Radiotherapy for locally advanced resectable T3–T4 laryngeal cancer—does laryngeal preservation strategy compromise survival?

Hideya Yamazaki¹*, Gen Suzuki¹, Satoaki Nakamura¹, Shigeru Hirano², Ken Yoshida³, Koji Konishi⁴, Teruki Teshima⁴ and Kazuhiko Ogawa⁵

¹Department of Radiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajiicho Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan
²Otorhinolaryngology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajiicho Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan
³Department of Radiology, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki-City, Osaka, 569-8866, Japan
⁴Department of Radiation Oncology, Osaka International Cancer Institute, Osaka 541-8567, Japan
⁵Department of Radiation Oncology, Osaka University Graduate School of Medicine, Yamadaoka 2-2, Suita, Osaka 565-0871, Japan

*Corresponding author. Department of Radiology, Kyoto Prefectural University of Medicine, 465 Kajiicho Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-8566 Japan. Phone: 81-75-251-5618, Fax: 81-75-251-5840, Email: hideya10@hotmail.com

(Received 2 July 2017; revised 14 August 2017; editorial decision 1 October 2017)

ABSTRACT

With the advancement of chemotherapy, a laryngeal preservation (LP) strategy was explored with the aim of improving maintenance of quality of life. Induction chemotherapy (ICT) following radiotherapy (RT) was considered a viable option because of its high initial response rate without hampering of overall survival (OS). Subsequently, concurrent chemoradiotherapy (CCRT) using CDDP became the standard of care for LP, showing the best LP ratio. For enhancing treatment intensity, ICT with taxan + CDDP + 5-FU (TPF-ICT) followed by RT showed superiority over ICT with CDDP + 5-FU (PF-ICT) followed by RT. Given that almost all randomized controlled trials investigating ICT include not only operable (endpoint, LP) but also inoperable (endpoint, OS) cases, physicians are faced with a dilemma regarding application in daily practice. In addition, increased treatment intensity causes augmentation of adverse events, which might reduce compliance. Thereafter, cetuximab, an effective drug with fewer adverse effects [bioradiotherapy (BRT)], emerged as another option. However, little evidence has confirmed its superiority over RT (or CCRT) in laryngeal cancer subpopulations. In spite of these developments, the OS of patients with laryngeal cancer has not improved for several decades. In fact, several studies indicated a decrease in OS during the 1990s, probably due to overuse of CCRT. Fortunately, the latter was not the case in most institutions. Currently, no other treatment has better OS than surgery. The eligibility criteria for LP and/or surgery largely depend upon the available expertise and experience, which differ from one institution to another. Therefore, a multidisciplinary team is required for the treatment of LP.

Keywords: laryngeal cancer; larynx preservation; concurrent chemoradiotherapy; induction chemotherapy

INTRODUCTION

Squamous cell carcinoma (SCC) of the head and neck is the sixth most common type of cancer worldwide, with over 650,000 new diagnoses every year [1], while laryngeal cancer accounts for ~200,000 deaths annually [2]. Although laryngeal cancer represents only 2–5% of all malignancies, it is particularly important to investigate this type of cancer because of its significant effects on the voice, swallowing, and quality of life. Surgery has been the primary treatment for locally advanced laryngeal cancer. During the mid-1980s, CDDP and 5-FU (PF) before resection had been incorporated into a highly effective induction chemotherapy regimen (PF-ICT), with response rates of 85–90% and complete response
(CR) rates of 35–55% [3, 4]. Thereafter, a combination of these chemotherapeutic agents with radiotherapy (RT) had been explored as a substitute for surgical intervention for laryngeal preservation (LP) [5, 6]. The Veterans Administration Laryngeal Cancer Study Group trial (henceforth, the VA study) confirmed the compatibility of ICT → RT and surgery → RT, supporting and emphasizing the merits of this regimen in maintaining quality of life by avoiding laryngectomy [7]. Concurrent CDDP + RT (concurrent chemoradiotherapy [CCRT] = with CDDP, unless otherwise stated) has also been validated for usefulness by the RTOG 99–11 trial and became and still is a standard of care for LP [8, 9]. Subsequent ICT studies carried out mainly in mixed populations (unresectable and resectable diseases) established the superiority of docetaxel, CDDP and 5-FU (TPF-ICT) over PF-ICT [10, 11]. Unexpectedly, after the establishment of CCRT’s role in LP, several studies noted a decline in the survival rates for laryngeal cancer patients during the late 1990s [12, 13], with a trend in increasing CCRT dissemination (and a simultaneous decrease in surgeries). The studies’ investigators hypothesized that overuse of CCRT may compromise survival, which brought about wide controversy. In addition, bioradiotherapy (BRT) emerged as an alternative treatment for cases where CDDP was unavailable, despite insufficient evidence for its effectiveness for laryngeal cancer subpopulations [14]. Consequently, we encountered difficulty in selecting from the various treatment options for locally advanced laryngeal cancer, which ranged from laryngectomy (surgery [S], with or without following RT) to LP treatment (upfront CCRT or ICT → RT/CCRT/BRT). In addition, considering LP as the primary endpoint carries the risk of obscuring the differences between disease control, LP rates, and quality of life. Therefore, the endpoint should be a combination of survival and laryngoesophageal function. Patients with advanced laryngeal cancer who present with poor functional status, manifested by severe airway compromise requiring a tracheostomy or enteric feeding, are poor candidates for LP. As a result, it is difficult to apply the outcomes of randomized controlled trials (RCTs) directly into daily clinical practice. Given the confounding nature of these considerations (indication, patient will, need for a multidisciplinary team, etc.), especially for resectable cases, we have produced this narrative review to discuss the role of RT in locally advanced resectable laryngeal cancer. This review summarizes retrospective and prospective clinical data in resectable T3–4 laryngeal cancer, investigating the larynx preservation strategy by radiotherapy, with a focus on the LP. To identify suitable publications, the search strategy was as follows. The Medline database was searched by entering all possible combinations of one of the following key words: ‘radiation/radiotherapy’, ‘laryngeal cancer’, ‘locally advanced’, ‘T3 or T4’, ‘larynx preservation’. Thus, the aim of this study was to raise and investigate two questions for resectable T3–4 laryngeal cancer: (i) Is an LP strategy feasible? (ii) Which treatment protocol is best?”

**RETROSPECTIVE DATA ABOUT T3-T4 LARYNGEAL CANCER**

T3 tumors are good candidates for LP after early RT, depending on patient preference (Table 1). In contrast, T4 tumors, especially large instances, have been treated mainly by surgery. Intensive research has been undertaken in order to improve patient outcomes for advanced disease. For instance, non-standard alternated fractionation (acceleration of hyperfractionation, etc.) has been extensively trialled in several institutions (Table 1) [15]. Mendenhall et al. reported that the probability of cure was ~65–80% for select low-volume (<5 cm³) T3 to T4 glottic SCCs after RT [16]. Shiao et al. reported that patients with a tumor volume ≥21 cm³ had significantly inferior 5-year overall survival (OS) compared with those with a tumor volume <21 cm³ (42% vs 64%; P = 0.003) [17]. Moreover, Mendenhall et al. recommended that higher-volume tumors, particularly those that compromised the airway, should be treated with laryngectomy and postoperative RT, because RT outcomes for T4 laryngeal cancer were generally poor and occasionally resulted in a non-functioning larynx [16, 18].

Fuller et al. eschewed LP in patients with both T3 and T4 laryngeal cancer who, after a pretreatment barium swallow test and/or video stroboscope evaluation, had poor baseline airway function, evidenced by demonstrable aspiration to a degree wherein airway protection after therapy was not possible [25]. For this reason, careful multidisciplinary evaluation, including direct pretherapy assessment by medical oncologists, head and neck surgeons, radiation oncologists, diagnostic radiologists, pathologists, and experienced speech pathology personnel, is imperative. Tracheostomy or feeding-tube dependency is also regarded as an indicator for poor future laryngoesophageal function; however, several experienced institutions have achieved good results for patients exhibiting these characteristics, even for those with T4 tumors [19, 20].

