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

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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 of 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 ($\leq$3.5 cm^3) T3 to T4 glottic SCCs after RT [16]. Shiao *et al.* reported that patients with a tumor volume of $\geq$21 cm^3 had significantly inferior 5-year overall survival (OS) compared with those with a tumor volume of <21 cm^3 (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/m^2 d1 + 5-FU 1000 mg/m^2 Days 1–5 every 3 weeks) → RT [66–76 Gy/1.8–2 Gy/fractions (fr)] for chemotherapy responders was found to be a

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) [23]	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/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) [23]	2009	36	FP→CCRT (or S)	3-year DFS 58%	3-year LFS 58%	3-year 78%
	Stenson (Chicago U) [19]	2011	55	CCRT: RT 70–75 Gy (AF)[a] + FHX	FPR 67.7%	88%	49%
	Rosenthal (MDACC) [27]	2015	161	S → RT	78%	NA	MST 64 M
			60	CCRT		33%	MST 64 M

PY = 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 + hydroxyuria, CCRT = concurrent chemoradiotherapy, S = surgery, AF = alternated fractionation, Ch H = Christie Hospital Holt Radium Institute, UF = University of Florida, MDACC = MD Anderson Cancer Center, PMH = Princess Margaret Hospital. [a](1.5 Gy × 2 or 2 Gy/day × 5 days → 9-day interval) × 5–7 times.

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 Tête et du Cou (GETTEC) Richard *et al.* presented results for patients with T3 laryngeal carcinoma [29]. They 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 Soo *et al.* compared CCRT (RT 66 Gy/33 fr + CDDP 20 mg/m^2 + 5-FU 1000 mg/m^2 d1 × 2) with S → RT (60 Gy/30 fr) in 119 patients and found no significant difference in 3-year DFS (50% vs 40%) [29]. 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 91–11 CCRT (concomitant CDDP 100 mg/m^2 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 2. Randomized control trials for organ preservation in resectable cases

Study (Tx year) Author PY	Site stage (MF)	%T T1–2/T3/T4 %N N0/N1/N2/N3	NO PT	Tx (% RT received) ICT (×3) unless otherwise stated	% Tx complete	Initial response to ICT (CCRT) CR/RR	LP¶	OS¶	Toxicity	
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)	54/18/11/17	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)	78/15/11/7	33	PF → RT (36%) (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
			173	PF → RT (83%) (or S)	84%[b]	21%/83%	71%, 68% ($P = 0.005$)	59%, 39%	61%	
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 TeÂ te 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. [a]Excluding T4 with thyroid cartilage or >1 cm BOT invasion. [b]Received more than 95% of the intended dose of radiotherapy (i.e. at least 67 Gy). [c]Probably 100%, but not exactly stated.

The Cleveland study Adelstein *et al.* confirmed the superiority of CCRT (5-FU 1000 mg/m^2/day and CDDP 20 mg/m^2/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/m^2 d1, CDDP 100 mg/m^2 Day 1, 5-FU 1000 mg/m^2 × 4 days) → RT (70 Gy/35 fr) increased LP and laryngeal dysfunction-free survival (LDFFS) better than PF-ICT (CDDP 100 mg/m^2 Day 1, 5-FU 1000 mg/m^2 × 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-ICT 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 (TTCC) performed a comparison study between PF-ICT (CDDP 100 mg/m^2 Day 1 + 5-FU 1000 mg/m^2 Day 1–5 every 3 weeks) and TPF-ICT (paclitaxel 175 mg/m^2 Day 1, CDDP 100 mg/m^2 Day 2, 5-FU 500 mg/m^2 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 (×2) (docetaxel 75 mg/m^2 Day 1, CDDP 75 mg/m^2 Day 1, 5-FU 750 mg/m^2 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 (×3) (docetaxel 75 mg/m^2, CDDP 80 mg/m^2 Day 1, 5-FU 800 mg/m^2 96 h every 3 weeks, $n = 51$) → CCRT over CCRT alone (CDDP 20 mg/m^2 Days 1–4, 5-FU 800 mg/m^2 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/m^2 = cis100 + RT 70 Gy/35 fr including intensity-modulated RT) or CDDP 40 mg/m^2 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) Author PY	Stage (MF) Endpoint	%T–T2/T3/T4 %N N0/N1/N2/N3	NO PT	RT (% received) ICT (×3) if otherwise stated	Tx % completed [without delay or reduced dose]	Initial response ICT (CCRT) CR/RR (CR/RR)	LP	OS¶	Toxicity	
ICT: PF vs TPF: control arm (PF-ICT → RT or CCRT)										
Resectable										
GORTEC2000–01 (2000–2005)	III/IV larynx 46%	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 (1999–2003)	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%, 62%	42% ($P = 0.014$)	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%	TPF better LP OS in unresectable subpopulation
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% ($P < 0.001$)	
			128	CCRT (92%)	71%	(48.6%/90.5%)	13.8 M	27.6 M, 7.9 M	2 (1.5%)	

