%; SF: 76%; P = 0.37) [22]. At the end of radiotherapy, patients treated with AF complained of more severe reactions than those treated with SF. Eight weeks after treatment, AF patients had more severe pain upon swallowing (P = 0.027). Four months after treatment, all types of toxicity symptoms, except for skin telangiectasia (P = 0.001), were similar in both treatment groups.

The Danish Head and Neck Cancer Group (DAHANCA) tested a unique AF strategy (5 or 6 fr/week) [23]. They randomized 694 non-metastatic glottic cancer patients into groups that received 5 or 6 weekly fractions of the same total dose. The locoregional control was 78.4% in the 6-fr/week group and 70.7% in the 5-fr/week group, with a corresponding hazard rate (HR) of 0.72 (95% confidence interval (CI): 0.53–0.97; P = 0.04). The effect of AF on loco-regional failure (LRF) was especially evident in well-differentiated tumors (HR = 0.42; 95% CI: 0.23–0.75) and in T1–T2 tumors (86% of included patients; HR = 0.60; 95% CI: 0.41–0.89). Severe acute mucositis was found in the 6-fr/week group, but the incidence of late morbidity was the same. In addition, a Dutch retrospective analysis of 1050 T1–2N0 glottic cancer patients showed that 6 fr/week resulted in 6% improvement in local control after 5 years compared with 5 fr/week, which is in line with the DAHANCA RCT (7.8%) [28].

The University of Florida reported excellent outcomes, not only by HF (1.2 Gy bis in die; BID.twice a day), but also using hypofractionated AF (2.25 Gy/d) in a retrospective analysis (Table 1) [13]. They reported a local control of 100% when carefully selected patients with tumors limited to one vocal cord and measuring 5–15 mm were treated with similar total doses of 61–67 Gy in 2.25 Gy/fr. In contrast, the local control was only 80% for patients treated with 2–2.2 Gy/fr [1]. Accordingly, the Osaka group conducted a RCT (2 versus 2.25 Gy) and found that hypofractionated AF (2.25 Gy/fr) improved 5-year local control by 15% compared with SF in 180 T1 patients [24]. The total radiation dose administered was 60 Gy/30 fr in 6 weeks for minimal tumors (two-thirds of vocal cord or less) or 66 Gy/33 fr over 6.6 weeks for larger than minimal tumors (more than two-thirds of vocal cord) in the 2-Gy arm, and 56.25 Gy/25 fr in 5 weeks for minimal tumors or 63 Gy/28 fr in 5.6 weeks for larger than minimal tumors in the 2.25-Gy arm. The 5-year local control was 77% for the 2-Gy arm and 92% for the 2.25-Gy arm (P = 0.002). No significant differences were found between these two arms in terms of acute mucosal, skin, or chronic adverse reactions.

The Radiation Therapy Oncology Group (RTOG 9512) study compared HF (1.2 Gy BID; 79.2 Gy/66 fr) versus SF (70 Gy/35 fr) for 239 T2N0 vocal cord carcinoma patients. HF increased local control by 8% (HF: 78%; SF: 70%; P = 0.14), corresponding to a 30% HR reduction [26]. The 5-year disease-free survival (DFS) rate in HF and SF patients was 49 and 40% (P = 0.13), respectively, and the overall survival was 72 and 63% (P = 0.29), respectively. HF had higher rates of acute skin, mucosal, and laryngeal toxicity. Late effects experienced by patients with Grade 3–4 carcinomas were 8.5% (95% CI: 3.4–13.6%) after SF and 8.5% (3.4–13.5%) after HF at 5 years.

The Korean Radiation Oncology Group (KROG 0201) compared SF (T1: 66 Gy/33 fr; T2: 70 Gy/35 fr) and hypofractionated AF (T1: 63 Gy/28 fr; T2: 67.5 Gy/30 fr) in 156 patients with T1–T2 glottic cancer [26]. As 282 patients were required, the study was closed prematurely due to poor accrual (only 156 patients). The 5-year local control rate was 77.8% for SF and 88.5% for AF (HR = 1.55; P = 0.213). No significant difference was observed in the toxicity profile between the two arms. In a subgroup exploratory analysis for T1a disease, the 5-year local PFS trended positively in the HF arm (76.7% versus 93.0%; HR = 3.65; P = 0.056).

The Japan Clinical Oncology Group (JCOG 0701) tried to confirm the non-inferiority of the efficacy of AF (2.4 Gy/fr) compared with SF in patients with T1–2N0M0 glottic tumors [27]. Those in
Table 2. Randomized control trials for laryngeal cancer

| Study (Tx year) Source (PY) | Site/Stage | NO PT | Treatment Schedule | Fractionation (Gy) | OTT (day) | cBED (Gy) | LC (Gain (%)) |
|-----------------------------|------------|-------|--------------------|-------------------|-----------|-----------|--------------|
| Osaka CC (1982–1992) [7]    | Glottic T1 | 137 SF | 5 × 5 cm field 2 Gy : 60 Gy | NA | PFS 88% | Late 17% vs 23% (P = 0.038) |
| Chatani (1996)              |            |       |                    |                   |           |           |              |
| Poland (1995–1998) [22]     | Larynx T1–3 | 199 SF | 2 Gy : 66 Gy | 88% | Small field (5 × 5 cm) recommended |
| Hliniak (2002)              |            |       |                    |                   |           |           |              |
| DAHANCA 6 (1992–1999) [23]  | GlotticT1–4 (T1–2: 85%) | 341 SF | 2 Gy: 68 Gy 5 fr/wk | LRC 70.6% | LRC AF better |
| Lyhne (2015)                |            |       |                    |                   |           |           |              |
| Osaka CC (1993–2001) [24]   | Glottic T1 | 88 SF | 2 Gy: 60–66 Gy | 77% | LC AF better |
| Yamazaki (2006)             |            |       |                    |                   |           |           |              |
| RTOG 9512 (1996–2003) [25]  | Glottic T2 | 119 SF | 2 Gy: 70 Gy | 70% | LC same (HF better tendency) |
| Trotti (2014)               |            |       |                    |                   |           |           |              |
| KORG 0201 (2002–2010) [26]  | Glottic T1–2 | 82 SF | 2 Gy:T1 66 Gy T2 70 Gy | 77.80% | LC Same (AF better tendency) |
| Moon (2014)                 |            |       |                    |                   |           |           |              |
| JCOG0701 (2007–2013) [27]   | Glottic T1–2 | 184 SF | 2 Gy:T1 66 Gy T2 70 Gy | 3-y 84.1% | LC almost the same |
| Kodaira (2016)               |            |       |                    |                   |           |           |              |