Notably, ‘unresectable’ does not always mean ‘inoperable’. The definition of ‘inoperable’ varies among institutions. Usually, the term unresectable has been used for infiltrative tumors that involve the cervical vertebrae, brachial plexus, deep muscles of the neck, and carotid artery. Poor prognostic factors have been considered to include direct invasion of the skin, mediastinal structures, or prevertebral fascia. Furthermore, patients who have refused surgery have also occasionally been included in the unresectable group.

**PROSPECTIVE STUDIES OF T3–T4 LARYNGEAL CANCER**

**From surgery to LP treatment**

The advent of systemic therapy (chemotherapy [CDDP, 5-FU, and Paclitaxel]) in the 1980s brought with it the potential for improving survival without performing functionally debilitating surgery [5, 6]. During the succeeding decades, two general substitution approaches evolved for the treatment of locally advanced cancers that require total laryngectomy (Table 2): ICT → RT (or CCRT), which is favored in Europe, and concomitant CDDP and standard fractionation RT (CCRT), which is preferred in North America.

**Comparison with surgery (control arm: S ± RT)**

The Veterans Administration Laryngeal Cancer Study Group trial The Veterans Administration Laryngeal Cancer Study Group trial (the VA study) provided the first key evidence to demonstrate LP feasibility [7]. PF-ICT (CDDP 100 mg/m² d1 + 5-FU 1000 mg/m² Days 1–5 every 3 weeks) → RT [66–76 Gy/1.8–2 Gy/fractions (fr)] for chemotherapy responders was found to be a
better strategy compared with laryngectomy (S) → RT. The ICT → RT regimen was able to preserve the larynx (62% at 3 years) without jeopardizing OS. The study revealed that the patients in the ICT group showed a greater number of local recurrences but fewer metastases. The Groupe d’Etude des Tumeurs de la Tete et du Cou (GETTEC) [29] compared S → RT with PF-ICT → RT (65–70 Gy/2 Gy/fr) in good responders (42% LP rate) and S → RT in poor responders. OS and disease-free survival (DFS) were significantly worse for ICT → S (P = 0.006 and P = 0.02, respectively). The 2-year OS for the ICT → RT and S → RT groups were 69% and 84%, respectively. Surgery was associated with a greater number of superior outcomes than the LP strategy.

Singapore study [29] compared CCRT (RT 66 Gy/33 fr + CDDP 20 mg/m² + 5-FU 1000 mg/m² d1 × 2) with S → RT (60 Gy/30 fr) in 119 patients and found no significant difference in 3-year DFS (50% vs 40%). The overall rate for organ preservation or avoidance of surgery at the primary site was 45%.

Comparison with RT alone (control arm: RT alone)

RTOG 9111 CCRT (concomitant CDDP 100 mg/m² on Day 1, Day 22 and Day 43 plus RT 70 Gy/35 fr) was established as a standard treatment by the pivotal Intergroup RTOG 91–11 trial, which demonstrated good local control and unparalleled LP with this CCRT regimen [8, 30]. The primary endpoint was laryngectomy-free survival (with laryngectomy or death treated as events in this trial). After 2 years, the CCRT arm exhibited a higher LP ratio (88%) than the ICT → RT (75%, P = 0.005) or RT (70%, P < 0.001) arm. Locoregional control rates were also significantly better with CCRT (78%) compared with ICT → RT alone (61%) and RT (56%). Moreover, 5-year OS rates for RT alone, CCRT, and ICT were 54%, 55% and 58%, respectively, all of which are relatively similar. However, the survival curves diverged after 4.5 years, with 10-year OS rates of 32%, 28% and 39% for RT only, CCRT, and ICT → RT, respectively, thus presenting ICT as the superior treatment. It is possible that unrecognized or under-reported late toxicities could have contributed to some of the non-cancer-related deaths that emerged with the long follow-up period.

Table 1. Retrospective outcome of radiotherapy for T3–4 laryngeal cancer

| T category | Author (institution) | PY | NO PT | Treatment | \(\%\) LC | \(\%\) LP | \(\%\) OS |
|------------|----------------------|----|-------|-----------|--------|--------|--------|
| T3         | Wylie (ChH) [21]     | 1999 | 114   | RT only: 50–55 Gy/3.3–3.4 Gy/fr (AF) | 68%    | NA     | 54%    |
|            | Hinerman (UF) [22]   | 2007 | 87    | RT only: 50–79.2 Gy/1.2–2 Gy/fr (AF) | 67%    | NA     | Stage III 52% |
|            | Wolden (Michigan U)  | 2009 | 73    | FP → CCRT (or S) 3-year DFS 88% | 3-year LFS 62% | 3-year 83% |
|            | Al-Mamagami (Netherlands) [24] | 2012 | 170   | CCRT [70 Gy/35 6 fr/week + CDDP] | 68% | 74% | 60% |
|            | Fuller (MDACC) [25]  | 2016 | 166   | CCRT or ICT → RT 10-year LRC 76% | 10-year 37% | 67% |
|            |                      |     |       | 121      | RT only | 18%   | 50%   |
|            |                      |     |       | 125      | S → RT | NA    | 46%   |
| T4         | Harwood (PMC) [26]   | 1981 | 56    | RT only: 50–55 Gy/2.2–2.5 Gy/fr (AF) | 56%    | NA     | 64.5% |
|            | Hinerman (UF) [22]   | 2007 | 22    | RT only: 50–79.2 Gy/1.2–2 Gy/fr (AF) | 82%    | NA     | Stage IVa 67% |
|            | Wolden (Michigan U)  | 2009 | 36    | FP→CCRT (or S) 3-year DFS 58% | 3-year LFS 58% | 3-year 78% |
|            | Stenson (Chicago U)  | 2011 | 55    | CCRT: RT 70–75 Gy (AF)+ FHX | FPR 67.7% | 88% | 49% |
|            | Rosenthal (MDACC) [27]| 2015 | 161   | S → RT | 78% | NA | MST 64 M |
|            |                      | 60   |       | CCRT     | 33%   | MST 64 M |

\(\%\) = year of publication, LC = local control rate (5 years unless otherwise stated), LP = larynx preservation (rate), LRC = locoregional control rate, FPR = functional preservation rate, OS = overall survival rate, DFS = disease-free survival rate, LFS = laryngectomy-free survival, MST = median survival time, NA = not available, RT = radiotherapy, ICT = induction chemotherapy, PF = CDDP + 5FU, FHX = 5-FU + hydroxyura, CCRT = concurrent chemoradiotherapy, S = surgery, AF = alternated fractionation, ChH = Christie Hospital Holt Radium Institute, UF = University of Florida, MDACC = MD Anderson Cancer Center, PMH = Princess Margaret Hospital. *(1.5 Gy × 2 or 2 Gy/day × 5 days → 9-day interval) × 5–7 times.*
Table 2. Randomized control trials for organ preservation in resectable cases

