Induction chemotherapy followed by cisplatin or cetuximab concomitant to radiotherapy for laryngeal/hypopharyngeal cancer: Long-term results of the TREMPLIN randomised GORTEC trial

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Induction chemotherapy followed by Cisplatin or Cetuximab concomitant to Radiotherapy for Laryngeal/Hypopharyngeal Cancer: long-term results of the TREMPLIN randomized GORTEC-trial.

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Abbreviations

ICT: induction chemotherapy

LCR: locoregional control rate

LEDFS: laryngo-esophageal dysfunction-free survival

OS: overall survival

TPF: docetaxel-cisplatin-5-fluorouracil

Keywords
larynx preservation
radiation therapy
quality of life
laryngo-esophageal dysfunction-free survival
induction chemotherapy

ABSTRACT

Background In Europe, induction chemotherapy (ICT) followed by radiotherapy is preferred to conventional chemoradiotherapy to avoid total laryngectomy in patients with laryngeal/hypopharyngeal cancer. In comparison to conventional radiotherapy, bioradiotherapy with cetuximab significantly improves locoregional control rates (LCR) and overall survival (OS) without any increase in unmanageable toxicity.

Methods Patients included had untreated non-metastatic stage III-IV laryngeal/hypopharyngeal invasive squamous cell carcinoma. Good responders after three cycles of TPF-ICT (docetaxel and cisplatin, 75 mg/m^2 each on day 1, and 5-fluorouracil, 750 mg/m^2/day on days 1-5) every 3 weeks, were randomized to receive radiotherapy (70 Gy) with concurrent cisplatin (100 mg/m^2/day on days 1, 22, and 43 of radiotherapy) or cetuximab (400 mg/m^2 loading dose, 250 mg/m^2/week during radiotherapy). Primary end-point was larynx preservation. Secondary end-points were laryngo-esophageal dysfunction-free survival (LEDFS), LCR, and OS.

Results 153 patients were enrolled. Among 126 TPF-ICT responders, 116 were randomized to receive either cisplatin (n=60) or cetuximab (n=56). Median follow-up was 77.5 months. 5-year OS rates were 66.6% [95%CI: 0.54–0.79] vs. 66.9% [95%CI: 0.54–0.79] (p=0.9), respectively. 5-year LCRs were 79.8% [95%CI: 69.5–90.0] vs. 67.8% [95%CI: 55.1–80.5%] (p=0.18). 5-year LEDFS was 62.2% [95%CI: 49.7–74.8%] vs. 56.2% [95%CI: 43.0–69.4] (p=0.38). Late grade 3/4 salivary gland and laryngeal toxicity occurred in 10.3% vs. 9.8% and 6.8% vs. 11.8% of patients receiving cisplatin-radiotherapy vs. cetuximab, respectively.

Conclusions No significant difference in LEDFS was observed between the two arms. TPF-ICT followed by conventional chemoradiotherapy or cetuximab was feasible and long-term toxicity was not statistically different between the two arms. LEDFS appears as a relevant endpoint.

Introduction

Until the early 1990s, the recommended treatment for locally advanced laryngeal or hypopharyngeal squamous cell carcinoma was total laryngectomy followed by conventional radiotherapy. For many decades, many "larynx preservation trials" were performed and two different approaches to larynx preservation were evaluated. In the USA, standard of care is now concurrent chemotherapy and radiotherapy [1]. In Europe, and particularly in France, induction chemotherapy (ICT) followed by radiotherapy tends to be preferred to concurrent chemoradiotherapy to avoid total laryngectomy.

Forastiere et al. showed that induction with cisplatin and 5-fluorouracil followed by radiotherapy had similar efficacy to concurrent chemoradiotherapy with cisplatin, with a different toxicity profile, and both protocols were superior to radiotherapy alone [2]. In the ICT approach, only good responders have a chance of avoiding surgery, whereas in the concurrent chemoradiotherapy approach all patients may avoid surgery. However, conventional chemoradiotherapy is associated with substantial acute and late toxicity. In a recent update of this trial, the authors concluded that laryngectomy-free survival was significantly better with either ICT or conventional chemoradiotherapy compared to radiotherapy alone, with no difference between arms, but the rate of non-cancer-related deaths doubled in the conventional chemoradiotherapy arm, possibly due to enhanced toxicity in this arm [3].