Tx = treatment, PY = publication year, Osaka CC = Osaka Medical Center for Cancer and Cardiovascular Diseases, DAHANKA: Danish Head and Neck Cancer Group, RTOG = The Radiation Therapy Oncology Group, KORG = Korean Radiation Therapy Oncology Group, JCOG = Japan Clinical Oncology Group, MF = median follow-up period, SF = standard fractionation, AF accelerated fractionation, HF = hyperfractionation, BID: twice a day, fx = fraction, OTT = Overall treatment time 5 years unless otherwise stated, LC = local control rate, PFS = progression-free survival rate, LRC = locoregional control rate, cBED = the biological equivalent dose (BED) corrected for overall treatment time, Acute = acute toxicity, Late = late toxicity. ¶ = 5 years unless otherwise stated.
the 2.4-Gy AF arm did not seem to show an increase in late events or worsening voice changes compared with the SF arm. Although non-inferiority was not confirmed, the similar efficacy (3-year local control, 89.7% versus 84.1%) and toxicity of AF to SF, as well as its practical convenience, indicate that AF has potential as a treatment option for early glottic cancer. Overall, the 5-year local control was modestly higher (3–10%) with alternate radiotherapy compared with SF for laryngeal/glottic carcinoma (Table 2), but the difference was borderline statistically significant. Yamoha et al.’s meta-analysis of three trials [24–26] yielded an HR for local control of 0.59 (95% CI: 0.43–0.81; P = 0.001), strongly supporting the use of AF in this setting [29].

The cBED calculation included OTT and repopulation of tumor cells. All trials used a higher cBED (0.3–4.2 Gy) for the AF arm (almost all trials used a 1 week shorter experimental arm), which resulted in 5–15% improvement in local control. As a result, their clinical data could be partially explained with the cBED equations presented above, which take the repopulation of tumor cells after Tlag into account. Therefore, the number of elapsed days is an important and dominant factor in laryngeal, especially glottic, cancer radiotherapy.

Randomized controlled trials examining alternate fractionation of locally advanced head and neck tumors, including non-laryngeal cancers

In 2006, a pivotal MARCH meta-analysis mainly dealing with locally advanced head and neck carcinoma was published [30]. The MARCH meta-analysis concluded that there was significant improvement in local control and overall survival using AF radiotherapy based on a collection of individual patient data from 15 RCTs with a total of 6515 patients and a median follow-up of 6 years. Tumor sites were mostly oropharyngeal (larynx 36.5%), and 5221 (74%) patients had Stage III–IV disease. AF improved locoregional control versus SF (6.4% at 5 years; P < 0.0001), particularly in local failure (HR = 0.82; 95% CI: 0.77–0.88; P < 0.001) and survival benefit (3.4% at 5 years; HR = 0.92; 95% CI: 0.86–0.97; P = 0.003), whereas the benefit to nodal control was less pronounced. The survival benefit was significantly higher with HF (8% at 5 years) than with AF radiotherapy (2% without total dose reduction and 1.7% with total dose reduction at 5 years; P = 0.02). The benefit was significantly higher in the youngest patients [HR: <50 years old, 0.78 (0.65–0.94); 51–60 years old, 0.95 (0.83–1.09); 61–70 years old, 0.92 (0.81–1.06); >70 years old, 1.08 (0.89–1.30); P = 0.007]. Therefore, there was little merit for the use of AF in patients aged 60 years or more, which should be kept in mind when treating elderly patients. The major trials are depicted in Table 3.

Moderate AF and HF schedules

RTOG 9003 tested several AF radiation schemes: HF (1.2 Gy BID; 81.6 Gy/68 fr over 7 weeks), continuous AF (AF-C: 72 Gy/42 fr over 6 weeks), and split-course AF (AF-S: 67.2 Gy/42 fr over 6 weeks with a 2-week rest after 38.4 Gy) compared with SF (70 Gy/35 fr over 7 weeks) [32]. Patients with Stage III or IV disease (Stage III–IV oral cavity, oropharynx, or supraglottic larynx or Stage II–IV base of tongue or hypopharynx; N = 1076) were randomized to four treatment arms. The three experimental AF arms were based on the radiation fractionation schedules developed at three leading academic institutions in the USA. The University of Florida has championed HF since 1978 [1], including a split-course HF schedule at the Massachusetts General Hospital [9] and an AF with concomitant boost schedule (AF-C) wherein a second fraction of 1.5 Gy was delivered in the afternoon of the last 12 treatment days at MD Anderson Cancer Center [1]. AF-C was designed with two additional premises: (i) the boost dose would be delivered to a smaller volume, making it more tolerable, and (ii) accelerated repopulation after initial radiation could best be overcome by treatment intensification when the tumor was growing at its fastest rate, which was at the end of the treatment course. At 5 years, HF was significantly superior in locoregional control (HR = 0.79; 95% CI: 0.62–1.00; P = 0.05) and overall survival (HR = 0.81; P = 0.05). Toxicity did not differ in the experimental arms compared with SF. This is the largest trial to test alteration in RCT fashion.