| Study (Tx year) | Site stage | %T | NO PT | Tx (% RT received) | % Tx complete | Initial response to ICT (CCRT) | LP[^] | OS[^] | Toxicity |
|----------------|------------|----|-------|-------------------|--------------|-------------------------------|-------|-------|----------|
| Author PY (MF) | (LA)       |    |       | ICT (×3) unless otherwise stated | CR/RR        |                               |       |       |          |
| **Control arm: surgery (S → RT)** | | | | | | | | | |
| VA study (1985–1988) | larynx III/IV | 9/65/26 | 166 | S → RT | NA | 45% | same OS (PF lower meta, lower LC) |
| Wolf 1991 (USA) [7] | (33 M) | 54/18/11 | 166 | PF → RT (NA) (or S) | 70% | RR 85% | 3-year 64%, FL 39% | 42% | mucositis G2 ≤ 38% | LP feasible |
| GETTEC (1986–1989) | larynx II–IV | all T3 | 30 | S → RT | NA | 2-year 84% | S OS better |
| Richard 1998 (France) [28] | (8.3Y) | 78/15/11 | 33 | PF → RT (or S) | 31% | 13 PT ≥ 80% reduction (39%) | 42% | 69% (P = 0.006) | G2 ≤ 33% | early closure: PT refused S |
| Singapore study (1996–2002) | bulky T4 or IVA | 18/26/56 | 60 | S → RT | NA | 3-year DFS 50% | same |
| Soo 2005 [29] | larynx 32% (6Y) | 49/46/5 | 59 | CCRT[^a] | 69% | 69.6%/92.8% | 45% | 40% | mucositis G3 ≤ 39% | early closure: poor accrual |
| **Control arm: radiotherapy (RT)** | | | | | | | | | |
| RTOG91–11 (1992–2000) | larynx III/IV[^a] | 11/79/10 | 173 | RT | 94%^b | 5-year 66%, 10-year 64% | 5-year 54%, 10-year 32% | high grade 81% | CCRT LP best, OS same |
| Forastiere 2013 (USA) [8, 30] | (10.8Y) endpoint LP | 50/21/28/2 | 172 | CCRT[^c] | 91%^b | 84%, 82% (P < 0.001) | 55%, 28% | 82% | CCRT acute worse, late same |
| Cleveland study (1990–1995) | III/IV larynx 18% | 28/39/33 | 50 | RT | NA[^c] | CR 66% | LP 45%, LS 34% | 48% | feeding tube 32% | CCRT LP better, OS same, toxicity worse |
| Adelstein 2000 (USA [31]) | (5 Y) | 47/47/6 | 50 | CCRT (FP) | NA[^c] | 94% (P < 0.001) | 77% (P < 0.001), 42% (P = 0.004) | 50% | 58% (P = 0.01) | |

Tx = treatment, PY = year of publication, MF = median follow-up period, ICT = induction chemotherapy, LP = larynx preservation (rate) (5 years unless otherwise stated), OS = overall survival, RT = radiotherapy, S = surgery, CCRT = concurrent chemoradiotherapy, PF = CDDP + 5FU, NA = not available, VA = Department of Veterans Affairs Laryngeal Cancer Study Group, GETTEC = Groupe d’Etude des Tumeurs de la Tete et du Cou, RTOG = Radiation Therapy Oncology Group, LS = laryngectomy-free survival, FL = functioning larynx, CR = complete response, PR = partial response, RR = response rate = CR + PR. ^Excluding T4 with thyroid cartilage or >1 cm BOT invasion. ^Received more than 95% of the intended dose of radiotherapy (i.e. at least 67 Gy). ^Probably 100%, but not exactly stated.
The Cleveland study  Adelstein et al. confirmed the superiority of CCRT (5-FU 1000 mg/m²/day and CDDP 20 mg/m²/day, on Day 1 and Day 22, +RT 66–72 Gy/1.8–2 Gy/fr) over RT alone (66–72 Gy/1.8–2 Gy/fr) for LP but not OS in 100 patients with resectable American Joint Committee on Cancer Stage III and IV disease [31]. Furthermore, 82% and 98% of the patients in the RT and CCRT arms had been rendered disease free (P = 0.02), respectively. For RT vs CCRT, the 5-year OS rates, OS rates with primary site preservation, and local control rates without surgical resection were 48% vs 50% (P = 0.55), 34% vs 42% (P = 0.004) and 45% vs 77% (P < 0.001), respectively.

Induction chemotherapy

Comparison with PF-ICT (control arm: PF-ICT → RT or CCRT)
To enhance treatment intensity, regimens containing taxan (docetaxel or paclitaxel) were intensely explored. Generally, TPF-ICT showed superior outcomes compared with PF for several RCTs. However, a number of these RCTs were criticized for their use of non-standard approaches, leaving the regimen suitable for replacing the present standard treatment.

Groupe d’Oncologie Radiothérapie Tête Et Cou (GORTEC) 2000–01 Pointeu et al. confirmed that TPF-ICT (docetaxel 75 mg/m² d1, CDDP 100 mg/m² Day 1, 5-FU 1000 mg/m² × 4 days) → RT (70 Gy/35 fr) increased LP and laryngeal dysfunction-free survival (LDFFS) better than PF-ICT (CDDP 100 mg/m² Day 1, 5-FU 1000 mg/m² × 5 days) → RT (70 Gy/35 fr) [32, 33]. For TPF-ICT and PF-ICT, the 5-year (10-year) LP rates were 74.0% and 70.3% (58.1% and 46.5%), whereas the 5-year (10-year) LDFFS rates were 67.2% and 63.7% (46.5% and 37.2%, P = 0.001), respectively. TPF-ICT did not show any significant improvement in OS, DFS or LCR compared with PF-ICT. Statistically fewer late Grade 3–4 toxicities of the larynx occurred with TPF-ICT than with PF-ICT (9.3% vs 17.1%, P = 0.038).

TAX 324  Posner and Loach et al. compared TPF-ICT with PF-ICT followed by 7 weeks of CCRT (RT 70–74 Gy/2 Gy/fr + carboplatin AUC 1 × 5 weekly) in resectable and unresectable cases [34–36]. TPF-ICT had a significantly better OS than PF-ICT [hazard ratio (HR) 0.74, P = 0.014], with 5-year OS rates of 52% and 42% for TPF-ICT and PF-ICT, respectively. The TPF-ICT and PF-ICT groups had a MST of 70.6 and 34.8 months, respectively. Progression-free survival (PFS) was also significantly better in patients treated with TPF-ICT than with PF-ICT (median 38.1 months vs 13.2 months). No significant difference was found for dependence on gastric feeding tubes (3% vs 11%) or tracheostomies (7% vs 11%) between the treatment groups. They also made a subpopulation analysis limited to laryngeal (54% of entire population) and hypopharyngeal cancers (74% operable: 90 PF-ICT and 76 TPF-ICT patients) [36]. OS rates for laryngeal cancer in the PF-ICT and TPF-ICT groups were 45% and 65% (P < 0.05), respectively. In the operable group, the 3-year laryngectomy-free survival rates for TPF and PF-ICT were 52% and 32% (P = 0.03), respectively. The main point of criticism was the use of a non-standard CCRT regimen (carboplatin).

The Spanish Head and Neck Cancer Cooperative Group  The Spanish Head and Neck Cancer Cooperative Group (TTCG) performed a comparison study between PF-ICT (CDDP 100 mg/m² Day 1 + 5-FU 1000 mg/m² Day 1–5 every 3 weeks) and TPF-ICT (paclitaxel 175 mg/m² Day 1, CDDP 100 mg/m² Day 2, 5-FU 500 mg/m² Days 2–6 every 3 weeks) [37]. Patients with a CR or partial response (PR) of ≥80% for the primary tumor received additional CCRT. The PF and TPF arms had CR rates of 14% and 33% (P < 0.001) and a median time to treatment failure (TTF) of 12 and 20 months (P = 0.006), respectively. TPF-ICT patients tended to have longer OS (37 months in the PF-ICT arm vs 43 months in the TPF-ICT arm; P = 0.06). Moreover, this difference was more evident in patients with unresectable disease (OS: 26 months in the PF-ICT arm vs 36 months in the TPF-ICT; P = 0.04). PF patients experienced more instances of Grade 2–4 mucositis than TPF patients (53% vs 16%; P < 0.001).

Comparison with upfront CCRT (control arm: CCRT)
Docetaxel-Based Chemotherapy Plus or Minus ICT to Decrease Events in Head and Neck Cancer (DeCIDE) Cohen et al. showed equivalent outcomes for TPF-ICT (x2) (docetaxel 75 mg/m² Day 1, CDDP 75 mg/m² Day 1, 5-FU 750 mg/m² Days 1–5) → CCRT (docetaxel, 5-FU, and hydroxyurea + RT 1.5 Gy twice per day every other week) and upfront CCRT in N2 or N3 disease [38]. Grade 3–4 toxicities included febrile neutropenia (11%) and mucositis (9%) during ICT and mucositis (49%), dermatitis (21%), and leukopenia (18%) during CCRT (both arms combined). Serious adverse events were more common in the ICT arm than in the CCRT arm (47% vs 28%; P = 0.002). There were no statistically significant differences in OS or RFS.

