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HEAD AND NECK

# Organ preservation in locally advanced head and neck cancer of the larynx using induction chemotherapy followed by improved radiation schemes

**Giovanni Franchin · Emanuela Vaccher · Doriano Politi · Emilio Minatel · Carlo Gobitti · Renato Talamini · Simon Spazzapan · Maria Gabriella Savignano · Mauro G. Trovò · Luigi Barzan**

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**Abstract** The present prospective study seeks to evaluate overall and disease free survival, response and organ preservation rate, and toxicity of an intensive chemotherapy regimen (CT) followed by unconventional radiotherapy (RT) in patients with locally advanced operable head and neck cancer. Between January 1998 and December 2006 (June 2005), 115 patients with locally advanced, operable head and neck cancer were evaluated. A total of 333 cycles of neoadjuvant CT (cisplatin–5FU, days 1, 14, 28) followed by hyperfractionated/accelerated radiotherapy were given to 108 patients. A total of 108 patients were evaluable and received the planned CT–RT treatment. Two months after the end of RT, 97.2% of patients had a clinical complete remission of the primary and 67.5% of the neck node site. The overall survival was 55% and cause-specific survival was 73% at 5 years. Of the 33 relapsed patients, 12 recurred only at the primary site and 10 patients had distant metastases. The overall organ preservation rate was 73.5%. The chemotherapy regimen reported an overall cardiotoxicity from 5FU in 14% of patients, with severe toxicity in 3%. The radiotherapy schedule developed 84% of Grade 3–4 mucositis in the observed patients. The accelerated CT–RT regimen is able to achieve a high rate of larynx preservation, a good tolerability, and a satisfactory cause-specific overall survival.

**Keywords** Unconventional radiotherapy · Intensive chemotherapy · Larynx · Phase II study · Organ preservation

G. Franchin (✉) · E. Minatel · C. Gobitti · M. G. Trovò
Department of Radiation Therapy,
Centro di Riferimento Oncologico, National Cancer Institute,
Via Franco Gallini 2, 33081 Aviano, Italy
e-mail: gfranchin@cro.it

E. Vaccher · S. Spazzapan
Department of Medical Oncology A,
Centro di Riferimento Oncologico,
National Cancer Institute, Aviano, Italy

D. Politi · M. G. Savignano · L. Barzan
Head and Neck Department,
Santa Maria degli Angeli General Hospital,
Pordenone, Italy

R. Talamini
Unit of Epidemiology and Biostatistics,
Centro di Riferimento Oncologico,
National Cancer Institute, Aviano, Italy

## Introduction

Chemotherapy (CT) followed by radical radiotherapy (RT) is proven to be a valid alternative to surgery in locally advanced operable head and neck cancer, involving the larynx. The overall results comparing surgery combined with RT versus CT followed by RT, tested in two large phase III randomized trials [1, 2], indicate that:

1. survival rate is comparable but not increased by CT–RT
2. preservation of laryngeal function is achieved in over 50% of patients
3. response to CT is predictive of RT response
4. CT–RT treated patients have decreased metastatic relapses.

Locoregional tumor control is likely to be affected by time elapsed from diagnosis and start of radical locoregional treatment but also by delay of definitive treatment (surgery and/or radiotherapy) due to the neoadjuvant CT.

Head and neck cancer potentially has a short doubling time and it will repopulate rapidly between the daily fractions of conventional fractionation RT: unconventional fractionation is able to reduce this fact. Furthermore, a reduction in both radiotherapy and chemotherapy treatment times might result in an increase of local tumor control.

In light of these findings, we have designed an institutional prospective phase II trial with a short course of neoadjuvant CT followed by unconventional fractionated RT (in the first period of the study we employed a hyperfractionated scheme and in the second an accelerated scheme). The objectives of the study were to assess the efficacy and evaluate the toxic effects of an intensive organ preservation modality, employing three CT cycles, with a week break, starting a few days after the diagnosis, followed by unconventional fractionated RT.

## Materials and methods

Major eligibility criteria included previously untreated stages III–IV head and neck tumors, no evidence of distant metastases, World Health Organization(WHO) performance status of 0–2, age $\leq$ 75 years, adequate renal and hematological functions.

All patients required total laryngectomies either for local extension of disease or, in some non-compliant patients, to avoid the risk of inhalation due to the need to extend the surgical procedure to include the base of the tongue. All patients were evaluated by the "Head and Neck Committee" of Aviano National Cancer Institute consisting of a surgeon, a medical and a radiation oncologist.