Upfront CCRT vs ICT(TPF) → CCRT: control arm CCRT

Mix (resectable and unresectable)

DECIDE (2004–2009)	N2/#3 larynx 13.6%	45(T0–2)/ 22/22	135	CCRT	94%	(21%/74%)	NA	65%[a]	Serious adverse events 28%	Same OS
Cohen 2014 [38]	(min 30 M) OS	0/0/88/11	138	TPF×2 → CCRT (90%)	86%	RR 64% (26%/ 79%)		64%[a]	47% $P = 0.002$	Underpowered

Others

Resectability NS

CONDOR (2008–2012)	Stage III–IV larynx 8%	18/35/47	27	TPF (×2–4) → 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]	(38 M) feasibility ≥90% RT	23/5/72	29	TPF (×2–4) → 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 chmotherapy, LP = larynx preservation rate, OS = overall survival time (5 years unless otherwise stated), PFS = progression-free survival rate, PF = CDDP + 5FU, 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, TTF = time to treatment failure. [a]Estimated from graph. [b]RT 72 Gy/1.8 + 1.5 Gy bid/6 wk + docetaxel 20 mg/m^2/wk × 4 for poor responder at TPF-ICT or RT 70 Gy/35 fr + carboplatin AUC 1·5/week × 7 weeks for good responder. [c]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 ($P < 0.0001$), 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 ($P < 0.0001$), with an absolute benefit of 6.5% at 5 years. A decrease in the effects of chemotherapy was observed with age ($P = 0.003$, 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/m^2 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 (TREMPLIN) (GORTEC + GETTEC)

The TREMPLIN 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 ≤ 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 → BRT and TPF-ICT → CCRT.

RTOG0522

Ang *et al.* made a comparison between CCRT and CCRT + cetuximab (BCCRT) [52]. RT (72 Gy/42 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/m^2 vs 191.1 mg/m^2) 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) Author PY	Stage larynx % (MF) Endpoint	%T T1–2/T3/T4 %N N0/N1/N2/N3	NO PT	RT (% received) ICT (×3) unless otherwise stated	Tx % completed [without delay or reduced dose]	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	RT[a]	unacceptable variation in RT 6% unevaluable RT 6%	3-year LRC 34%	36.4% MST 49 M	acneiform rush G3 ≤0.5%	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% ($P < 0.001$)	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 = treatment, PY = 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. TREMPLIN = Radiotherapy With Cisplatin Vs Radiotherapy With Cetuximab After Induction Chemotherapy for Larynx Preservation, RTOG = Radiation Therapy Oncology Group. [a]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/m^2/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 (TREMPLIN, 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 52 817 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 (×2) (docetaxel 50 mg/m^2 d1, CDDP 60 mg/m^2 d4, 5-FU 600 mg/m^2 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 intra-arterial 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.

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