Paccagnella et al. suggested the superiority of TPF-ICT (x3) (docetaxel 75 mg/m², CDDP 80 mg/m² Day 1, 5-FU 800 mg/m² 96 h every 3 weeks, n = 51) → CCRT over CCRT alone (CDDP 20 mg/m² Days 1–4, 5-FU 800 mg/m² Week 1 and Week 6, 66–70 Gy, n = 50) in terms of initial response [39]. TPF-ICT → CCRT achieved 50% of the primary endpoint (CR at 6–8 weeks after CCRT), whereas CCRT alone achieved 21% (P = 0.004). The CCRT and TPF-ICT → CCRT groups had an MST of 33.3 and 39.6 months (P = 0.268), respectively. This study used a non-standard chemotherapeutic drug dose for CCRT (Table 3).

Other trials

The CONDOR trial
The CONDOR trial examined the role of alternated RT after four courses of TPF-ICT → CCRT × 4 (CDDP 100 mg/m² = cis100 + RT 70 Gy/35 fr including intensity-modulated RT) or CDDP 40 mg/m² weekly with accelerated RT (=cis40 + accelerated RT; ART: 6 fr/wk = 70 Gy/6 wks) [40]. Unfortunately, the data safety monitoring board advised premature termination of the study, because only 22% and 41% (32% in total) of the patients treated with cis100 + RT (n = 27) and cis40 + ART (n = 29) could receive the planned CDDP dose during CCRT, respectively. This trial revealed the difficulty of performing CCRT after TPF-ICT.
Table 3. Randomized control trials of induction chemotherapy (ICT) including unresectable cases

| Study (Tx year) | Stage | %T–T2/T3/T4 | NO PT | RT (%) received | Tx % completed [without delay or reduced dose] | Initial response ICT (CCRT) | LP | OS% | Toxicity |
|----------------|-------|-------------|-------|----------------|-----------------------------------------------|-----------------------------|-----|------|----------|
| Author PY      | (MF)  | Endpoint    |       |                |                                               |                             |     |      |          |
| Resectable     |       |             |       |                |                                               |                             |     |      |          |
| GORTEC2000–01  | III/IV larynx | 18/67/15 | 103   | PF → RT (47%) or CCRT (9%) | 80% [32%] | 30.1%/59.2% | 3-year 57% | 5y 50.9%, 10y 30.2% | G3- late 17.1% | TPF better LP same OS |
| Pointeu 2009 [32, 33] | (105 M) LP | 39/23/33/4 | 110   | TPF → RT (61%) or CCRT (15%) | 90% [62.7%] | 41.8%/80% (P = 0.002) | 70% (P = 0.03) | 41.9%, 23.5% | 9.3% (P = 0.035) |
| Mix (resectable and unresectable) |       |             |       |                |                                               |                             |     |      |          |
| TAX 324        | III/IV Larynx | 18% | 25(T1–2)/32/43 | 245 | PF → CCRT (carboplatin) (75%) | 73% | 15%/64% | 3-year 32%, 3-year LFS 32%, 3-year LRC 70% | 52% | feeding tube dependent 11%, tracheostomies 11% | TPF better LP OS |
| Posner 2007 [34–36] | (72.2 M) OS PFS | 16/20/50/14 | 255 | TPF → CCRT (carboplatin) (79%) | 68% | 17%/72%(P = 0.07) | 52% (P = 0.02), 52% (P = 0.014) | 42% | 3%, 7% |
| TTCC (1998–2001) | III/IV larynx | 16% | 11(T1–2)/34/55 | 193 | PF → CCRT (42%) | 36% | 14%/68% (78%/88%) | NA | 2-year 32%, MST 37M (unresectable 26 M) | mucositis Grade 3 ≤53% |
| Hitt 2005 (Spain) [37] | (24 m) CR rate | 21/19/47/13 | 189 | T (paclitaxel) PF → CCRT (60%) | 60% | 33% (P < 0.001)/80% (88%/98%) | 43% 43M (P = 0.06), (36M P = 0.03) | 16% (P < 0.001) |
|                |       |             |       |                |                                               |                             |     |      |          |
### Upfront CCRT vs ICT(TPF) → CCRT: control arm CCRT

#### Mix (resectable and unresectable)

| Study                        | Protocol | N2/#3 | CCRT (%) | TTP/TTCR (%) | TPFx2 → CCRT (%) | RR 64% (26%/79%) | LP 64%a 47% | Serious adverse events 28% | Same OS | Notes |
|------------------------------|----------|-------|----------|---------------|------------------|------------------|-----------|----------------------------|---------|-------|
| DECIDE (2004–2009)           |          | 45(T0–2)/22/22 | 135 CCRT | (21%/74%) | NA | 65%a |                     |         | Underpowered |
| Cohen 2014 [38] (min 30 M)   |          | 0/0/88/11 | 138 TPFx2 → CCRT (90%) | 86% | RR 64% (26%/79%) | 64%a | 47% P = 0.002 |         |         |

#### Others

### Resectability NS

| Study                        | Protocol | N2/#3 | CCRT (%) | TTP/TTCR (%) | TPFx2 → CCRT (%) | RR 64% (26%/79%) | LP 64%a 47% | Serious adverse events 28% | Same OS | Notes |
|------------------------------|----------|-------|----------|---------------|------------------|------------------|-----------|----------------------------|---------|-------|
| CONDOR (2008–2012)           |          | 18/35/47 | 27 TPF (x2–4) → CCRT (90% allocated) | [22%] | 6.5%/61.3% (81.5%) | 2-year PFS 70% | 72% | Febrile neutropenia 18% (during TPF) |         | Early closure: low-feasibility |
| Driessen 2016 (Holland) [40]  |          | 23/5/72 | 29 TPF (x2–4) → CCRT cis 40 (90% allocated) | [41%] | (72.4%) | 78% | 79% | G3–4 26% |         |       |

*Tx = treatment, PY = year of publication, MF = median follow-up period, RT = radiotherapy, CCRT = concurrent chemoradiotherapy, ICT = induction chemotherapy, LP = larynx preservation rate, OS = overall survival time (5 years unless otherwise stated), PFS = progression-free survival rate, PF = CDDP + SFU, TPF = Taxan + CDDP + 5-FU, GORTEC = Groupe d’Oncologie Radiothérapie Tête Et Cou, EORTC = European Organization for Research and Treatment of Cancer, TTCC = Spanish Head and Neck Cancer Cooperative Group, DECIDE = Docetaxel-Based Chemotherapy Plus or Minus IC to Decrease Events in Head and Neck Cancer, CR = complete response, PR = partial response, RR = response rate = CR + PR, NA = not available, TTP = time to treatment failure, *Estimated from graph. 5RT 72 Gy/1.8 + 1.5 Gy bid/6 wk + docetaxel 20 mg/m²/wk × 4 for poor responder at TPF-ICT or RT 70 Gy/35 fr + carboplatin AUC 1-5/week × 7 weeks for good responder. *Low surgical curability or LP candidate.
In addition, Hitt et al. showed that ICT had significantly better PFS than CCRT alone in the per protocol population [41]. These data suggested that ICT could be beneficial for patients who can complete the treatment protocol. On the other hand, ICT might only delay CCRT in those who are unable to complete the treatment protocol, without any benefit except for additional therapeutic toxicity. Therefore, patient selection is an important issue for future trials [42, 43]. Michigan University [43] and Popovtzer et al. proposed chemotherapy selection during the first cycle of TPF-ICT [42], with responses being determined by examination and positron emission tomography (PET)-CT. In those studies, responders (>50% tumor reduction) underwent chemoradiation, whereas non-responders underwent laryngectomy. A total of 83% of the patients responded to the treatment, while 17% had stable or progressive disease. After 2 years, the median OS rate, LP rate and disease-specific survival rate were 80%, 83% and 86%, respectively. Response to a single TPF cycle was associated with 2-year OS (92% vs 50%; \( P = 0.02 \)).