Staging procedures included either computed tomography (CT) scan or magnetic resonance (MR) imaging of the head and neck region, a chest X-ray, a laryngo-pharyngoscopy, broncoscopy and esophagoscopy, with biopsy of suspected lesions, and liver ultrasound. A PET-CT was prescribed only when there was reasonable suspicion of distant metastases.

Patients were re-staged according to the 2002 UICC/TNM classification. At the time of esophagoscopy, the placement of a percutaneous endoscopic gastrotomy (PEG) was planned in patients with weight loss up to 10%. Dental status evaluation and fluoride-prophylaxis/prescription were carried out in all patients.

### Treatment

#### *CT schedule*

Induction CT consisted of three courses of intravenous Cisplatin (100 mg/m²) and continuous 120-h infusion of 5-Fluorouracil (1,000 mg/m² per day). Chemotherapy was planned on days 1, 14, and 28. Response to CT was evaluated clinically and by CT-scan 10 days from the third CT cycle; criteria were evaluated according to WHO definitions. Patients with partial remission <50% at the primary site, underwent surgical resection followed by RT; all others received radical RT.

#### *RT schedule*

External beam RT was delivered with a 6 Mv Linear Accelerator after 2 weeks from the end of the CT cycles. From January 1998 to June 2002, the first group of 52 patients was treated with a hyperfractionated RT schedule consisting of a total 7,440 cGy delivered in 62 fractions(2 daily fractions of 120 cGy each) with a 6-h interval between fractions. Shrinking fields techniques were used; a boost of 2,400 cGy in 20 fractions delivered by a multiple co-planar field technique. The planned total treatment time was 6.5 weeks as previously reported [3].

From July 2002 to December 2006 due to logistical patients' difficulties and outcomes reported in a RTOG study [4], a second group of 56 patients were treated by concomitant-boost RT: 180 cGy per fraction to 5,400 cGy in 30 fractions over 6 weeks to the gross tumor. At 3,240 cGy in 18 fractions, a second dose of 150 cGy by conformal RT at 6 h intervals, was given to the macroscopic tumor, for a total dose of 1,800 cGy in 12 fractions. On the whole, the primary tumor received 7,200 cGy in 42 fractions and uninvolved nodes received 5,400 cGy in 30 fractions in 6 weeks.

Patients with at least 1 lymph node >3 cm at the original diagnosis and patients with clinical residual mass persistence in the neck at 2 months from the end of RT, underwent a selective neck dissection. Clinical examinations with a fiber-optic laryngoscope were performed weekly during RT treatment to define toxicity and response. Patients were followed up every 2 months for the first 6 months; every 3 months in years 1–3, every 6 months in years 3–5, and annually thereafter.

No routine biopsy procedures were employed to confirm complete remission; they were obtained in case of suspected relapse or disease persistence only.

### Statistics

Overall survival was calculated from the date of CT start to the time of death (including all types of death) or last active follow-up. Cancer-specific survival was calculated from the date of CT start to the time of death from head and neck cancers or last follow-up.

Disease-free survival (DFS) was computed from the date of clinical complete remission (CR) to date of relapse.

Patients who failed to reach CR were excluded from the analysis.

Kaplan–Meier method [5] and a log-rank test was used to test differences in clinical characteristics between subgroups. In all cases, statistical significance was claimed for $P \leq 0.05$.

## Results

A total of 115 patients with respectable, only with laryngectomy, biopsy proven, squamous cell carcinoma of the oropharynx, hypopharynx and larynx, were evaluated to enter into the accelerated CT–RT trial between January 1998 and December 2006. Seven patients failed to complete the planned therapeutic program and were lost to evaluation for the combined CT–RT regimen. Two of the seven non-evaluable patients died during the first 2 weeks after study initiation: one from massive pulmonary thromboembolism and the other from diabetic imbalance. Five patients did not receive RT given no response to CT after chemotherapy. They received salvage surgery according to protocol specification and they were included for statistical analysis in the group of patients who had no larynx preservation. A total of 108 patients, object of the study, completed the therapeutic program fully.

Of these evaluable patients, 100 were men and 8 were women. Average age at diagnosis was 59 (range 38–77). A previous clinical history of malignancy was reported in 5.5% of the patients which were truly considered cured.

The primary cancer site was the hypopharynx in 45 patients (87% pyriform sinus), larynx in 37 and oropharynx in 26 patients (52% base of tongue). Clinical patients' characteristics, tumor stage and histological grade are reported in Tables 1 and 2: 79% had tumors classified as T3–T4 and 61% as N2–N3;84% had a stage IV disease. In 60% of the patients, the tumor grade was classified as G3–G4 according to the WHO classification [6].