The benefit of adding chemotherapy to radiotherapy was confirmed in three meta-analyses [4] and should be considered as the new standard therapy for locally advanced cancer, including larynx preservation. More recently, three randomized phase III trials have demonstrated the superiority of adding docetaxel to standard cisplatin-5-fluorouracil ICT compared to cisplatin-5-fluorouracil alone, followed by radiotherapy alone or with concurrent carboplatin [5–7]. We recently published the long-term results of the GORTEC 2000-01

phase III trials and confirmed the superiority of the docetaxel-cisplatin-5-fluorouracil (TPF) regimen compared to cisplatin-5-fluorouracil alone, in terms of larynx preservation, preservation of larynx function and late toxicity [8].

A randomized trial comparing bioradiotherapy with cetuximab to radiotherapy alone showed a significant improvement in locoregional control rate (LCR) and overall survival (OS), without any increase in grade 3/4 acute mucositis or stomatitis. Transient all-grade acne-like rash and infusion-related reactions were observed more often in the bioradiotherapy arm but were manageable [9, 10].

This phase II, randomized, multicenter trial was design to assess the tolerability and compliance with a sequential approach, TPF-ICT followed by either conventional chemoradiotherapy with cisplatin or bioradiotherapy with cetuximab. The aim of this trial was to evaluate OS and larynx preservation in comparison to a phase III trial of TPF-ICT followed by radiotherapy for larynx preservation [11]. GORTEC (Groupe Oncologie Radiothérapie de la Tête et du Cou) and GETTEC (Groupe d'Etude des Tumeurs de la Tête et du Cou) had joint responsibility for this trial. Here, we report the long-term results including late toxicity, laryngo-esophageal dysfunction-free survival (LEDFS) [12] and causes of death.

Patients and Methods

Study population

Eligibility criteria were established from the GORTEC 2000-01 trial [7]. Operable patients with untreated stage III or IV laryngeal or hypopharyngeal invasive squamous cell carcinoma who required total laryngectomy, from 20 French centers and aged 18–75 years, were enrolled between March 2006 and April 2008. The inclusion and exclusion criteria have been described previously [11]. All the patients gave their written informed consent in accordance

with institutional guidelines. The trial was registered as ClinicalTrials.gov number: NCT00169247.

Treatments

Patients received three cycles of TPF (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5-fluorouracil 750 mg/m^2 by 24-h continuous infusion for 5 days) every 3 weeks. Two weeks after the end of ICT, a global evaluation was performed including a computed tomography scan of the neck and chest, and endoscopy under general anesthesia. Patients who responded well to ICT were defined as having a partial response (at least 50% regression of their primary tumor) if they recovered normal larynx mobility, or complete regression of the tumor. The study protocol stipulated that only good responders to ICT were eligible for randomization. Patients with <50% decrease in tumor volume after TPF-ICT underwent salvage total laryngectomy followed by radiotherapy.

All patients received radiotherapy (70 Gy in 35 fractions, one fraction/day, 5 days/week). In the control group, patients received three cycles of 100 mg/m^2 cisplatin on days 1, 22, and 43 of radiotherapy. In the experimental group, patients received a weekly perfusion of cetuximab at a dose of 250 mg/m^2 during radiotherapy after a loading dose of cetuximab 400 mg/m^2 during the week preceding radiotherapy (total of eight doses).

The CONSORT flow diagram for this trial is shown in Figure 1.

Follow-up and end-points

Primary end-point was larynx preservation at 3 months post-radiotherapy, defined as the absence of any residual disease that would justify salvage total laryngectomy. Secondary end-points were larynx function preservation rate, LCR, OS, quality of life, cause of death, long-term toxicity rates, and LEDFS defined in accordance with new international guidelines

[12]. This end-point was evaluated as the time from randomization to events including death, local relapse, total or partial laryngectomy, tracheotomy at ≥2 years, or a feeding tube at ≥2 years.

Follow-up was assessed by clinical evaluation every 3 months during the first year, every 6 months during the next 3 years, and then every year until death or censoring. An endoscopic evaluation was performed at 3 months and 18 months post-treatment, and in cases of suspected recurrence, and computed tomography of the neck and chest was scheduled at 3 and 6 months post-treatment and every 6 months thereafter. Toxic effects were graded according to the RTOG toxicity scoring system [13] for acute and late radiotherapy toxic effects. The cut-off for designating late toxicity was 3 months after the end of radiotherapy.