In Poland, a unique 7-d/week fractionation with continuous accelerated irradiation (CAIR) schedule intended to reduce the total AF treatment duration by 2 weeks was implemented [36]. The 5-year local control was 75% in the CAIR and 33% in the SF group (P < 0.00004), with significant improvement in DFS and overall survival. Notably, CAIR patients encountered severe toxicity with 2-Gy fractions, and radiation necrosis developed in five patients (22%) as a consequent late effect. Then, the single dose was reduced from 2 to 1.8 Gy, which improved toxicity so that it was no longer severe. This result implied that while 14 Gy/week could be too toxic, 12.6 Gy/week is a feasible schedule if a total dose reduction is not intended.

Next, the CAIR-2 study compared the original CAIR schedule (once a day, 7 d/week) and AF-C (once a day, 3 d/week, and BID, 2 d/week) in 345 patients with squamous cell carcinoma of the oral cavity, larynx, and oro- or hypopharynx (Stage T2–4N0–1M0) [37]. The total dose ranged from 66.6–72 Gy (T2: 66.6–68.4 Gy; T3–T4: 70.2–72 Gy), with 1.8 Gy/fr, and the number of fractions ranged from 37–40 fr over 37–40 d. Locoregional control at 5 years was 63% for CAIR versus 65% for AF-C, and the corresponding overall survival was 40 and 44%, respectively. Confluent mucositis was the main acute toxicity, with an incidence of 89% in CAIR and 86% in AF-C patients. The 5-year rate of Grade 3–4 late radiation morbidity was 6% for both regimens.

Very accelerated AF schedule

The European Organization for Research and Treatment of Cancer (EORTC 22851) tested an interesting experimental AHF applying 3 fr/d (6 Gy, 3 fr/d, 72 Gy/45 fr over 5 weeks; first course: 28.8 Gy/18 fr over 8 d, 12–14 d split; second course: 43.2 Gy/27 fr/7 d) to SF (70 Gy/35 fr over 7 weeks) in T2, T3, and T4 head and neck cancers (hypopharynx excluded) in 512 patients younger than 75 years [37]. AF showed a significantly better 5-year locoregional control (P = 0.02), with a 13% gain (95% CI: 3–23) over SF. This improvement was of larger magnitude in patients with poorer prognoses (N2–N3, any T; T4 any N) than those in more favorable stages. Specific survival tended to favor the AF arm (P = 0.06). Acute and late toxicity were increased in the AF arm. However, late
| Study (Tx year) Source (PY) | Site/Stage % of larynx (MF) | NO PT | Treatment Schedule | Fractionation (Gy) Single dose: total dose | OTT(day) reduction | cBED (Gy) | LC % | LC Survival | LC Toxicity |
|---------------------------|-----------------------------|-------|-------------------|-------------------------------------------|------------------|-----------|------|-------------|-------------|
| **Moderate accelerated AF** |                             |       |                   |                                           |                  |           |      |             |             |
| RTOG 79–13 (1979–83) [31] | Stage III–IV or T2N0 BT, NP, MS | 93    | SF                | 1.8–2 Gy: 66–73.8 Gy                     | 2-y LRC 29%      | 32%       |      |             |             |
| MARCIAL (1987)            | Larynx 9–12% (NA)           | 94    | HF                | 1.2 Gy BID: 60 Gy −12 to −24 −2.2 to −2.8 30% (NS) | 1%               | 28%       |      |             | 13% (P = 0.12) |
| RTOG9003 (1991–1997) [32] | Stage II–IV                 | 268   | SF                | 2 Gy: 70 Gy                             | LRC 29.3%        | 19.3%     |      |             |             |
| Beitler (2014)            | Larynx 15–16% (14.1Y)       | 263   | HF                | 1.2 Gy BID: 81.6 Gy −1                   | 6.8               | 37.1% (P = 0.05) | 7.8% | 26.1% (P = 0.05) |             |
| India (1998–2004) [33]    | Stage III–IV                | 142   | SF                | 2 Gy: 66 Gy                             | 2-y LRC 55%      | 2-y DFS 52% |      |             |             |
| Ghoshal (2008)            | Larynx 25.6% (24M)          | 143   | AF-C              | 1.8 Gy(+1.5 Gy)/67.5 Gy/6wk<sup>1</sup> | −6               | −0.8      | 29%  | 0.3%        | 22.4%       |
| IAEA (1999–2004) [34]     | Stage I–IV                  | 450   | SF                | 2 Gy: 66–70 Gy                          | LRC 30%          | 28%       |      |             |             |
| Overgaard (2010)          | Larynx 24% (99M)            | 458   | AF                | Same dose: 6/w −7                       | 4.2              | 42%(P = 0.004) | 12% | 35% (P = 0.07) |             |
| ARTSCAN (1998–2006) [35]  | Except glottic T1–2, N0     | 367   | SF                | 2 Gy: 68 Gy                             | LRC 64.9%        | MST 5.4y   |      |             |             |
| Zackrisson (2015: Sweden) | Larynx 21% (5.3Y)           | 366   | AF-C              | 2(+1.1 Gy) BID: 68 Gy/4.5 wk<sup>4</sup> | −15              | 5.6       | 65.50% | 0.6%        | 5.1 y       |
| CAIR (1993–1996) [36]     | T2–4N0–1M0                  | 49    | SF                | 1.8 or 2 Gy:72 (60–76) Gy              | 33%              | 20%**     |      |             |             |
| Składowski (2006:Poland)  | Larynx 42% (37 M)           | 51    | AF                | Same dose: 7/wk −12                     | 7.2              | 75% (P < 0.01) | 43% | 62%**       |             |