### CT evaluation

A total of 333 CT cycles were administered: the median time from histological report date to start of CT and from first medical examination to start of CT were 32 and 9 days, respectively. The third Cisplatin/5-Fluorouracil cycle was deleted in 5 patients and in 15 the dose was reduced by 25% due to toxicity (4 patients did not receive a third cycle due to toxicity). Overall, 82% of the patients received CT according to the protocol. At 2 weeks from the end of CT, a complete remission in the primary site was observed in 22 patients (20.3%) and 17 patients (15.7%) achieved a complete node remission. The chemotherapy-related toxicity was well managed by adequate supportive care: grade G3–G4 leucopenia, anemia, and thrombocytopenia were reported in only 4.5, 6.5 and 3% of the patients, respectively. Grade 3–4 mucositis developed in 17.5% and conventional cardiovascular toxicity occurred in 20%, with tachyarrhythmias and sinus bradycardia (inferior to 59 heart rate beats/min) reported in 36 cycles. Severe symptomatic bradycardia (sinus heart rate < 39 beats/min) occurred in two patients and one patient had a myocardial ischemia.

**Table 1** Characteristics of the patients

| | |
|---|---|
| Median age | 59 years (range 38–78) |
| Sex | |
| Male | 100 (92.5%) |
| Female | 8 (7.5%) |
| WHO performance status | |
| 0 | 45 (43.3%) |
| 1 | 52 (48.1%) |
| 2 | 11 (8.6%) |
| Site of primary | |
| Oropharynx | 26 (24%) |
| Larynx | 37 (34.4%) |
| Hypopharynx | 45 (41.6%) |

*WHO* World Health Organization

### RT evaluation

Of the 108 patients receiving RT, 52 were treated consecutively by hyperfractionated schedule (7,440 cGy in 62 fractions) and 56 by concomitant boost technique (7,200 cGy in 42 fractions): all concluded the planned RT treatment. The median interval between end of CT and start of RT was 17 days (range 12–30) and median duration of RT was 44 days (range 41–67).

All patients in the study experienced a grade 2–3 (WHO) mucositis except nine in whom it was reported as grade 4; in four patients treatment was interrupted due to radiotherapy-related toxicity (range 7–25 days). Moreover, 23 patients needed hospitalization: 14 to receive parenteral nutrition as well as supportive care to treat dehydration and electrolyte imbalance for a median of 29 days (range 4–52), 10 only for logistic reasons (difficulty of administering 2 daily-fractions).

The median overall treatment time from the first day of CT to the last day of RT was 101 days (range 83–122).

Two months after RT, 97.2% of patients had a clinical complete remission in the primary site and only three patients required salvage surgery for tumor persistence at clinical evaluation, confirmed by CT scan or MR. The rate of complete response was not significantly different between the two radiotherapy regimens measured by

**Table 2** Primary tumor and nodal stage

| Stage T | Stage N (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | N0 | N1 | N2a | N2b | N2c | N3 | Total |
| T2 | 1 (4.5) | 5 (25) | 4 (50) | 6 (27.2) | 7 (28) | 6 (54.5) | 29 |
| T3 | 8 (36.3) | 11 (55) | 3 (37.5) | 9 (40.9) | 12 (48) | 1 (9) | 44 |
| T4 | 13 (59) | 4 (20) | 1 (12.5) | 7 (31.8) | 6 (24) | 4 (36.3) | 35 |
| Total | 22 | 20 | 8 | 22 | 25 | 11 | 108 |