Statistical analyses

The sample size rationale came from the GORTEC 2000-01 trial database [7]. Of the 110 patients randomly assigned to the TPF arm, four died during ICT. After TPF, 85 patients were responders and one died before radiotherapy; therefore a total of 84 patients (76%) started radiotherapy. After radiotherapy, six patients had residual/persistent disease, which corresponded to an immediate larynx preservation rate (larynx in place, free of disease) of 70%.

Sample size and decision rules were based on a one-stage Fleming design with a 5% type I error and 90% power. For an expected 80% larynx preservation rate at 3 months post-treatment and a null hypothesis of 60%, 43 eligible patients were needed in each arm. If a 55% response rate in patients amenable to further chemotherapy could be expected after TPF, 156 patients had to be included to obtain these 86 eligible patients. Patients were randomly assigned to a treatment arm by a central office after post-ICT eligibility was established. OS

was calculated from randomization, and 95% confidence intervals (CIs) were calculated for means and percentages.

StatView 3.0 (Abacus Concepts, Berkeley, CA) and R v.2.10.1 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/) were used for all statistical analyses.

Results

Study population

A total of 156 patients were screened for the study and 153 were enrolled between March 2006 and April 2008. Two patients were excluded because of ineligibility and one was excluded because of a technical problem. All 153 patients included started ICT with TPF. Four patients died during ICT (two from toxicity, one from concurrent disease, and one from rapid disease progression). Of the 149 evaluable patients after ICT, 23 were poor responders and were offered immediate salvage surgery (seven refused and underwent radiotherapy). Among the 126 responders, 10 (6%) were excluded and 116 were randomly assigned to either cisplatin (n=60) or cetuximab (n=56) (Figure 1). The analyses were performed after a median follow-up of 77.5 months [95%CI: 62.8–86.5]. At randomization, there was no statistical difference between the two arms regarding any clinical characteristic except for gender [11].

Efficacy

Of the 153 patients that started ICT with TPF, 113 (74%) underwent three cycles of treatment at the planned doses. The remaining 40 patients (26%) received fewer cycles and/or reduced doses because of acute toxicity. The rate of response (PR and CR) good responders after ICT was 82.4% (126/153).

5-year OS was 66.6% [95%CI: 0.54–0.79] vs. 66.9% [95%CI: 0.54–0.79] for the cisplatin and cetuximab arms, respectively. There was no statistical difference between the two arms regarding OS (HR=1.04 [95%CI: 0.55–1.98], *p*=0.9) (Fig. 2a).

LRC rate was not significantly improved in the cisplatin arm vs. the cetuximab arm. 5-year LRC rates were 79,8% [95%CI: 69.5–90.0] vs. 67.8% [95%CI: 55.1–80.5] for the cisplatin and cetuximab arms, respectively (HR=1.65 [95%CI: 0.79–3.41], *p*=0.18) (Fig. 2b).

5-year LEDFS rates were 62.2% [95%CI: 49.7–74.8] vs. 56.2% [95%CI: 43.0–69.4]. After about 1 year, the curves begin to separate favoring cisplatin, although the difference was not statistically significant (HR=1.29 [95%CI: 0.72–2.31], *p*=0.38) (Fig. 2c). At 5 years, 19 patients had undergone a laryngectomy (cisplatin n=8, cetuximab n=11), 14 patients for local relapse and five due to laryngeal toxicity. At 5 years, 13 patients had a tracheotomy and/or a feeding tube (cisplatin n=4, cetuximab n=9) (Table 1). Only one patient had a feeding tube without tracheotomy.

Larynx vs hypopharynx

A sub-group analysis was performed regarding primary tumor site. At 5 years, for patient with hypopharyngeal or laryngeal tumors, there was no significant difference regarding OS, LRC or LEDFS. Patients with a laryngeal tumor seem to have a better locoregional prognosis than patients with a hypopharyngeal tumor although this was not statistically significant. At 5 years, for laryngeal tumors, there was a trend in favor of cisplatin vs. cetuximab for LCR (HR=2.67 [95%CI: 0.79–8.95]) and LEDFS (HR=1.31 [95%CI: 0.47–3.68]) (Fig. 3).