*Continued*
Table 3. Continued

| Study (Tx year) Source (PY) | Site/Stage % of larynx (MF) | NO PT | Treatment Schedule | Fractionation (Gy) Single dose: total dose | OTT(day) reduction | cBED (Gy) Gain | LC¶ | LC Gain | Survival¶ | Toxicity |
|---------------------------|----------------------------|-------|--------------------|---------------------------------|------------------|---------------|------|---------|-----------|----------|
| CAIR-2 (1996–2006) [37]   | T2–4N0–1M0                  | 172   | AF                 | 1.8 Gy: 66.6–72 Gy              | −19              | 11.4          | 60%  | 40%     |           | LC OS Toxicity same |
| Skladowski (2013;Poland)  | Larynx 47.8% (90 M)         | 173   | AHF                | Same dose: Tu and Fr BID        | −19              | 11.4          | 65%  | 5%      | 44%       | LC OS Toxicity same |

Very accelerated AF

| Study (PY) | Site/Stage % of larynx (MF) | NO PT | Treatment Schedule | Fractionation (Gy) Single dose: total dose | OTT(day) reduction | cBED (Gy) Gain | LC¶ | LC Gain | Survival¶ | Toxicity |
|------------|----------------------------|-------|--------------------|---------------------------------|------------------|---------------|------|---------|-----------|----------|
| EORTC 22851 (1985–1995) [38] | T2–4 except HP | 253   | SF                 | 2 Gy: 70 Gy                      | LRC 46%          | MST 24m       |      |         |           | LRC AHF better, OS Same |
| Horiot (1997) | Larynx 13.5% (4Y9M) | 247   | AHF                | 1.6 Gy TID: 72 Gy/5wk³           | 9.2              | 59% (P = 0.02) | 13%  | 21 m    |           | AHF too toxic (two myelitis) |
| CHART (1990–1995) [39, 40] | Except T1N0 oral, OP, HP, L | 366   | SF                 | 2 Gy: 66 Gy                      | 10½ LR 43%       | 26%           |      |         |           | LC OS same |
| Saunders (2010;UK) | Larynx 46% (NA) | 552   | AHF                | 1.5 Gy TID: 54 Gy –29            | 3.2              | 50%           | 7%   | 29%     |           | Acute Late, AHF better (see text) |
| Vancouver trial (1991–1995) [41] | Stage III/IV | 41    | SF                 | 2 Gy:66 Gy                      | 3 y 44.3%        | 3 y 56.8%     |      |         |           | Early closure for toxicity (G4) |
| Jackson (2001) | Larynx 50% (NA) | 41    | AHF                | 2 Gy BID: 66 Gy –22              | 13.2             | 49.1%         | 4.8% | 59.4%   |           | AHF too toxic |
| TROG (1991–1998) [42] | Stage III/IV | 171   | SF                 | 2 Gy: 70 Gy                      | LRC 47%          | DFS 40%       |      |         |           | LRC same |
| Poulsen (2001) | Larynx 13% (53M) | 172   | AHF                | 1.8 Gy BID: 59.4 Gy –25          | 3.4              | 52%           | 5%   | 46%     |           | Acute AHF worse, Late better |
| GORTEC (1994–1198) [43] | Unresectable T3–4, N0–3 | 129   | SF                 | 2 Gy: 70 Gy                      | 6y 58%**         | 17%**        |      |         |           | LC AHF better, OS same |
| Bouhis (2006) | Larynx 4% (6Y<) | 137   | AHF                | 2 Gy BID:62–64 Gy –25            | 9                | 82% (P < 0.01) | 24%  | 22.0%   | 75% (P < 0.0001) | Acute AHF worse, Late same |
severe damage occurred in 14% of patients in the AF arm versus 4% in the SF arm, and two cases of radiation-induced myelitis occurred after doses of 42 and 48 Gy to the spinal cord. Therefore, this regimen was considered too toxic, and a less toxic scheme should be investigated.

Continuous, hyperfractionated, accelerated radiotherapy (CHART: 1.5 Gy, 3 fr/d, 54 Gy/36 fr over 12 d) was tested by 11 centers in the UK in 918 patients (except those with T1N0 tumors) compared with SF (66 Gy/33 fr over 6.5 weeks) [39, 40]. Severe and early acute mucositis increased with CHART, but healed by 8 weeks. Locoregional control, local control, nodal control, disease-free interval, freedom from metastasis, and overall survival showed no differences between the two arms. In exploratory subgroup analyses, there was evidence of a greater response to CHART in younger patients \((P = 0.041)\) and patients with poorly differentiated tumors \((P = 0.030)\). In the larynx, there was evidence of a trend towards increasing benefit with more advanced T-stage \((P = 0.002)\). CHART reduced severity in a number of late morbidities, most strikingly for skin telangiectasia, mucosal ulceration, and laryngeal edema. Ten-year estimates of severe xerostomia were 23% for CHART and 31% for conventional radiotherapy \((HR = 0.8414; 95\% CI: 0.7238–0.9788; P = 0.03)\). In the CHART arm, 50% of patients presented with signs of laryngeal edema compared with 60% in the conventional arm \((P = 0.05)\), whereas mucosal necrosis was observed in 5 and 9%, respectively \((P = 0.02)\). Osteoradionecrosis occurred in 0.4% of patients after CHART and 1.4% of patients after SF.

The Vancouver trial demonstrated severe toxicity with AF \((2 \text{ Gy BID, 66 Gy/33 fr over 22–25 d})\) in patients with Stage III/IV head and neck cancer \((50\% \text{ larynx})\) [41]. Grade 4 toxicity caused the trial to be discontinued after 82 of the planned 226 patients had been randomized; these 82 patients included patients with tumors of the oral cavity, oropharynx, hypopharynx or larynx, and a Zubrod performance status of 0–1. Prescribed cisplatin doses were 100 mg/m² q3W for two and three cycles, respectively. No differences were observed in 5-year overall survival \((59\% \text{ versus } 56\%; P = 0.18)\), DFS \((45\% \text{ versus } 44\%; P = 0.42)\), locoregional control \((69\% \text{ versus } 72\%; P = 0.76)\) or metastasis \((18\% \text{ versus } 22\%; P = 0.06)\). There were also no overall differences in Grade 3–4 acute mucositis \((33\% \text{ versus } 40\%)\) and worst Grade 3–4 late toxicity \((26\% \text{ versus } 21\%)\).