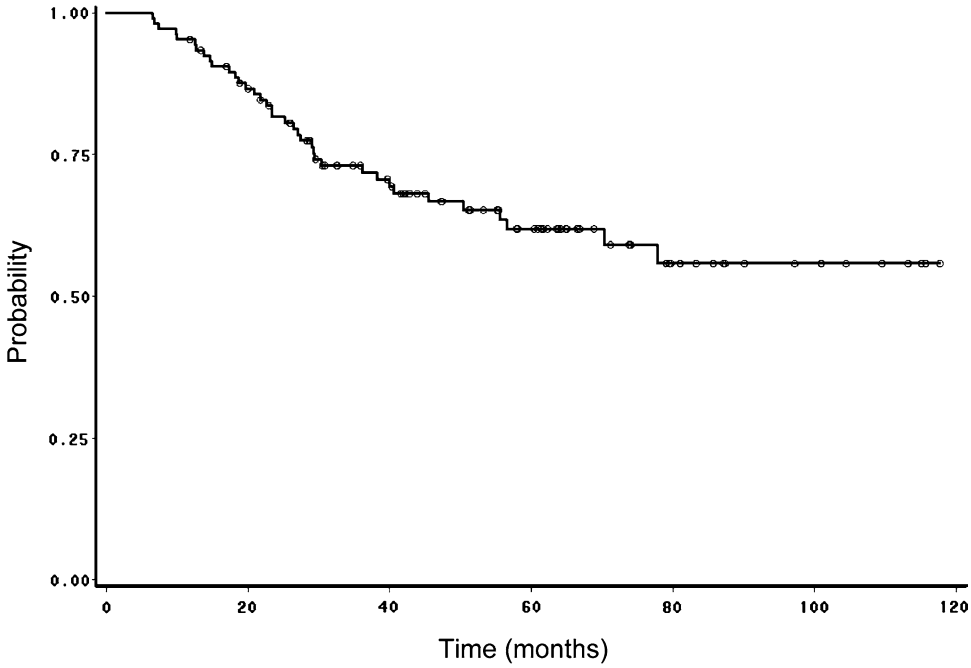


**Fig. 1** Overall survival of 108 patients with locally-advanced head and neck cancer time (months) probability

univariate analysis [chi-square (log-rank test) = 0.01; $P = 0.94$). At the end of RT, clinically complete response in neck-nodes was recorded in 95 patients (87.7%): 13 patients underwent neck dissection on residual node-disease and, according to protocol direction, other 25 patients were submitted to adjuvant surgery given initial lymph node stage.

Figures 1, 2 and 3 show the 5-year overall survival, 5-year cancer-specific overall survival, and disease-free survival, at the median follow up of 58 months (range 14–84), respectively. Figure 4 shows the disease-free survival by RT schedule.

At the time of analysis, 67 patients (62.6%) are alive and free of disease, 23 patients died from cancer, 15 died from intercurrent disease or a second primary tumor and three patients are alive but with continued presence of the disease and undergoing CT. Overall organ preservation rate was 73.5%. The data in Table 3 summarize our study outcome: the cumulative rate of locoregional persistent disease after CT–RT was 15.0% (16 patients). From the end of RT, the median time for local relapse was 8 months (range 4–32); evidence of progression was noted in only three patients after 2 years: one in the neck and two at distant sites.

An univariate analysis was performed to identify the covariables determining the disease free survival and overall specific survival. We analyzed: primary site, histological grade, "T" and "N" stage, lymph node characteristics, elapsed time between time of diagnosis and start of CT, overall time of CT–RT, elapsed time between end of CT and start of RT, response to CT and RT. Only the site of primary tumor presentation was of borderline significance for larynx cancer versus hypopharynx or oropharynx ($P = 0.06$): all other possible prognostic factors were not significant.

## Discussion

Avoiding larygectomy in locally advanced squamous cell head and neck cancer involving the larynx remains a challenge. The combined induction cisplatin-chemotherapy obtained a high response rate but multiple randomized trials [7–9] have failed to demonstrate any significant improvement in the overall survival. The only reported result after neoadjuvant CT appears to be a decrease in the development of distant metastatic disease, with an estimated reduction