Long-term toxicity

Mucous membrane, salivary gland, laryngeal, bone and subcutaneous tissue toxicities were the most frequent events reported. There were no significant differences between the two

arms in terms of late grade 3 or grade 4 toxicities. At the last follow-up, late grade 3 or 4 salivary gland and laryngeal toxicities occurred in 10.3% vs. 9.8% and 6.8% vs. 11.8% of patients in the cisplatin and cetuximab arms, respectively (Table 2).

Causes of death

At the last evaluation, 48 patients had died: 22 in the cisplatin arm and 26 in the cetuximab arms. Twenty-seven patients died from their original cancer (cisplatin n=13, cetuximab n=14), seven from a second cancer (cisplatin n=2, cetuximab n=5), and six because of concurrent disease (cisplatin n=4, cetuximab n=2). Two patients died because of longer-term laryngeal toxicity. The causes of death are shown in Table 3.

Discussion

Until the 1980s, total laryngectomy, performed as initial treatment, was considered the most appropriate therapy for patients with locally advanced laryngeal or hypopharyngeal cancer. Although this strategy can provide disease control, it has a negative impact on patients' quality of life. Larynx preservation trials have been conducted on patients with locally advanced laryngeal/hypopharyngeal cancer in an attempt to avoid total laryngectomy and to preserve laryngeal function. In evidence-based medicine, the gold standard aims of treatment are survival and cure [14], but quality of life now appears to be as important as survival. In 2009, a consensus panel created a new end-point for this purpose: LEDFS [12]. This end-point is measured as the time from randomization to events including death, local relapse, total or partial laryngectomy, tracheotomy at ≥2, or a feeding tube at ≥2 years. To our knowledge, we present the first randomized clinical trial using this new end-point. In our study, there was no statistical difference between the two groups regarding LEDFS. Regarding the primary end-point of our study, the 5-year larynx preservation rate was

statistically improved in the cisplatin arm vs. the cetuximab arm: 96.6% [95%CI: 0.88–0.99] vs. 81.1% [95%CI: 0.68–0.9] (p=0.02), respectively (Figure 4 – supplementary data). We are now convinced that the best outcome for the patient is not simply to keep his/her larynx in place but to maintain a functioning larynx without disease recurrence. With follow-up period of our study, larynx preservation at 3 months was not a clinically relevant end-point. These data confirm the new recommendations of the international consensus panel.

The limitations of our study are its randomized phase II design and the small number of patients in each arm that did not allow any solid comparison between the arms. In addition, the unbalanced gender ratio (eight females in the conventional chemoradiotherapy arm vs. one in the bioradiotherapy arm) may have introduced a positive bias in favor of the conventional chemoradiotherapy arm, because all randomly assigned female patients were alive with a functional larynx.

TPF-based ICT followed by conventional chemoradiotherapy or bioradiotherapy was feasible but had substantial long-term toxicity. Conventional chemoradiotherapy or bioradiotherapy were difficult to deliver after ICT because of limiting acute toxicity. In a recent study of TPF-ICT followed by conventional chemoradiotherapy for locoregionally advanced nasopharyngeal cancer, only 24% (58/241) of patients in the ICT plus concurrent chemoradiotherapy group received six cycles of chemotherapy with a cumulative cisplatin dose of 480 mg/m², because of acute toxicity [15]. When compared to the actualized results of the GORTEC 2000-01trial [8], we found a better LCR for TPC-ICT followed by conventional chemoradiotherapy (p=0.004), but the inclusion criterion were different. In the GORTEC 2000-01, operable patients with untreated stage III or IV laryngeal or hypopharyngeal invasive squamous cell carcinoma requiring total laryngectomy were included in the trial to receive TPF-ICT. In the TREMPLIN trial, only good responders to TPF-ICT were randomized. TPF-ICT followed by radiotherapy alone remains the reference

arm. TPF-ICT followed by radiotherapy with concurrent chemotherapy or concurrent biotherapy can be carried out in well selected patients. Further clinical research is therefore needed to assess the value of exclusive conventional chemoradiotherapy, TPF-ICT, new ICT regimens, and the place of immunotherapy in curative and organ preservation approaches.

Conclusion

This study demonstrates that TPF-ICT followed by conventional chemoradiotherapy or bioradiotherapy is feasible. No significant differences were observed between the two arms regarding efficacy or long-term toxicities.