**Meta-analysis of chemotherapy in head and neck cancer**

The pivotal Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) study was first reported in 2002 and updated in 2009 (87 trials and 16 485 patients) [44, 45]. These studies concluded that CCRT proved to be considerably more successful than alternative treatments. Adding ICT (PF-ICT) to locoregional treatment was associated with a slight improvement in OS and distant failure. The HR of death was 0.88 (95% CI 0.80–0.96), with an absolute chemotherapy benefit of 4.5% at 5 years. CCRT showed a more pronounced benefit compared with ICT. The HR for CCRT was 0.81 (95% CI 0.74–0.89), with an absolute benefit of 6.5% at 5 years. A decrease in the effects of chemotherapy was observed with age (95% CI 0.99, test for trend). In addition, despite current intensive efforts, no form of acceleration can potentially fully compensate for the lack of concurrent chemotherapy [15, 46].

Several meta-analyses have been performed to answer subsequent questions [47–49]. Comparing PF-ICT and TPF-ICT in 1772 patients, Blanchard et al. [9] showed that TPF-ICT had an absolute benefit of 7.4% after 5 years and was associated with a significant reduction in progression, locoregional failure, and distant failure when compared with PF-ICT [9]. However, only 49% of patients treated with taxanes were able to complete sequential CCRT as planned. Kim et al. also concluded that ICT using TPF-ICT followed by CCRT did not improve OS [11], although PFS and response rates were significantly improved. Furthermore, Gyawali et al. concluded that concurrent CCRT should be preferred over ICT at present [10] (Table 4).

**BRT (cetuximab)—is BRT safer than CCRT?**

**The Bonner trial**

Bonner et al. introduced BRT (cetuximab + RT) for the treatment of advanced head and neck cancers [15, 51]. After comparing RT and BRT (an initial dose of 400 mg cetuximab, a monoclonal antibody against the epidermal growth factor receptor, followed by 250 mg/m² weekly for the duration of RT), response rates of 64% and 74% were found in the RT and BRT arms \( (P = 0.02) \), respectively. The median durations of locoregional control were 24.4 and 14.9 months for BRT and RT (HR 0.68; \( P = 0.005 \)), respectively. BRT significantly prolonged PFS (HR 0.70; \( P = 0.006 \)) and OS. Except for acneiform rash and infusion reactions, the incidence of Grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups. However, subpopulation analysis showed that BRT was not superior to RT alone for laryngeal cancer [53]. Although BRT has been extensively explored since this trial, it has thus far failed to establish its superiority in laryngeal cancer treatment.

**Radiotherapy With Cisplatin Vs Radiotherapy With Cetuximab**

**After Induction Chemotherapy for Larynx Preservation (TREMLIN) (GORTEC + GETTEC)**

The TREMLIN study compared CCRT and BRT for LP [50] in 153 operable patients (laryngeal or hypopharyngeal cancer, T2–T3 and N0–N3) after TPF-ICT. The primary endpoint was LP 3 months after treatment, with an expected rate of 80%. Secondary endpoints were laryngeal function preservation (LFP) and OS at 18 months. Among the 156 patients who received TPF-ICT, 126 (86%) achieved PR \( \leq 2 \) and 23 patients \( < \) PR (non-responders received S [16] or RT [7]). Subsequently, 116 patients (76% of those included in the TPF-ICT group) were categorized into CCRT (60) (70 Gy/35 fr) or BRT (56) (70 Gy/35 fr). No significant difference between BRT and CCRT was observed with regard to LP at 3 months (95% and 93%), LFP (87% and 82%) or OS at 18 months (92% and 89%). Unfortunately, considering the 24% of patients who dropped out, the trial did not reach the expected 80% LP 3 months after treatment. Though BRT was shown to be as toxic as CCRT, causing the same rate of Grade 3 to 4 acute mucositis, it had worse in-field skin toxicity. More local failures (8.3% vs 14.3% at 18 months) among patients treated with cetuximab raised the possibility that BRT may be inferior to CCRT for achieving local control in laryngeal cancer. This is the only RCT providing evidence for the similarity in the outcomes of TPF-ICT \( \rightarrow \) BRT and TPF-ICT \( \rightarrow \) CCRT.

**RTOG0522**

Ang et al. made a comparison between CCRT and CCRT + cetuximab (BCCRT) [52]. RT (72 Gy/32 fr/6 weeks: twice a day for 6 days) was delivered as scheduled. When IMRT was used, the protocol was changed to twice a day once a week for 5 weeks (70 Gy/35 fr/6 weeks). Compared with CCRT, BCCRT had more frequent RT interruptions (26.9% vs 15.1%), similar CDDP delivery (mean, 185.7 mg/m² vs 191.1 mg/m²) and more Grade 3–4 radiation mucositis (43.2% vs 33.3%), rash, fatigue, anorexia, and hypokalemia toxicities but less late toxicity. Similar outcome was obtained; 3-year PFS (61.2% vs 58.9%), 3-year OS (72.9% vs 75.8%), locoregional failure (19.9% vs 25.9%) and distant metastasis (13.0% vs 9.7%; \( P = 0.08 \)). Patients with p16-positive oropharyngeal carcinoma (OPC) showed better PFS (72.8% vs 49.2%; \( P < 0.001 \)) and OS (85.6% vs 60.1%, \( P < 0.001 \)) than those with p16-negative OPC. Subpopulation analysis showed an inclination similar to that shown in the Bonner trial, wherein CCRT seemed to be superior to BCCRT in patients with laryngeal cancer.
**Table 4. Randomized control trials for bioradiotherapy (BRT) including unresectable cases**

| Study (Tx year) | Stage larynx % (MF) Endpoint | %T | RT (% received) | Tx % completed | LP | OS || Toxicity |
|-----------------|-----------------------------|----|-----------------|----------------|----|-----|-----------------|------------|
| **Resectable**  |                             |    |                 |                |    |     |                 |            |
| TREMPRIN (2006–2008) | III/IV larynx 41% | 14/56/30 | 60 | TPF → CCRT (74% TPF allocated) | 90% CCRT allocated | 3 M 95%, LFP 87% | 18 M 92% | mucositis Grade 3 ≤46% (in-field 26%) | TPF→BRT same efficacy |
| Lefebvre 2013 [50] | (36 M) 3 M LP | 36/26/38/0 | 56 | TPF → BRT (74% TPF allocated) | 95% BRT allocated | 93%, 82% | 89% | 45% (57%) | BRT toxic as CCRT |
| **Resectability NS** |                             |    |                 |                |    |     |                 |            |
| Bonner trial (1999–2002) | III/IV larynx 25% | 31/39/30 | 213 | RTa | unacceptable variation in RT 6% unevlauable RT 6% | 36.4% MST 49 M | 19%, 82% | 45% (P < 0.001) | BRT OS better in entire group |
| Bonner 2006 [14, 51] | (54 M) NA | 19/19/53/9 | 211 | BRT | 4%, 9% | 47% | 45.6% (P = 0.03) 54 M | 8% (N = 0.001) | BRT not superior to RT in larynx |
| RTOG 0522 (2005–2009) | III/IV larynx 23% | 39/37/24 | 447 | CCRT | radiation interruptions 42% | LRF 19.9% 3-year 72.9%, PFS 61.2% | mucositis Grade 3 ≤33.3% | same PFS, OS |
| Ang 2014 [52] | (3.8-year) PFS | 11/9/75/5 | 444 | BCCRT | 51% (P < 0.001) | 25.9% | 75.8%, 58.9% | 43.2% | P16 important |
| Italy PII (2011–2014) | III/IV larynx 26% | 24/33/43 | 35 | CCRT cis40 | 100% | 2-year LC 53% | 2-year 78% | severe 3%, RT stop 10 days <0% | early closure: poor accrual |
| Magrini 2016 [53] | (19.3 M) Tx compliance | 36/44/20 | 35 | BRT | 91% | 80% P = 0.07 | 68% | 19% (P = 0.044), 13% (P = 0.05) | BRT toxic than expected |