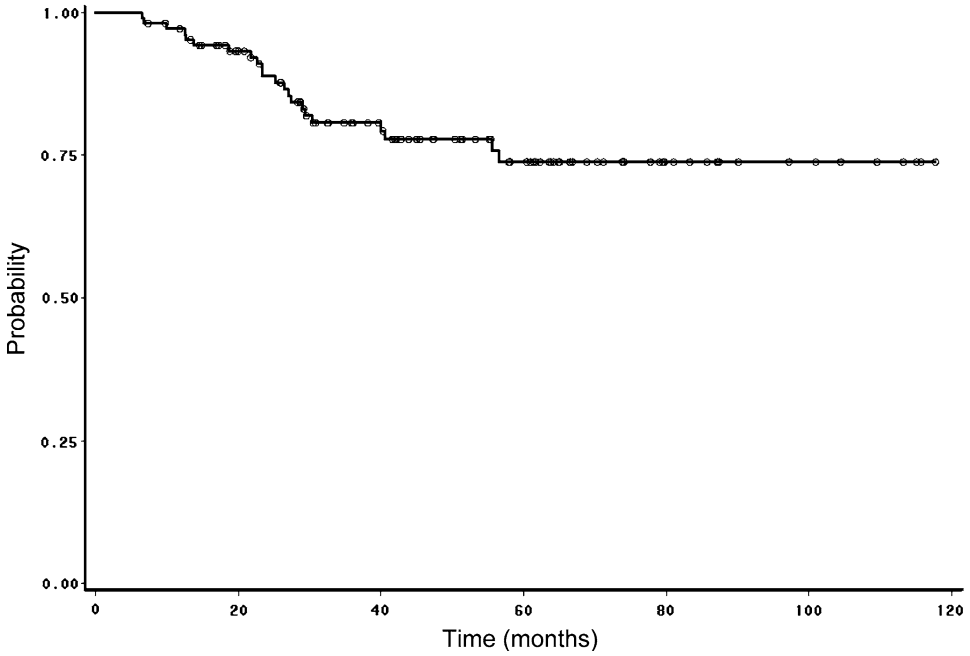


**Fig. 2** Cancer specific survival of 108 patients with locally-advanced head and neck cancer time (months) probability

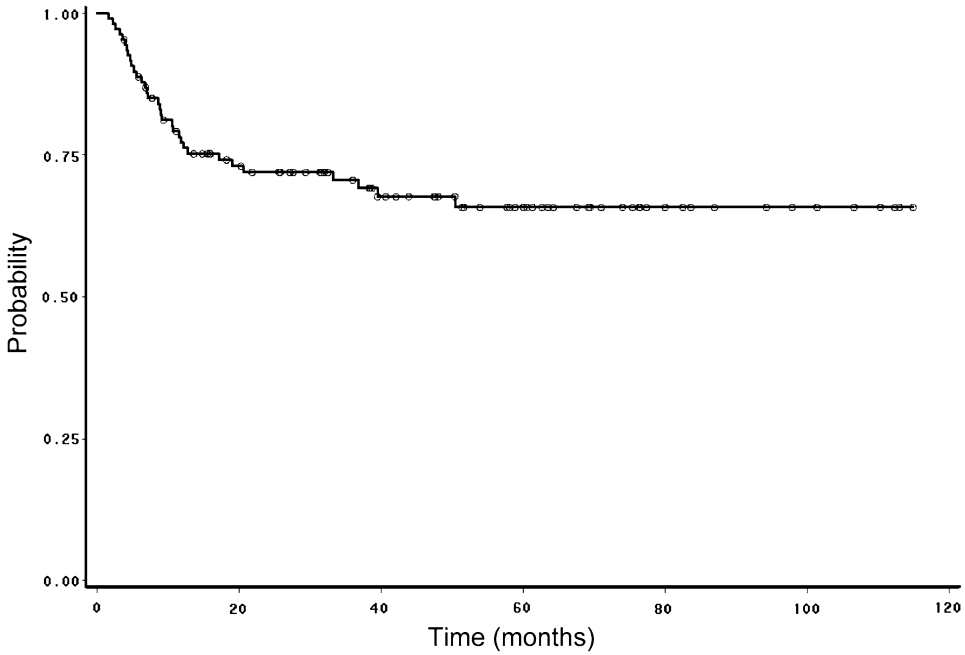


**Fig. 3** Disease free survival of 105 clinical complete remission patients with locally-advanced head and neck cancer time (months) probability

of approximately 65–45% [10]. Despite these encouraging results on distant metastases, in the randomized studies [11–13], lack of a good overall survival was determined by locoregional failure. For this reason, more effective RT–CT combination regimens, and particularly an unconventional RT schedule associated with a more aggressive CT, are advisable.

Our schedule intended to face a series of relevant problems:

1) The use of an optimal CT scheme (Cisplatin–5FU) delivered to full dosage in the shortest time to avoid delay of locoregional treatment, also aimed to decrease chemotherapy clone-resistant cells and prevent their rapid growth.
2) The adoption of an unconventional, more effective RT schedule (hyperfractionated or concomitant boost RT regimen).
3) A reduction of the CT–RT overall treatment time sequence.
4) Homogeneity in total laryngectomy prescription by the same Head and Neck surgical team.