The optimal larynx preservation strategy remains to be defined, as has the role of new-targeted therapies, such as monoclonal antibodies targeting epidermal growth factor receptor or immunotherapy. The various therapeutic options available must be compared using commonly agreed definitions and standardized evaluation criteria. This is the first study to use the composite criteria of LEDFS that takes into account the three principal therapeutic goals: long-term survival, control of disease and laryngo-esophageal function. Our study suggests that larynx preservation defined as “larynx in place or not” should not be used anymore in future larynx preservation trials.

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Notes

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Figure legends

Figure 1. Consort flowchart diagram

Figure 2. Efficacy results at 5 years. **(a)** Overall survival (OS) rates were not statistically different (p=0.9, two-sided log-rank test). **(b)** Locoregional control rates (LCR) were not statistically different (p=0.18, two-sided log-rank test). **(c)** Laryngo-esophageal dysfunction-free survival (LEDFS) rates were not statistically different (p=0.38, two-sided log-rank test)

Figure 3. Efficacy results for laryngeal tumors at 5 years. (a) Locoregional control rates (LCR) were not statistically different (p=0.1, two-sided log-rank test). **(b)** Laryngo-esophageal dysfunction-free survival (LEDFS) rates were not statistically different (p=0.6, two-sided log-rank test).

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Table 1. Laryngo-esophageal outcomes at 5 years in the two patient groups.

	Total (N=50)	**Cisplatin (N=23)**	**Cetuximab (N=27)**	**p-value**
Local relapse	20 (40)	8 (35)	12 (44)	0.56
Laryngectomy	19 (38)	8 (35)	11 (40)	0.77
Local relapse	14 (28)	5 (22)	9 (33)	0.54
Toxicity	5 (10)	3 (13)	2 (7)	0.65
Tracheotomy or feeding tube	13 (26)	4 (17)	9 (33)	0.34
Death	37 (74)	19 (83)	18 (66)	0.34

All values shown are n (%).
p-values estimated by Monte-Carlo simulation

Table 2. Late adverse events observed in the two patient groups.

Adverse events	Cisplatin (N=58)	Cetuximab (N=51)	p-value
No. of patients with at least one AE	50 (86.2)	49 (96.1)	0.10
Mucositis	20 (34.5)	22 (43.1)	0.43
CTCAE grade 3-4	3 (5.2)	1 (2.0)	0.99
Bones	7 (12.0)	1 (2.0)	0.07
CTCAE grade 3-4	1 (1.7)	1 (2.0)	0.99
Salivary glands	41 (70.7)	33 (74.5)	0.53
CTCAE grade 3-4	6 (10.3)	5 (9.8)	0.99
Subcutaneous tissue	31 (53.4)	36 (70.6)	0.09
CTCAE grade 3-4	3 (5.2)	2 (3.9)	0.99
Larynx	37 (63.8)	35 (68.6)	0.69
CTCAE grade 3-4	4 (6.9)	6 (11.8)	0.51
Others	31 (53.4)	21 (41.2)	0.25
CTCAE grade 3-4	4 (6.9)	2 (3.9)	0.68