Tx = year of publication, MF = median follow-up period, RT = radiotherapy, ICT = induction chemotherapy, BRT = bioradiotherapy, BCCRT = biochemoradiotherapy, CCRT = concurrent chemoradiotherapy, LP = larynx preservation (rate), OS = overall survival rate (5 years unless otherwise stated), LC = local control rate, LRC = locoregional control rate, LRF = locoregional failure rate, PFS = progression-free survival rate, LFP = larynx function preservation, SFL = survival with functioning larynx, NS = not stated. TREMPRIN = Radiotherapy With Cisplatin Vs Radiotherapy With Cetuximab After Induction Chemotherapy for Larynx Preservation, RTOG = Radiation Therapy Oncology Group. *70 Gy/35 fr or 72–76.8 Gy (1.2 Gy twice a day) concomitant boost 72 Gy.
Magrini et al. made a direct comparison (Phase II trial) between CCRT (70 Gy/35 fr + CDDP 40 mg/m²/wk) and BRT, concluding that BRT lowered compliance, increased acute toxicity rates, and had similar efficacy as compared with CCRT [53]. The endpoints included compliance, toxicity and efficacy. The study was discontinued early because of slow accrual after the enrollment of 70 patients. RT discontinuation for more than 10 days occurred in 13% and 0% of the patients receiving BRT and CDDP (P = 0.05), respectively. Hematologic, renal and GI toxicities were more frequent in the CDDP arm, whereas cutaneous toxicity and the need for nutritional support were more frequent in the BRT arm. Serious adverse events were higher in the BRT arm than in the CDDP arm (19% vs 3%, P = 0.044; including 4 vs 1 toxic deaths). Although efficacies were similar, BRT toxicity was higher than expected.

A German LP trial [54] utilized a protocol with three cycles of TPF-ICT (dose according to the TAX 323 trial) CCRT (concomitant boost RT) with or without cetuximab for 16 weeks (starting with ICT and continuing with RT) in 180 patients. In case of non-response after the first cycle, salvage laryngectomy was performed. The investigators omitted 5-FU following four therapy-related deaths at the beginning of the trial. The addition of cetuximab to TPF-ICT seems to have profound effects on toxicity. Studies attempting to add cetuximab to TPF-ICT showed excessive toxicity. Therefore, current research has explored the possibility of omitting 5-FU and replacing it with cetuximab.

Petrelli et al. performed a meta-analysis including 15 trials (1808 patients) to assess the role of BRT [55]. Overall, CCRT significantly improved 2-year OS (response rate = 0.66; P = 0.02), 2-year PFS (response rate = 0.68; P = 0.002), and 2-year locoregional control rate (response rate = 0.63; P = 0.005) compared with BRT. BRT had a toxicity profile similar to CCRT and was difficult to deliver after TPF-ICT. The aforementioned studies (TREPLMIN, PARADIGM and DeCIDE) suggested that, despite the fascinating nature of strategies using ICT and CCRT or BRT to control both locoregional and distant metastases, they have been difficult to implement because of their association with severe toxicities.

Thereafter, Mesia et al. (TTCC2007/02) reported feasible results for TPF-ICT (×3) → BRT in 93 patients with resectable laryngeal cancer (A phase 2 study, with patients treated between 2008 and 2011) [56]. Among the 93 patients, 76 were responsive (37 CR + 38 PR = 81% response rate), while 73 patients (78%) received BRT. The 3-year actuarial rates for survival with functional larynx, laryngectomy-free survival, and OS were 70%, 72% and 78%, respectively. The acute toxicity observed during both ICT and BRT was expected, with only one toxicity-related death (local bleeding) during BRT.

Zenda et al. also postulated the feasibility of TPF-ICT × 3 → BRT in a Japanese population of 54 patients, 19% of which had laryngeal cancer (2013–2015) [57]. The response rates for ICT and RT were 72% and 76%, respectively. Among the 54 patients, 50 (93%) received ≥2 courses of ICT, whereas 41 (76%) had full-dose RT. The rate of treatment completion was thus 76%. The frequencies of Grade 3–4 neutropenia, febrile neutropenia, and allergic/infusion reactions were 93%, 39% and 11%, respectively.

**DISCUSSION**

LP strategy may decrease OS

Despite treatment, the 5-year OS of locally advanced laryngeal cancer ranges from 30% to 70%. Chen et al. [12] reviewed 2.817 patients treated between 1985 and 2007 using the National Cancer Database, noting an increase in the administration of radiation with or without chemotherapy from <7% to 45%. Primary total laryngectomy decreased from 42% to 32%. The 4-year OS rates for total laryngectomy, CCRT, and RT were 51%, 48% and 38%, respectively. Using SEER data, Pulte et al. reported improvements in survival rates for head and neck cancer patients but not laryngeal cancer patients during the late 20th century [58]. This has also proven to be true for a recent series of cases diagnosed in the period 2004–2012, as reported by the National Cancer Database Analysis group in the USA [59, 60]. A total of 1559 cases treated with S → RT, 1597 with CCRT, and 386 with ICT were included. After adjusting for covariates, CCRT was found to be associated with inferior OS compared with S → RT (HR 1.55; P < 0.01) and ICT (HR, 1.25 P < 0.01). These reports sparked controversy. For example, inappropriate patient selection for the LP strategy may decrease survival of locally advanced laryngeal cancer. Several important factors still need to be known before RCT outcomes can be translated into routine clinical work.

**Limitations of RCTs**

Locally advanced (Stage III/IV) tumors are considered to include cancers of Stages T2N1 to T4N3, which are evidently different categories. The aforementioned RCTs sometimes included patients with T3 tumors without cord fixation and T4 tumors with minimal cartilage invasion. For instance, the VA study showed that <60% of the population had tumors with cord fixation, whereas all patients in the French GETTEC study presented with cord fixation, resulting in a superior OS after surgery.

In addition, T category migration is an important confounding factor. Significant differences in the assessment of vocal cord fixation have been found between experts and trainees [61], which may lead to misclassifications of T2 and T3 categories. Given that gross cartilage invasion was also difficult to detect using CT images [62], a substantial ratio of T4 tumors diagnosed using CT images may have actually been T3 tumors after pathological examination. This is also true for magnetic resonance imaging (MRI) usage, which improved the diagnostic accuracy of T4 cartilage invasion. Therefore, a discrepancy in T category classification exists between the previously used CT examinations and the more recently used MRI-based examinations.

Compliance with chemoradiotherapy (CRT) is another problem that needs to be addressed when interpreting RCTs. The VA and GETTEC trials reported that only 7% and 0% of the patients discontinued CTX, respectively. Moreover, the RTOG 9011 trial showed that 7% of the responders discontinued CTX after two cycles of ICT, whereas 70% of those receiving CCRT completed all three cycles of CTX. On the other hand, Givens et al. showed that only 48% of the patients (including 16% with larynx) completed the planned CTX cycles [63]. A cumulative CDDP dosage of 200 mg or more indicated better outcomes when administered concurrently.
with RT [66]. Recent results suggest that larger amount of CDDP is associated with survival benefit in patients with human papillomavirus (HPV)-negative but not HPV-positive LAHNC, with the exception of the T4 or N3 subset wherein a higher cumulative cisplatin dose was associated with a trend toward improved OS [64].

Therefore, a huge bias exists between routine clinical practice and RCTs, such that most patients included in RCTs belong to a healthier population with less severe comorbidities, better functional status, and a lesser likelihood of suffering from adverse events related to treatments [65].

It is also important to emphasize that previous key trials were performed using two-dimensional RT techniques and that the use of more advanced RT techniques, such as IMRT and particle therapy, could probably lead to less late radiation toxicity. Whether today’s modern conformal radiation delivery systems reduce late normal tissue toxicity (other than that to the parotids) remains to be established [25].

Surgery remains as a best treatment for T4 disease for OS and requirement of multidiscipline team for LPF

Sanabria et al. recommended that total laryngectomy be considered for advanced T4 laryngeal cancers in non-academic settings, given that its survival outcomes appear to be better than those for CCRT, according to the results of many observational studies [65]. CCRT can be acceptable for patients with T3 tumors given the condition that all resources for treatment administration, follow-up, and surgical salvage are available. Nakayama et al. noted that organ-sparing approaches require (i) a high level of skill and cooperation among various disciplines, (ii) adequate compliance from patients, and (iii) careful documentation and appropriate surveillance [66].