In summary, multiple meta-analyses have reported that alternated radiotherapy could not appeal its merit if combined with chemotherapy [29, 51]. For example, Gupta et al. carried out a meta-analysis including five RCTs, involving 1171 patients and 627 deaths [50]. The overall HR of death was 0.73 \((95\% \text{ CI; } 0.62–0.86)\), which significantly favored CRT over AF \((P < 0.0001)\): DFS \((HR = 0.79; 95\% \text{ CI; } 0.68–0.92; P = 0.002)\) and LRC \((HR = 0.71; 95\% \text{ CI; } 0.59–0.84; P < 0.0001)\). CRT did not elevate the ratio of severe acute toxicity \((\text{dermatitis and mucositis})\); however, hematological toxicity, nephrotoxicity and late xerostomia were significantly increased with CRT. At present, no form of acceleration can potentially compensate fully for the lack of concurrent chemotherapy [29, 51].

On the other hand, RTOG 9011 unveiled the result of a long-term decrease in the survival rate in the CRT arm \((\text{one possible explanation is toxicity of the chemotherapy}) \ [51]); however, no deterioration in survival was found in the HF arm of RTOG 9003 for 5 years or later [32], which imply the safety of alternation strategy than CRT strategy over the long term. In addition, only the GORTEC trial provided data comparing CRT and alternated radiotherapy, and no data is available for comparing HF and CRT. Therefore, there is a room for examine the role of HF if its benefit would overcome the institutional and patient inconvenience.
**Table 4. Randomized control trials for combination of alternated fractionation and chemotherapy for locally advanced head and neck cancer, including cancer of the larynx**

| Study (Tx year) | Source (PY) | Site/Stage | NO PT | Treatment | Fractionation Schedule | LC/OS (PFS) | Toxicity |
|----------------|-------------|------------|-------|-----------|------------------------|-------------|----------|
| EORTC 24954   | (1996–2004) | HPC & Larynx | 224   | ICT-SF   | 41PF x 4→RT (2 Gy:70 Gy) | 69.2% 48.5% | A/G3–4 mucositis 3%/L fibrosis 16% |
| Lefebvre (2009)|             | Larynx 48% (6.5Y) | 226   | Alt ICT-RT | 42PF x 4/Alt RT (2 Gy:60 Gy) | 67.7% 51.9% | 21%/11% |
| RTOG0129 (2002–2005) | 46 | Stage III–IV | 361   | SF/CRT | 2 Gy:70 Gy+3CDDP × 3 | LRC 72% 56% | A/G3–5 82.3%/L3–5 56.5% |
| Nguyen-Tan (2014)|             | Larynx 26% (4.8Y) | 360   | AF-C/CRT | 1.8 (+1.5 Gy):72 Gy/6 wk1+4CDDP × 2 | 69% 59% | 77.8%/37.9% |
| GORTEC99–02 (2000–2007) | 47 | Stage III–IV | 279   | SF/CRT | 2 Gy:70 Gy+5CF × 3 | 3-y LRC 58.3% 3 y 42.6% | A/G3–4: 69%/3tubing 66% |
| Bourhis (2012) |             | Larynx 6% (5.2Y) | 280   | AF-C/CRT | 1.8 (+1.5 Gy):70 Gy/6wk2+4CF × 2 | 54.6% 39.40% | 76%/64% Tubing 3tub AF worse |
|                 |             |            | 281   | AF     | 1.8 Gy BID: 64.8 Gy | 50.1% (P = 0.045) 36.5% (P = 0.04) | 84% (P = 0.0001)/70% (P = 0.045) |
| India (2000–2007) | 48 | Stage II–IV | 57    | SF     | 2 Gy: 66–70 Gy | 32% 36% | 1/G2–3 Skin 19%/1/G2–3 Xerostomia 23% |
| Ghosh–Laskar (2016) |             | Larynx 16% (54M) | 65    | SF/CRT | 2 Gy: 66–70 Gy+6CDDP × 6 | 49% (P = 0.049) 56% | 23%/42% |
|                 |             |            | 64    | AF     | 2 Gy: 66–70 Gy 6 fr/wk | 27% 41% | 20%/31% Acute SF better, Late same |
| Thailand (2003–2007) | 49 | Stage III–IV | 48    | SF/CRT | 2 Gy: 66 Gy+5CF × 3 | 70% 76% | A/G3–4 mucositis 41.7% |
| Chitapanarux (2013) |             | Larynx 48% (43M) | 37    | AF-C   | 2 (+1.2 Gy): 70 Gy/6wk3+4CF × 2 | 55% (P = 0.18) 63.5% (P = 0.05) | 67.6% (P = 0.01) |
| CONDOR (2009–2012) | 50 | Stage III–IV | 27    | ICT-SF/CRT | 3TPF x 4→2 Gy:70 Gy+3CDDP × 3 | 12 wks RR 81.5% 2 y 78% | A/G3–4 mucositis 26% Early closure for non feasibility |

*Note: AF = alternating fractionation, CDDP = cisplatin, SF = simultaneous fractionation, CRT = chemoradiotherapy, ICT = integrated chemoradiotherapy, LC = locoregional control, OS = overall survival, PFS = progression-free survival.
For definitive radiotherapy, there is an extensive body of published data regarding the management of early glottic cancer with concurrent or 2-Gy/W Alternating Fractions, including tumor and patient factors related to local failure, tumor control, and overall survival. Several RCTs have evaluated the impact of concurrent radiotherapy on local control and overall survival. The results of these studies suggest that concurrent radiotherapy, with or without chemotherapy, offers improved local control compared to radiotherapy alone, although the optimal combination of concurrent chemotherapy and radiotherapy remains uncertain. The choice of treatment should be individualized based on patient factors, including tumor size, T-category, histology, and extent of disease. In general, the addition of chemotherapy to radiotherapy is associated with improved local control, but this benefit may vary depending on the specific chemotherapy regimen used.