In our Department, the waiting time from the first Head and Neck Committee medical examination to the start of RT

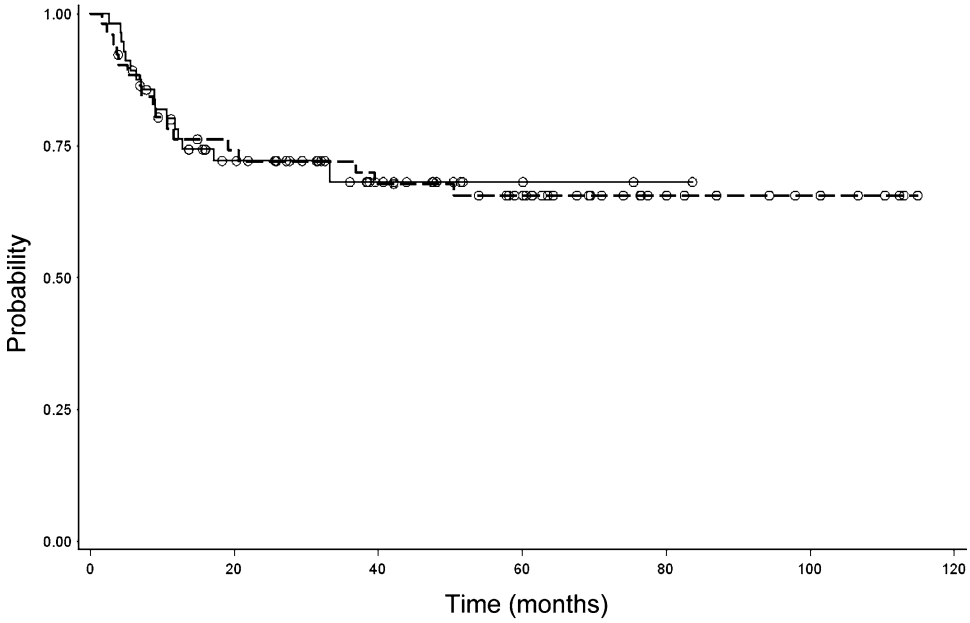


**Fig. 4** Disease free survival of 105 clinical complete remission patients with locally-advanced head and neck cancer by radiotherapy schedule (*continuous lines* concomitant boost vs. *discontinuous lines* hyperfractionation) time (months) probability

treatment is on average 35 days (range 15–56) due to the number of patients treated daily which may influence local tumor control. In fact, at an International Federation of Head and Neck Oncologic Society Meeting (27 June–1 July 2006, Prague, Czech Republic) [14], Overgaard presented a study to determine the impact of waiting time on tumor growth in head and neck cancer patients: in 53 patients, two scans at a median interval of 28 days during waiting radiotherapy time (range 5–125) were evaluated and he reported that 57% of the patients had increases of tumor volume, 30% progressive disease and 19% progressed to higher stages. We have postulated that starting an intensive schedule of CT immediately after the first clinical examination is necessary to kill the maximal number of tumor cells and allow a stabilization of tumor volume, and simultaneously begin the locoregional radical treatment in the shortest time possible.

In our study, at the end of CT cycles, we obtained 20.3% complete remission and an 87% total response rate, achieving a 97.2% complete response after RT treatment.

We emphasize that CT began within 9 days from our first clinical examination (range 5–18). Therefore, no patients developed an increase in tumor volume during the waiting/combined-treatment time, and this should be considered an improvement in prognosis and disease probability control [15, 16].

In recent years, prospective randomized studies showed that the association of CT–RT obtained higher locoregional control and overall survival rates compared with RT alone or neoadjuvant CT associations [17–24].

A large metaanalysis of 63 trials and 10,741 patients reported a 4% absolute survival advantage at 5 years (CT plus RT) but only for the concomitant modality and no benefit was reported for adjuvant and/or neoadjuvant CT. Moreover, an abstract presented at the 2006 ASCO meeting,regarding results of Intergroup RTOG 91–11 [11] with a long follow up period (6.9 years),reported a comparable rate of improvement in laryngectomy-free survival (LFS) both with neoadjuvant and concomitant RT–CT, but without any advantage in overall survival. On the other hand, the superior efficacy of concurrent CT–RT is associated with considerable toxic effects such as high grade mucositis with dysphagia and weight loss requiring the interruption of treatment, supportive care, and hospitalization.

In our patient-group, 60% of tumors were poorly differentiated, 42% of patients presented a hypopharyngeal primary site cancer and 63% had advanced lymph node disease classified as stage N2–N3: all these patients were categorized at greatest risk of developing distant metastases and therefore candidates for systemic therapy.

Major issues in head and neck cancer treatment are to reach a high local control to avoid laryngectomy, but simultaneously to improve specific overall survival. The published data regarding concomitant RT–CT reported survival between 24 and 68% at 3–5 years [17, 18, 22]. Using a schedule employing neoadjuvant CT followed by concomitant CT–RT, the 3-year overall survival was 51–70% [25–28], with a locoregional relapse rate of 7–25% and a distant progression rate of 7–17%.

In our study, we reported a 55% of overall survival and a 73% cause-specific overall survival, with a disease free survival of 65% at 5 years and an organ preservation rate of 73.5%.