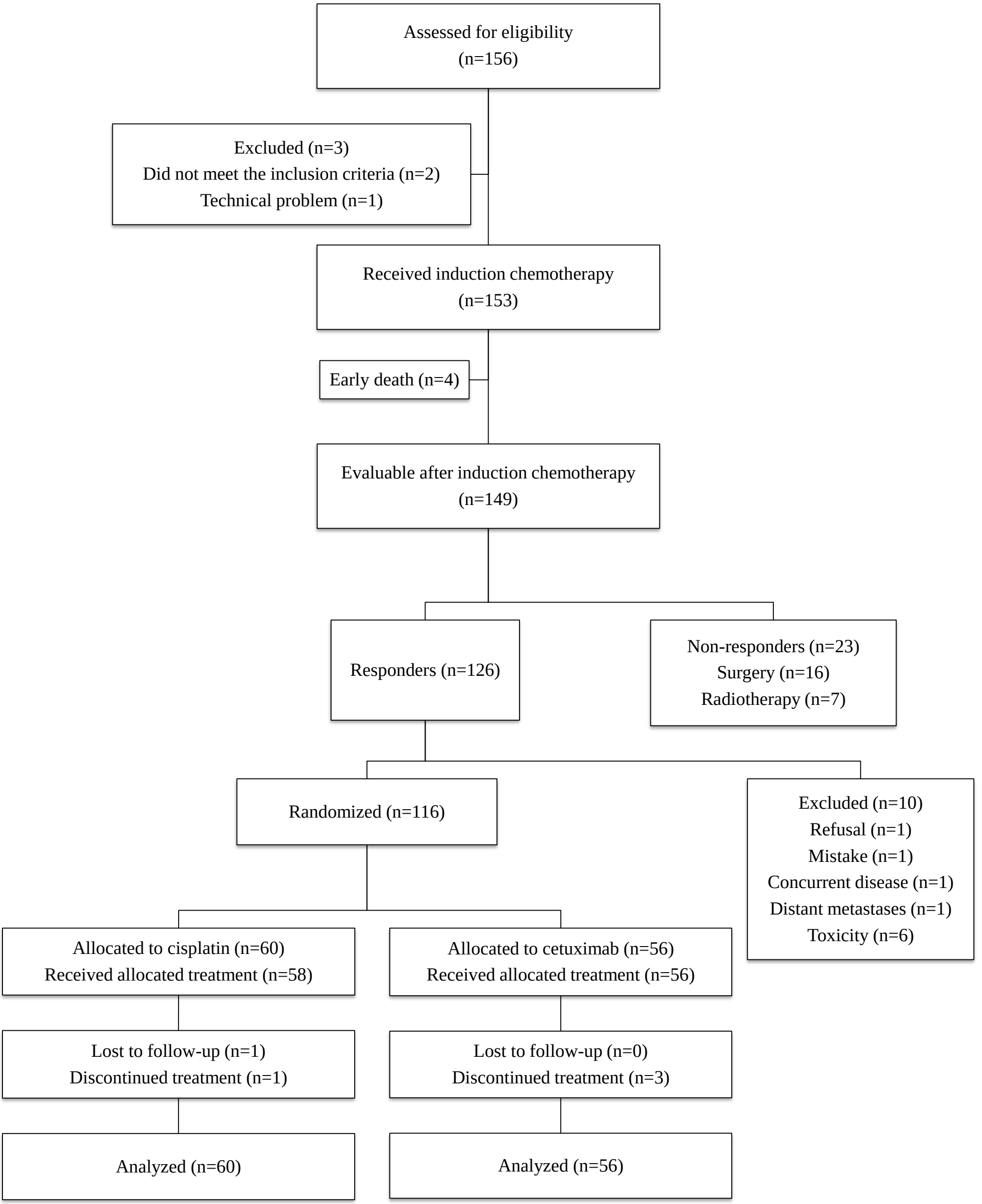
All values shown are n (%).
p-values estimated by Monte-Carlo simulation

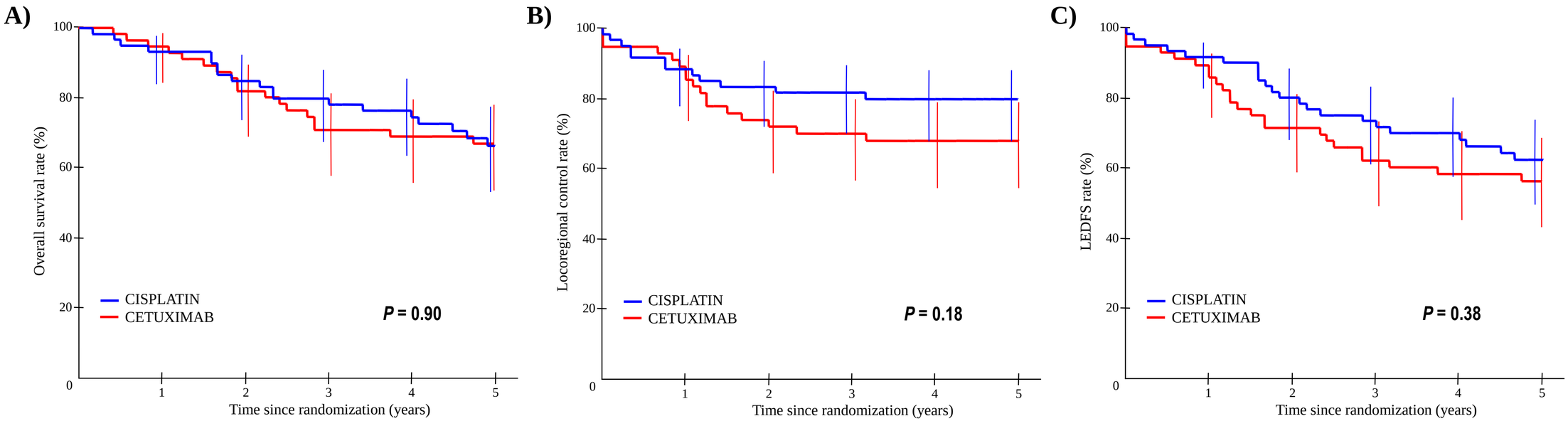
Table 3. Causes of death in the two patient groups.