No strategy could add a merit in elder population

It should also be noted that all strategies to improve outcome, including CCRT, accelerated RT, and BRT, could not establish their merit with increasing age, showing no difference in survival vs conventional RT alone in patients older than 70 years of age [17, 43, 51, 67]. Therefore, elderly patients should be given special consideration, carefully weighing the risks and benefits, before a treatment plan is decided upon.

New paradigm shift

A new paradigm shift involving new drugs or technology is needed to improve not only OS but also LFP. For example, HPV status could shed new light on the treatment algorithm of patients with oropharyngeal cancer [14]. Treatment intensity could potentially be reduced in patients positive for the virus. Several candidates of molecular markers are also awaiting confirmation (p53, bclx, EGF, etc.) [68].

Several new drug combinations have also been explored. Komatsu et al. explored experimental CCRT using TPF (α2) (docetaxel 50 mg/m² d1, CDDP 60 mg/m² d4, 5-FU 600 mg/m² d1–5) in 140 patients [69]. The response rate and 5-year OS rate were 97.1% and 79.2%, respectively. Among patients with laryngeal or hypopharyngeal carcinoma, the 5-year laryngectomy-free survival rate was 64.9%. Hoshikawa et al. reported on CCRT using Nedaplatin and S-1 [70]. Primary site tumors and neck lymph nodes exhibited CR rates of 91% and 64.3%, respectively, with a 4-year OS of 85.3%. Several institutions have also explored intraarterial chemotherapy with good results. Suzuki et al. reported 3-year OS and LP rates of 92% and 93%, respectively [71].

CONCLUSION

Regarding the first question, ‘Is an LP strategy feasible?’, the answer is ‘yes’ if the goal is set at improving the LP ratio. However, appropriate eligibility criteria are still emerging and currently vary depending on the institution.

Regarding the second question ‘Which treatment protocol is best?’ At present, this cannot be answered because the goal can vary (superior OS, better Quality of Life, less morbidity), depending on patient and physician preference.

In conclusion, options for LP, including CCRT, ICT, and BRT, have successfully emerged over the past several decades, without an improvement in OS. A new paradigm shift involving new systemic therapies, molecular markers, and/or technology is needed to improve not only OS rates but also LFP.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FUNDING

The authors have no funding source.

REFERENCES

1. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. CA Cancer J Clin 2002;55:74–108.
2. Michigan Medicine. Comprehensive Cancer Centre. What Patients Should Know in Decision Making. http://www.mcanancer.org/head-and-neck-cancer/voicebox/what-patients-should-know (10 April 2017, date last accessed).
3. Kish J, Drelichman A, Jacobs J et al. Clinical trial of CDDP and 5-FU infusion as initial treatment for advanced squamous cell carcinoma of the head and neck. Cancer Treat Rep 1982;66:471–4.
4. Decker DA, Drelichman A, Jacobs J et al. Adjuvant chemotherapy with cis-diamminodichloroplatinum II and 120-hour infusion 5-fluorouracil in Stage III and IV squamous cell carcinoma of the head and neck. Cancer 1983;51:1353–5.
5. Jacobs C, Goffinet DR, Goffinet L et al. Chemotherapy as a substitute for surgery in the treatment advanced resectable head and neck cancer: a report from the Northern California Oncology Group. Cancer 1987;60:1178–83.
6. Karp DD, Vaughan CW, Carter R et al. Larynx preservation using induction chemotherapy plus radiation therapy as an alternative to laryngectomy in advanced head and neck cancer: a long-term follow-up report. Am J Clin Oncol 1991;14:273–9.
7. Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324:1685–90.
8. Forastiere AA, Goepfert H, Maor M et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091–8.

9. Blanchard P, Bourhis J, Lucas B et al. Taxane–cisplatin–fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. *J Clin Oncol* 2013;31:2854–60.

10. Gyawali B, Shimokata T, Honda K et al. Chemotherapy in locally advanced head and neck squamous cell carcinoma. *Cancer Treat Rev* 2016;44:10–6.

11. Kim R, Hahn S, Shin J et al. The effect of induction chemotherapy using docetaxel, cisplatin, and fluorouracil on survival in locally advanced head and neck squamous cell carcinoma: meta-analysis. *Cancer Res Treat* 2016;48:907–16.

12. Chen AY, Fedewa S, Zhu J. Temporal trends in the treatment of early- and advanced-stage laryngeal cancer in the United States, 1985–2007. *Arch Otolaryngol Head Neck Surg* 2011;137:1017–24.

13. Hoffman HT, Porter K, Karnell LH et al. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope* 2006;116:1–13.

14. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;11:21–8.

15. Yamazaki H, Suzuki G, Nakamura S et al. Radiotherapy for laryngeal cancer—technical aspects and alternate fractionation. *J Radiat Res* 2017;58:495–508.

16. Mendenhall WM, Dagan R, Bryant CM et al. Definitive radiotherapy for squamous cell carcinoma of the glottic larynx. *Cancer Control* 2016;23:208–12.

17. Shiao JC, Mohamed ASR, Messer JA et al. Quantitative pre-treatment CT volumetry: association with oncologic outcomes in patients with T4a squamous carcinoma of the larynx. *Head Neck* 2017;39:1609–20.

18. Mucha-Malecka A, Składowski K. High-dose RT alone for patients with T4-stage laryngeal cancer. *Strahlenther Onkol* 2013;189:632–8.

19. Stenson KM, Maccracken E, Kannavakkam RW et al. Chemoradiation for patients with large-volume laryngeal cancers. *Head Neck* 2012;34:1162–7.

20. Wagner MM, Curé JK, Caudell JJ et al. Prognostic significance of thyroid or cricoid cartilage invasion in laryngeal or hypopharyngeal cancer treated with organ preserving strategies. *Radiat Oncol* 2012;7:219.

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

22. 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.

23. Worden FP, Moyer J, Lee JS et al. Chemoselection as a strategy for organ preservation in patients with T4 laryngeal squamous cell carcinoma with cartilage invasion. *Laryngoscope* 2009;119:1510–7.

24. Al-Mamgani A, Tans L, van Rooij P et al. A single-institutional experience of 15 years of treating T3 laryngeal cancer with primary radiotherapy, with or without chemotherapy. *Int J Radiat Oncol Biol Phys* 2012;83:1000–6.

25. Fuller CD, Mohamed AS, Garden AS et al. Long-term outcomes after multidisciplinary management of T3 laryngeal squamous cell carcinomas: improved functional outcomes and survival with modern therapeutic approaches. *Head Neck* 2016;38:1739–51.

26. 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.

27. Rosenthal DJ, Mohamed AS, Weber RS et al. Long-term outcomes after surgical or nonsurgical initial therapy for patients with T4 squamous cell carcinoma of the larynx: A 3-decade survey. *Cancer* 2015;121:1608–19.

28. Richard JM, Sancho-Garnier H, Pessey JJ et al. Randomized trial of induction chemotherapy in larynx carcinoma. *Oral Oncol* 1996;34:224–8.

29. Soo KC, Tan EH, Wee J et al. Surgery and adjuvant RT vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison. *Br J Cancer* 2005;93:279–86.

30. Forastiere AA, Zhang Q, Weber RS et al. Long-term results of RTOG 91–11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31:845–52.

31. Adelstein DJ, Lavertu P, Saxton JP et al. Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and IV squamous cell carcinoma of the head and neck. *Cancer* 2000;88:876–83.

32. Pintouret Y, Garaud P, Chapet S et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst* 2009;101:498–506.

33. Janoray G, Pointreau Y, Garaud P et al. Long-term results of the TAX 324 randomised phase III and IV squamous cell carcinoma of the larynx: an analysis of dose–time volume factors. *J Natl Cancer Inst* 2005;93:279–86.

34. Posner MR, Hershock DM, Blajman CR et al. Induction chemotherapy using docetaxel, cisplatin, and 5-fluorouracil alone or in combination with docetaxel for larynx preservation. *J Natl Cancer Inst* 2013;105:368–79.

35. Lorch JH, Goloubeva O, Haddad RI et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck. *N Engl J Med* 2007;357:1705–15.

36. Lorch JH, Goloubeva O, Haddad RI et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck. *N Engl J Med* 2007;357:1705–15.