Our data using an unconventional CT–RT combination in a consecutive, unselected, patient population reported

**Table 3** Results and toxicity

| | |
|---|---|
| Response at the end of CT | |
| Total response | 87% |
| Complete response | 20.3% |
| CT toxicity (grades 3–4) | |
| Hematological | 15 (13.8) |
| Non-hematological | 27 (25%) |
| Cardiotoxicity[a] | 15 (14%) |
| Response at the end of RT | |
| Complete remission | |
| Primary | 105 (97.2%) |
| Neck nodes | 95 (87.9%) |
| RT toxicity (grades 3–4) | |
| Mucositis | 84 (77%) |
| Dermatitis | 16 (15%) |
| Otitis | 2 (1%) |
| Laryngeal edema | 14 (13%) |
| RT-interruptions | 4 (3%) |
| Rate of organ preservation | 83/113 patients (73.5%)[b] |
| Pts with treatment failure | 33 (30.5%) |
| Site of failure | |
| Primary | 12 (11.1%) |
| Neck | 5 (4.6%) |
| Both | 6 (5.6%) |
| Distant metastases | |
| Distant only | 7 (6.5%) |
| Distant and locoregional | 3 (2.8%) |
| Second primary tumors | 15 (13.8%) |

[a] 3/15 (3%) pts had severe cardiotoxicity

[b] 5 patients who failed to respond to CT were subsequently treated with surgery

comparable results to published studies using different timing of CT–RT associations [29–32]. The sequential, accelerated CT followed by unconventional fractionated RT was well tolerated; only four patients temporarily interrupted RT treatment for severe mucositis.

In conclusion, we confirm a good efficacy for the combined CT–RT regimen in locally advanced head and neck tumors whose objective is laryngeal preservation, even with sequential CT–RT. However, the problem of locoregional disease control can still be improved; the development of new pharmaceutical products combined with radiotherapy is the innovative solution for a better therapeutic outcome [33]. This outcome can be further improved by using dose-intensity radiotherapy with the IMRT technique delivered either with a Linac or Tomotherapy equipment.

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## References

1. No authors listed (1991) Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer: the Department of Veteran Affairs Laryngeal Cancer Study Group. N Engl J Med 324(24):1685–1690
2. Lefebvre JL, Chevalier D, Luboinski B et al (1996) Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial: EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 88:890–899. doi:10.1093/jnci/88.13.890
3. Franchin G, Vaccher E, Gobitti C et al (2005) Neoadjuvant accelerated chemotherapy followed by hyperfractionated radiation therapy in patients with operable, locally advanced head and neck carcinoma. Oral Oncol 41:526–533. doi:10.1016/j.oraloncology.2004.12.013
4. Fu KK, Pajak TF, Trotti A et al (2000) A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas; first report of RTOG 9003. Int J Radiat Oncol Biol Phys 48(1):7–16. doi:10.1016/S0360-3016(00)00663-5
5. Kaplan EL, Meier P (1958) Non-parametric estimation from incomplete observations. J Am Stat Assoc 53:457–481. doi:10.2307/2281868
6. International Histological Classification of Tumors (1967–1981). vol 1–25. World Health Organization. Geneva
7. Cohen EE, Lingen MW, Vokes EE (2004) The expanding role of systemic therapy in head and neck cancer. J Clin Oncol 22:1743–1752. doi:10.1200/JCO.2004.06.147
8. Paccagnella A, Orlando A, Marchiori C et al (1994) Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. J Natl Cancer Inst 86:265–272. doi:10.1093/jnci/86.4.265
9. Pignon JP, Bourhis J, Domenge C, Designe L, MACH-NC Collaborative Group (2000) Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 355:949–955
10. Merlano M, Benasso M, Corvo R et al (1996) Five-year update of a randomized trial of alternating radiotherapy and chemotherapy ccompared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. J Natl Cancer Inst 88(9):583–589. doi:10.1093/jnci/88.9.583
11. Forastiere AA, Maor M, Weber RS, et al (2006) ASCO Annual Meeting Proceedings Part 1. J Clin Oncol 24 (18S):5517
12. Laramore GE, Scott CB, Al-Sarraf M et al (1992) Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. Int J Radiat Oncol Biol Phys 23:705–713
13. Sculler DE, Metch B, Mattox D et al (1988) Preoperative chemotherapy in advanced respectable head and neck cancer: final report of the Southwest Oncology Group. Laryngoscope 98:1205–1211
14. Jensen AR, Nellemann H, Overgaard J (2006) Growth of H/N carcinoma during waiting time for radical treatment (051); oral presentation. 3rd World Congress of the International Federation of Head/Neck Oncologic Societies. Prague, Czech Republic. June 27–July 1 2006
15. Jensen AR, Nellemann HM, Overgaard J (2007) Tumor progression in waiting time for radiotherapy in head and neck cancer. Radiother Oncol 84(1):5–10. doi:10.1016/j.radonc.2007.04.001
16. Waaijer A, Terhaard CH, Dehnad H et al (2003) Waiting times for radiotherapy: consequences of volume increase for the TCP in oropharyngeal carcinoma. Radiother Oncol 66(3):271–276. doi:10.1016/S0167-8140(03)00036-7