**DISCUSSION**

The concept of accelerated radiotherapy is based on the theoretical advantage of delivering a higher total dose in a shorter time, thereby reducing the opportunity for tumor cells to repopulate. However, the clinical benefit of accelerated radiotherapy has not been consistently demonstrated in all types of head and neck cancer. There is evidence that accelerated radiotherapy is associated with higher rates of acute toxicity, particularly skin reactions and mucositis, compared to standard fractionation. Moreover, the increased risk of late toxicity, such as xerostomia and scarring, is a concern, especially in patients who require long-term swallowing and speaking functions.

Several RCTs have compared different accelerated fractionation schedules with standard fractionation. These trials have demonstrated that accelerated radiotherapy can achieve similar locoregional control rates compared to standard fractionation, with a reduction in the overall treatment time. However, the impact of accelerated radiotherapy on overall survival has been more variable. In general, accelerated radiotherapy may be associated with a slight decrease in overall survival compared to standard fractionation, possibly due to an increased risk of distant metastases.

In conclusion, accelerated radiotherapy offers the potential for improved locoregional control in patients with early glottic cancer. However, the benefit of accelerated radiotherapy must be weighed against the increased risk of acute toxicity and potential long-term complications. Further studies are needed to identify the optimal accelerated fractionation schedule and to determine whether accelerated radiotherapy can improve overall survival in patients with early glottic cancer.
and imply that the important threshold of elapsed days was ~40–45 d. Overall, the evidence of a positive effect from reduced treatment time on locoregional control is convincing. The effect of AF on LRF was especially evident in well-differentiated tumors in the DAHANCA trial, which is in agreement with other studies [43]. This indicates that AF repopulation demands a certain degree of cellular differentiation in order to respond adequately to the induced trauma [2, 21, 22]. To secure such a response, the tumor needs to have a functional mechanism capable of regeneration, which is most likely to happen in well-differentiated tumors. Furthermore, the reaction might be controlled by signaling from the surrounding normal mucosa, and the response is, therefore, seen only in the T-site and not the nodal metastases [23, 28].

Very accelerated schedules were used in several RCTs (Table 3) [39–43]. CHART and TROG showed a marginal benefit in favor of the AF arm [39, 40, 42], suggesting that the total dose might have been too low (CHART: 54 Gy in 12 d; TROG: 59.5 Gy in 4 weeks) to obtain a significant benefit in terms of tumor control. In contrast, GORTEC (2 Gy BID, 62–64 Gy total) showed superior local control when the total dose was maintained at higher levels [28, 42]. Therefore, when using very AF, it may be important to keep the total dose as high as is reasonably achievable. In contrast, using higher total doses (16–25.2 Gy, weekly) in association with strong AF schedules, such as in the EORTC 22851 (72 Gy in 5 weeks, between moderate and very accelerated) and Vancouver trials (66 Gy in 3.5 weeks) [38, 41], increased acute toxicity, as seen in GORTEC, and may also increase late effects. It is important to note that those studies left lessons of severe adverse reactions [43]. On the other hand, the harmful effects of larger doses/day used in AF can be compensated for by delivering a lower total dose in this situation, and the gain made in reducing the overall time compensates for the small reduction in total dose administered.

cBED is a useful indicator when speculating the alternation radiotherapy schedule, considering repopulation has occurred 28 day or later radiotherapy. A higher cBED implied better local control in multiple RCTs (Table 2). Again, the gain from the reduction in overall time exceeded the loss resulting from a reduction in the total dose (or BED10), which reflects the cBED concept. Table 2 shows that a 0.5–6.2-Gy cBED gain yielded a 5–15% improvement in local control. A meta-analysis in 2006 indicated a 6% gain in locoregional control using alternate fractionation, which was reproduced in several succeeding RCTs published thereafter. On the other hand, cBED did not apply in very AF and CRT and several forms of moderate AF-C (acceleration in late period of treatment) or AF-S. Additionally, there was no useful indicator of toxicity if the alternation radiotherapy schedule was applied (i.e. BED3 because it does not include the OTT concept), even though several RCTs set their schedule according to BED3 for late toxicity. In future, dose–volume analyses including time factors using 3D data could be fruitful for improving local control and reducing toxicity.

In some of these trials, the AF and HF regimens were feasible and were beneficial in locoregional control but had a modest effect on survival [43]. This discrepancy between the marked benefit observed in locoregional control and the limited effect on survival has already been reported [30]. Since the combination of chemotherapy has already been established as a standard regimen, AF could not be used as a new standard regimen. One more limitation is that almost all prior trials were performed with 2D radiation therapy. However, it seems unlikely that we would compare IMRT-based HF (or AF-C) with SF/CRT [32]. Improvements in radiation techniques and the development of new biological agents and biomarkers force us to reconsider all therapeutic combinations [32].

In addition, from the point of view of health economics, the moderate hypofractionated schedule can be expected to win out over the SF or HF schedule, because the shorter OTT achieved with the hypofractionation scheme reduces the socio-economic burden for patients and radiotherapeutic institutions; patients benefit from the reduced costs and treatment time. This would enable radiotherapeutic institutions to maintain the mechanical and human resources required to meet the increasing demand for radiotherapy. In conclusion, properly modified alternate fractionation could be a good option for improving local control without elevating late toxicity for head and neck squamous cell carcinoma. However, in locally advanced cancer, chemotherapy overcomes the efficacy of alternate fractionation and limits its role in early glottic cancer and/or situations where chemotherapy cannot be used.