	Total (N=48)	**Cisplatin (N=22)**	**Cetuximab (N=26)**
Cancer	27 (56)	13 (59)	14 (54)
Acute toxicity	0 (0)	0 (0)	0 (0)
Late toxicity	2 (4)	1 (5)	1 (4)
Second cancer	7 (15)	2 (9)	5 (19)
Concurrent disease	6 (13)	4 (18)	2 (8)
Other cause	1 (2)	0 (0)	1 (4)
Unknown cause	5 (10)	2 (9)	3 (12)

All values shown are n (%).

Figure 4. Larynx preservation rate at 5 years. Larynx preservation rate was superior in the Cisplatin arm vs in the Cetuximab arm (96.6% (95%IC 88.3% to 99.1%) vs 81.1% (95%IC 67.8% to 89.8%), p=0.02).

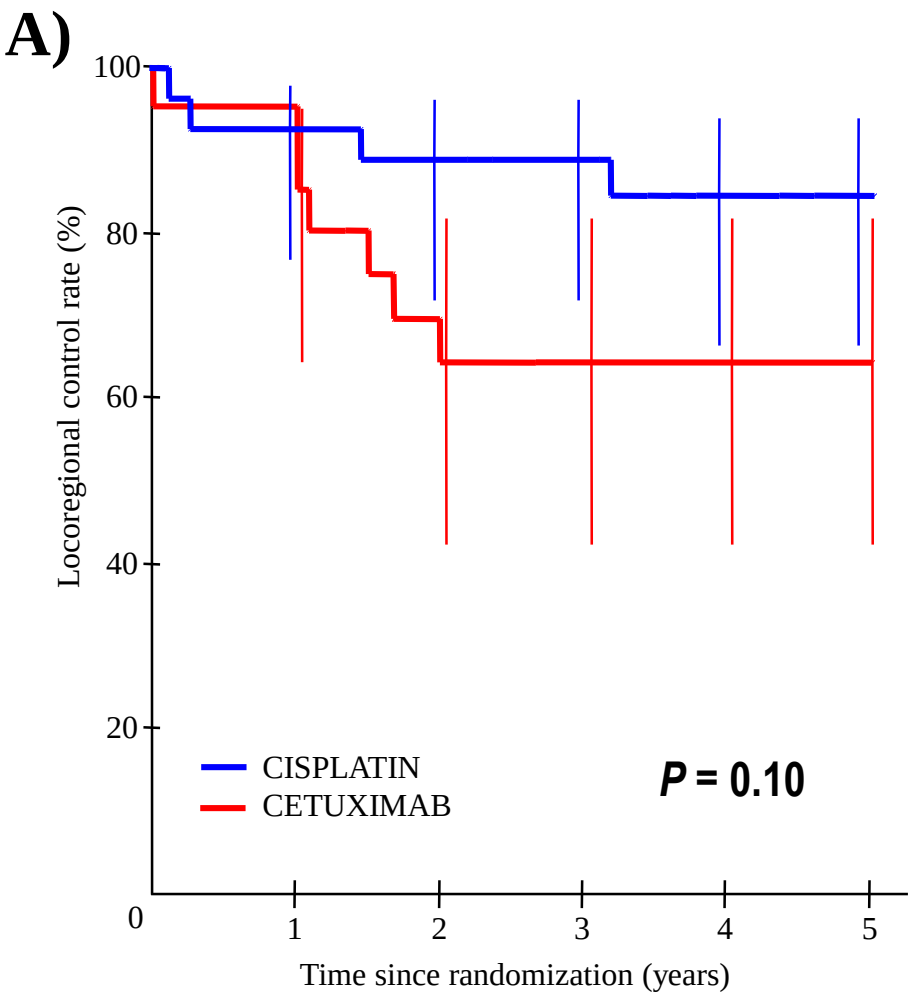

Assessed for eligibility
(n=156)
Excluded (n=3)
Did not meet the inclusion criteria (n=2)
Technical problem (n=1)
Received induction chemotherapy