17. Forastiere AA, Goepfert H, Maor M et al (2003) Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 349:2091–2098. doi:10.1056/NEJMoa031317
18. Adelstein DJ, Sharan VM, Earle AS et al (1990) Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. Cancer 65:1685–1691. doi:10.1002/1097-0142(19900415)65:8<1685::AID-CNCR2820650804>3.0.CO;2-S
19. Calais G, Alfonsi M, Bardet E et al (1999) Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 91:2081–2086. doi:10.1093/jnci/91.24.2081
20. Adelstein DJ, Saxton JP, Lavertu P et al (2002) Maximizing local control and organ preservation in stage IV squamous cell head and neck cancer with hyperfractionated radiation and concurrent chemotherapy. J Clin Oncol 20(5):1405–1410. doi:10.1200/JCO.20.5.1405
21. Adelstein DJ, Saxton JP, Rybicki LA et al (2006) Multi-agent concurrent chemoradiotherapy for locoregionally advanced squamous cell head and neck cancer: mature results from a single institution. J Clin Oncol 24:1064–1071. doi:10.1200/JCO.2005.01.5867
22. Brizel DM, Albers ME, Fisher SR et al (1998) Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced Head and Neck cancer. N Engl J Med 338(25):1798–1804. doi:10.1056/NEJM199806183382503
23. Denis F, Garaud P, Bardet E et al (2004) Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced stage oropharynx carcinoma. J Clin Oncol 22:69–76. doi:10.1200/JCO.2004.08.021
24. Jeremic B, Milicic B, Dagovic A et al (2004) Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, non-metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 22(17):3540–3548. doi:10.1200/JCO.2004.10.076
25. Machtay M, Rosenthal DI, Hershock D et al (2002) Organ preservation therapy using induction plus concurrent chemoradiation for advanced resectable oropharyngeal carcinoma: a Univ. of Pennsylvania Phase II trial. J Clin Oncol 19(20):3964–3971. doi:10.1200/JCO.2002.11.026
26. Hainsworth JD, Meluch AA, McClurkan S et al (2002) Induction paclitaxel, carboplatin, and infusional 5 FU followed by concurrent radiation therapy and weekly paclitaxel/carboplatin in the treatment of locally advanced head and neck cancer: a phase II trial of the Minnie Pearl Cancer Research Network. Cancer J 8(4):311–321. doi:10.1097/00130404-200207000-00007
27. Vokes EE, Stenson K, Rosen FR et al (2003) Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hyroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. J Clin Oncol 21:320–326. doi:10.1200/JCO.2003.06.006
28. Psyrri A, Kwong M, DiStasio S et al (2004) Cisplatin, fluorouracil, and leucovorin induction chemotherapy followed by concurrent cisplatin chemoradiotherapy for organ preservation and cure in patients with advanced head and neck cancer: long term follow-up. J Clin Oncol 22:3061–3069. doi:10.1200/JCO.2004.01.108
29. Guadagnolo B, Haddad R, Posner M et al (2005) Organ preservation and treatment toxicity with induction chemotherapy followed by radiation therapy or chemoradiation for advanced laryngeal cancer. Am J Clin Oncol 28(4):371–378. doi:10.1097/01.coc.0000162423.13431.8d
30. Posner M, Hershock D, Blajman C, TAX 324 Study Group et al (2007) Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357(17):1705–1715. doi:10.1056/NEJMoa070956
31. Ang KK, Harris J, Garden AS et al (2005) Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: radiation therapy oncology group phase II trial 99-14. J Clin Oncol 23(13):3008–3015. doi:10.1200/JCO.2005.12.060
32. Urba S, Wolf G, Eisbruch A et al (2006) Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 24(4):593–598. doi:10.1200/JCO.2005.01.2047
33. Bonner JA, Harari PM, Giralt J et al (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354(6):567–578. doi:10.1056/NEJMoa053422