ACKNOWLEDGEMENTS
The authors are extremely grateful to Dr Masashi Chatani, Prof. Toshihiko Inoue (Inoue To) and Prof. Takehiro Inoue (Inoue Ta) for their leadership throughout these studies.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

REFERENCES
1. Mendenhall WM, Werning JW, Hinemann RW et al. Management of T1–2 glottic carcinoma. Cancer 2004;100: 1786–92.
2. Coutard H. Principles of x-ray therapy of malignant diseases. Lancet 1934;2:1–8.
3. Izuno I, Sone S, Oguchi M et al. Treatment of early vocal cord carcinoma with 60Co gamma rays, 8/10 MV x-rays, or 4 MV x-rays— are the results different? Acta Oncol 1990;29:637–9.
4. Chatani M, Matayoshi Y, Masaki N. Radiation therapy for larynx carcinoma: long-term results of stage I glottic carcinoma. Strahlenther Onkol 1993;169:102–6.
5. Parsons JT, Greene BD, Speer TW et al. Treatment of early and moderately advanced vocal cord carcinoma with 6-MV X-rays. Int J Radiat Oncol Biol Phys 2001;50:953–9.
6. Harwood AR, Hawkins NV, Rider WD et al. Radiotherapy of early glottic cancer—II. Int J Radiat Oncol Biol Phys 1979;5: 473–6.
7. Chatani M, Matayoshi Y, Masaki N et al. Radiation therapy for early glottic carcinoma (T1N0MO). The final results of prospective randomized study concerning radiation field. Strahlenther Onkol 1996;172:169–72.
8. Spayne JA Warde P, O’Sullivan B et al. Carcinoma-in-situ of the glottic larynx: results of treatment with radiation therapy. Int J Radiat Oncol Biol Phys 2001;49:1235–8.
9. Wong CC. Carcinoma of the glottis. *Radiation Therapy for Head and Neck Neoplasms*. 3rd edn. London: Willey-Liss Inc, 1997, 228–40.

10. Warde P, O’Sullivan B, Bristow RG et al. T1/t2 glottic cancer managed by external beam radiotherapy: the influence of pre-treatment hemoglobin on local control. *Int J Radiat Oncol Biol Phys* 1998;41:347–53.

11. Cellai E, Frata P, Magrini SM et al. Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers. I. The case of T1N0 disease. *Int J Radiat Oncol Biol Phys* 2005;63:1378–86.

12. Nomiya T, Nemoto K, Wada H et al. Long-term results of radiotherapy for T1a and T1bN0M0 glottic carcinoma. *Laryngoscope* 2008;118:1417–21.

13. Chera BS, Amdur RJ, Morris CG et al. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;78:461–6.

14. Garden AS, Forster K, Wong PF et al. Results of radiotherapy for T2N0 glottic carcinoma: does the ‘2’ stand for twice-daily treatment? *Int J Radiat Oncol Biol Phys* 2003;55:322–8.

15. Slevin N, Vasanthan S, Dougal M. Relative clinical influence of tumor dose versus dose per fraction on the occurrence of late normal tissue morbidity following larynx radiotherapy. *Int J Radiat Oncol Biol Phys* 1993;25:23–8.

16. Frata P, Cellai E, Magrini SM et al. Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers. II. The case of T2N0 disease. *Int J Radiat Oncol Biol Phys* 2005;63:1387–94.

17. Harwood AR, Beale FA, Cummings BJ et al. T3 glottic cancer: an analysis of dose time–volume factors. *Int J Radiat Oncol Biol Phys* 1980;6:875–80.

18. Wylie JP, Sen M, Swindell R et al. Definitive radiotherapy for 114 cases of T3N0 glottic carcinoma: influence of dose–volume parameters on outcome. *Radiother Oncol* 1999;53:15–21.

19. Jackson SM, Weir LM, Hay JH et al. A randomised trial of AF versus conventional radiotherapy in head and neck cancer. *Radiother Oncol* 1997;43:39–46.

20. Hinerman RW Mendenhall WM, Morris CG et al. T3 and T4 true vocal cord squamous carcinomas treated with external beam irradiation: a single institution’s 35-year experience. *Am J Clin Oncol* 2007;30:181–5.

21. Harwood AR, Beale FA, Cummings BJ et al. T4NOMO glottic cancer: an analysis of dose–time volume factors. *Int J Radiat Oncol Biol Phys* 1981;7:1507–12.

22. Hliniak A, Gwiazdowska B, Szutkowski Z et al. A multicentre randomised/controlled trial of a conventional versus modestly AF radiotherapy in the laryngeal cancer: influence of a 1 week shortening overall time. *Radiother Oncol* 2002;62:1–10.

23. Lyhne NM, Primdahl H, Kristensen CA et al. The DAHANCA 6 randomized trial: effect of 6 vs 5 weekly fractions of radiotherapy in patients with glottic squamous cell carcinoma. *Radiother Oncol* 2015;117:91–8.

24. Yamazaki H, Nishiyama K, Tanaka E et al. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys* 2006;64:77–82.

25. Trotti A III, Zhang Q, Bentzen SM et al. Randomized trial of hyperfractionation versus conventional fractionation in T2 squamous cell carcinoma of the vocal cord (RTOG 9512). *Int J Radiat Oncol Biol Phys* 2014;89:958–63.

26. Moon SH, Cho KH, Chung EJ et al. A prospective randomized trial comparing hyperfractionation with conventional fractionation radiotherapy for T1–2 glottic squamous cell carcinomas: results of a Korean Radiation Oncology Group (KROG-0201) study. *Radiother Oncol* 2014;110:98–103.

27. Kodaira T, Kagami Y, Shibata T et al. final analysis of a randomized phase III trial of accelerated versus conventional fractionation radiotherapy for glottic cancer of T1–2N0M0 (JCOG0701). *Int J Radiat Oncol Biol Phys* 2016;96:940.