37. Wittt R, Lopez-Pousa A, Martinez-Trufero J et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol* 2005;23:8636–45.
48. Budach W, Bölke E, Kammers K et al. Induction chemotherapy.

46. Gupta T, Kannan S, Ghosh-Laskar S et al. Systematic review.

45. Pignon JP, le Maitre A, Maillard E et al. Meta-analysis of.

44. Pignon JP, Bourhis J, Domenge C et al. Chemotherapy added.

43. Vainshtein JM, Wu VF, Spector ME et al. Chemoselection: a.

42. Popovtzer A, Burnstein H, Stemmer S et al. Phase II organ-

41. Hitt R, Grau JJ, Lopez-Pousa A et al. A randomized phase III

trial comparing induction chemotherapy followed by chemora-

diagnosis versus chemoradiotherapy alone as treatment of

unresectable head and neck cancer. Ann Oncol 2014;25:216–25.

40. Popovtzer A, Burnstein H, Stemmer S et al. Phase II organ-

preservation trial: concurrent cisplatin and radiotherapy for

advanced laryngeal cancer after response to docetaxel, cisplatin,

and 5-fluorouracil-based induction chemotherapy. Head Neck

2017;39:227–33.

39. Paccagnella A, Ghi MG, Loreggian L et al. Concomitant che-

moradiotherapy versus induction docetaxel, cisplatin and 5-

fluorouracil (TPF) followed by concomitant chemoradiotherapy

in locally advanced head and neck cancer: a phase II random-

ized study. Ann Oncol 2010;21:1515–22.

38. Cohen EE, Karrison TG, Kocherginsky M et al. Phase III random-

ized trial of induction chemotherapy in patients with N2 or

N3 locally advanced head and neck cancer. J Clin Oncol 2014;

32:2735–43.

37. Petrelli F, Coim a, Riboldi V et al. Concomitant platinum-

based chemotherapy or cetuximab with radiotherapy for locally

advanced head and neck cancer: a systematic review and meta-

analysis of published studies. Oral Oncol 2014;50:1041–8.

36. Mesia R, Garcia-Saenz JA, Lozano A et al. Could the addition of

cetuximab to conventional radiation therapy improve organ

preservation in those patients with locally advanced larynx

cancer who respond to induction chemotherapy? An organ preser-

vation Spanish Head and Neck Cancer Cooperative Group

Phase 2 study. Int J Radiat Oncol Biol Phys 2017;97:473–80.

35. Zenda S, Ota Y, Kiyota N et al. A multicenter phase II trial of
docetaxel, cisplatin and cetuximab (TPE) followed by cetuximab
concurrent with radiotherapy in patients with local advanced
squamous cell carcinoma of the head and neck (ECRIPS study).
J Clin Oncol 2017;35(suppl):abstract 6071.

34. Pulte D, Brenner H. Changes in survival in head and neck can-
cers in the late 20th and early 21st century: a period analysis.
Oncologist 2010;15:994–1001.

33. Timmermans AJ, de Gooijer CJ, Hamming-Vrieeze O et al. T3–
T4 laryngeal cancer in The Netherlands Cancer Institute; 10-
year results of the consistent application of an organ-preserv-

ing/sacrificing protocol. Head Neck 2015;37:1495–503.

32. Stokes WA, Jones BL, Bhatia S et al. A comparison of overall

survival for patients with T4 larynx cancer treated with surgical

versus organ-preservation approaches: a National Cancer Data

Base analysis. Cancer 2017;123:600–8.

31. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuxi-
mab for squamous-cell carcinoma of the head and neck. N Engl
J Med 2006;354:567–78.

30. Lefebvre JL, Pointreau Y, Rolland F et al. Induction chemother-

apy followed by either chemoradiotherapy or bioradiotherapy

for larynx preservation: the TREMPLIN randomized phase II

study. J Clin Oncol 2013;31:853–9.

29. Ang KK, Zhang Q, Rosenthal DI et al. Randomized phase III

trial of concurrent accelerated radiation plus CDDP with or

without cetuximab for stage III to IV head and neck carcinoma:
RTOG 0522. J Clin Oncol 2014;32:2940–50.

28. Magrini SM, Buglione M, Corvò R et al. Cetuximab and radiother-
ysis versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. J Clin Oncol 2016;34:427–35.

27. Dietz A, Flentjie M, Hagen R et al. Induction chemotherapy

(1C) docetaxel (T), cisplatin (P), 5-fluorouracil (F) (TPF), or

TP followed by concomitant boost radiotherapy (R) with or

without cetuximab (E) for functional organ preservation (FOP)
of resectable laryngeal and hypopharyngeal cancer (LHSCC): first results of the phase II randomized DeLOS-II study. J Clin Oncol 2014;32(15_suppl):abstract 6016.

26. Zenda S, Ota Y, Kiyota N et al. A multicenter phase II trial of
docetaxel, cisplatin and cetuximab (TPE) followed by cetuximab
concurrent with radiotherapy in patients with local advanced
squamous cell carcinoma of the head and neck (ECRIPS study).
J Clin Oncol 2017;35(suppl):abstract 6071.

25. Pulte D, Brenner H. Changes in survival in head and neck can-
cers in the late 20th and early 21st century: a period analysis.
Oncologist 2010;15:994–1001.

24. Timmermans AJ, de Gooijer CJ, Hamming-Vrieeze O et al. T3–
T4 laryngeal cancer in The Netherlands Cancer Institute; 10-
year results of the consistent application of an organ-preserv-

ing/sacrificing protocol. Head Neck 2015;37:1495–503.

23. Stokes WA, Jones BL, Bhatia S et al. A comparison of overall

survival for patients with T4 larynx cancer treated with surgical

versus organ-preservation approaches: a National Cancer Data

Base analysis. Cancer 2017;123:600–8.

22. Rosow DE, Sulica L. Laryngoscopy of vocal fold paralysis: evaluation

of consistency of clinical findings. Laryngoscope 2010;120:1376–82.

21. Beiter JJ, Muller S, Grist WJ et al. Prognostic accuracy of computed

tomography findings for patients with laryngeal cancer undergoing laryngectomy. J Clin Oncol 2010;28: 2318–22.

20. Givens DJ, Karnell LH, Gupta AK et al. Adverse events asso-
ciated with concurrent chemoradiation therapy in patients with

head and neck cancer. Arch Otolaryngol Head Neck Surg 2009;

135:1209–17.
64. Spreafico A, Huang SH, Xu W et al. Impact of cisplatin dose intensity on human papillomavirus–related and –unrelated locally advanced head and neck squamous cell carcinoma. *Eur J Cancer* 2016;67:174–82.
65. Sanabria A, Chaves AL, Kowalski LP et al. Organ preservation with chemoradiation in advanced laryngeal cancer: the problem of generalizing results from randomized controlled trials. *Auris Nasus Larynx* 2017;44:18–25.
66. Nakayama M, Okamoto M, Hayakawa K et al. Clinical outcomes of 849 laryngeal cancers treated in the past 40 years: are we succeeding? *Jpn J Clin Oncol* 2014;44:57–64.
67. Bourhis J, Overgaard J, Audry H et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;368:843–54.
68. Ow TJ, Pitts CE, Kabarriti R et al. Effective biomarkers and radiation treatment in head and neck cancer. *Arch Pathol Lab Med* 2015;139:1379–88.
69. Komatsu M, Shiono O, Taguchi T et al. Concurrent chemoradiotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) in patients with locally advanced squamous cell carcinoma of the head and neck. *Jpn J Clin Oncol* 2014;44:416–21.
70. Hoshikawa H, Kishino T, Mori T et al. Clinical outcomes of nedaplatin and S-1 treatment with concurrent RT in advanced head and neck cancer. *Acta Otolaryngol* 2015;135:103–8.
71. Suzuki G, Yamazaki H, Ogo E et al. Predisposing factors for larynx preservation strategies with non-surgical multimodality treatment for locally advanced (T3–4) larynx, hypopharynx and cervical esophageal disease. *Anticancer Res* 2014;34:5205–10.