28. Lyhne NM, Johansen J et al. Pattern of failure in 5001 patients treated for glottic squamous cell carcinoma with curative intent—a population based study from the DAHANCA group. *Radiother Oncol* 2016;118:257–66.

29. Yamoah K, Showalter TN, Ohri N. Radiation therapy intensification for solid tumors: a systematic review of randomized trials. *Int J Radiat Oncol Biol Phys* 2015;15:737–45.

30. Bourhis J, Overgaard J, Audry H et al., on behalf of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;368:843–54.

31. Marcial VA, Pajak TF, Chang C et al. Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, pharynx, larynx, and sinuses, using radiotherapy as the only planned modality: (preliminary report) by the Radiation Therapy Oncology Group (RTOG). *Int J Radiat Oncol Biol Phys* 1987;13:41–7.

32. Bholer J, Zhang Q, Fu KK et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 2014;89:13–20.

33. Ghoshal S, Goda JS, Mallick I et al. Concomitant boost radiotherapy compared with conventional radiotherapy in squamous cell carcinoma of the head and neck—a phase III trial from a single institution in India. *Clin Oncol (R Coll Radiol)* 2008;20:212–20.

34. Overgaard J, Mohanty BK, Begum N et al. Five versus six fractions of radiotherapy per week for squamous cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial. *Lancet Oncol* 2010;11:553–60.

35. Zackrisson B, Kjellén E, Söderström K et al. Mature results of a phase III trial from a Swedish comparison study of conventional versus accelerated radiotherapy in head and neck squamous cell carcinoma—the ARTSCAN trial. *Radiother Oncol* 2015;117:99–105.

36. Slawekowska K, Maciejewski B, Golen M et al. Continuous accelerated 7-days-a-week radiotherapy for head-and-neck cancer: long-term results of phase III clinical trial. *Int J Radiat Oncol Biol Phys* 2006;66:706–13.

37. Slawekowska K, Hutnik M, Wygoda A et al. Radiation-free weekend rescued! Continuous accelerated irradiation of 7-days per week is equal to accelerated fractionation with concomitant boost of 7 fractions in 5-days per week: report on phase 3
clinical trial in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 2013;85:741–6.
38. Horiot JC, Bontemps P, van den Bogaert W et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol 1997;44:111–21.
39. Dische S, Saunders M, Barrett A et al. A randomized multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother Oncol 1997;44:123–36.
40. Saunders MI, Rojas AM, Parmar MK et al. Mature results of a randomized trial of accelerated hyperfractionated versus conventional radiotherapy in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2010;77:3–8.
41. Jackson SM, Hay JH, Flores AD et al. Local control of T3N0 glottic carcinoma by 60 Gy given over five weeks in 2.4 Gy daily fractions. One more point on the biological effective dose (BED) curve. Radiother Oncol 2001;59:219–20.
42. Poulsen MG, Denham JW, Peters LJ et al. A randomised trial of accelerated and conventional radiotherapy for stage III and IV squamous carcinoma of the head and neck: a Trans-Tasman Radiation Oncology Group Study. Radiother Oncol 2001;60:113–22.
43. Bourhis J, Lapeyre M, Tertochaux J et al. Phase III randomized trial of very AF compared with conventional radiation therapy in squamous cell head and neck cancer: a GORTEC trial. J Clin Oncol 2006;24:2873–8.
44. Pignon JP, Bourhis J, Domenge C et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949–55.
45. Lefebvre JL, Rolland F, Tesselaar M et al. EORTC Head and Neck Cancer Cooperative Group; EORTC Radiation Oncology Group. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. J Natl Cancer Inst 2009;101:142–52.
46. Nguyen-Tan PF, Zhang Q, Ang KK et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol 2014;32:3858–66.
47. Bourhis J, Sire C, Graff P et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99–02): an open-label phase 3 randomised trial. Lancet Oncol 2012;13:145–53.
48. Ghosh-Laskar S, Kalyani N, Gupta T et al. Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in loco-regionally advanced carcinoma of head and neck: results of a prospective randomized trial. Head Neck 2016;38:202–7.
49. Chitapanarux I, Tharavichitkul E, Kamnerdsupaphon P et al. Randomized phase III trial of concurrent chemoradiotherapy vs accelerated hyperfractionation radiotherapy in locally advanced head and neck cancer. J Radiat Res 2013;54:1110–7.
50. Driessen CM, de Boer JP, Gelderblom H et al. Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil followed by randomization to two cisplatin-based concomitant chemoradiotherapy schedules in patients with locally advanced head and neck cancer (CONDOR study) (Dutch Head and Neck Society 08–01): a randomized phase II study. Eur J Cancer 2016;52:77–84.
51. Gupta T, Kannan S, Ghosh-Laskar S et al. systematic review and meta-analysis of conventionally fractionated concurrent chemoradiotherapy versus altered fractionation radiotherapy alone in the definitive management of loco-regionally advanced head and neck squamous cell carcinoma. Clin Oncol (R Coll Radiol) 2016;28:50–61.
52. Kok G. Influence of the size of the fraction dose on normal and tumor tissue in cobalt-60 radiation treatment of carcinoma of the larynx and inoperable carcinoma of the breast. Radiol Clin Biol 1971;40:100–15.
53. Rudoltz MS, Benammar A, Mohiuddin M. Prognostic factors for local control and survival in T1 squamous cell carcinoma of the glottis. Int J Radiat Oncol Biol Phys 1993;26:767–72.
54. Fowler JF. How worthwhile are short schedules in radiotherapy? A series of exploratory calculations. Radiother Oncol 1990;18:165–81.
55. Dische S, Saunders MI, Bennett MH et al. Cell proliferation and differentiation in squamous cancer. Radiother Oncol 1989;15:19–23.
56. Hlatky L, Olesiak M, Hahndeltd P. Measurement of potential doubling time for human tumor xenografts using the cytokinesis-block method. Cancer Res 1996;56:1660–3.