(n=153)
Early death (n=4)
Evaluable after induction chemotherapy
(n=149)
Responders (n=126)
Non-responders (n=23)
Surgery (n=16)
Radiotherapy (n=7)
Randomized (n=116)
Excluded (n=10)
Refusal (n=1)
Mistake (n=1)
Concurrent disease (n=1)
Distant metastases (n=1)
Toxicity (n=6)
Allocated to cisplatin (n=60)
Received allocated treatment (n=58)
Allocated to cetuximab (n=56)
Received allocated treatment (n=56)
Lost to follow-up (n=1)
Discontinued treatment (n=1)
Lost to follow-up (n=0)
Discontinued treatment (n=3)
Analyzed (n=60)
Analyzed (n=56)



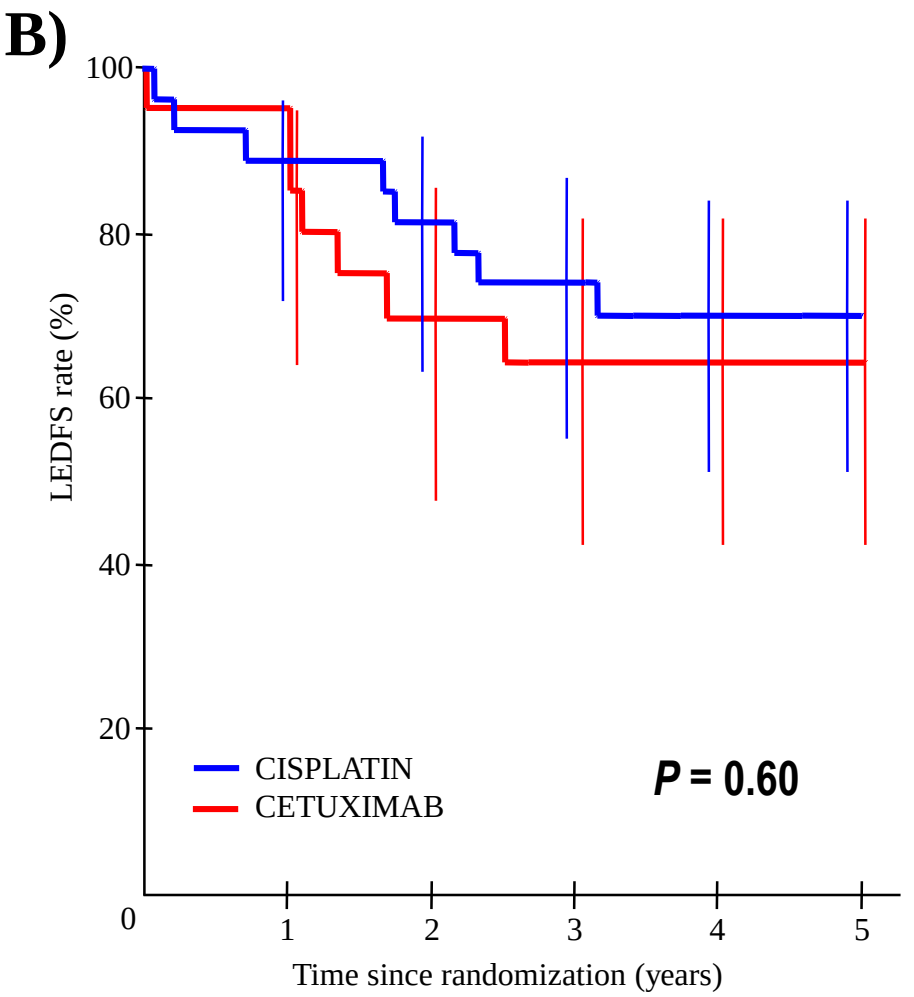
CISPLATIN	60	56	51	47	40	31
CETUXIMAB	56	53	45	38	35	33

CISPLATIN	60	53	49	45	39	31
CETUXIMAB	56	47	38	33	30	28

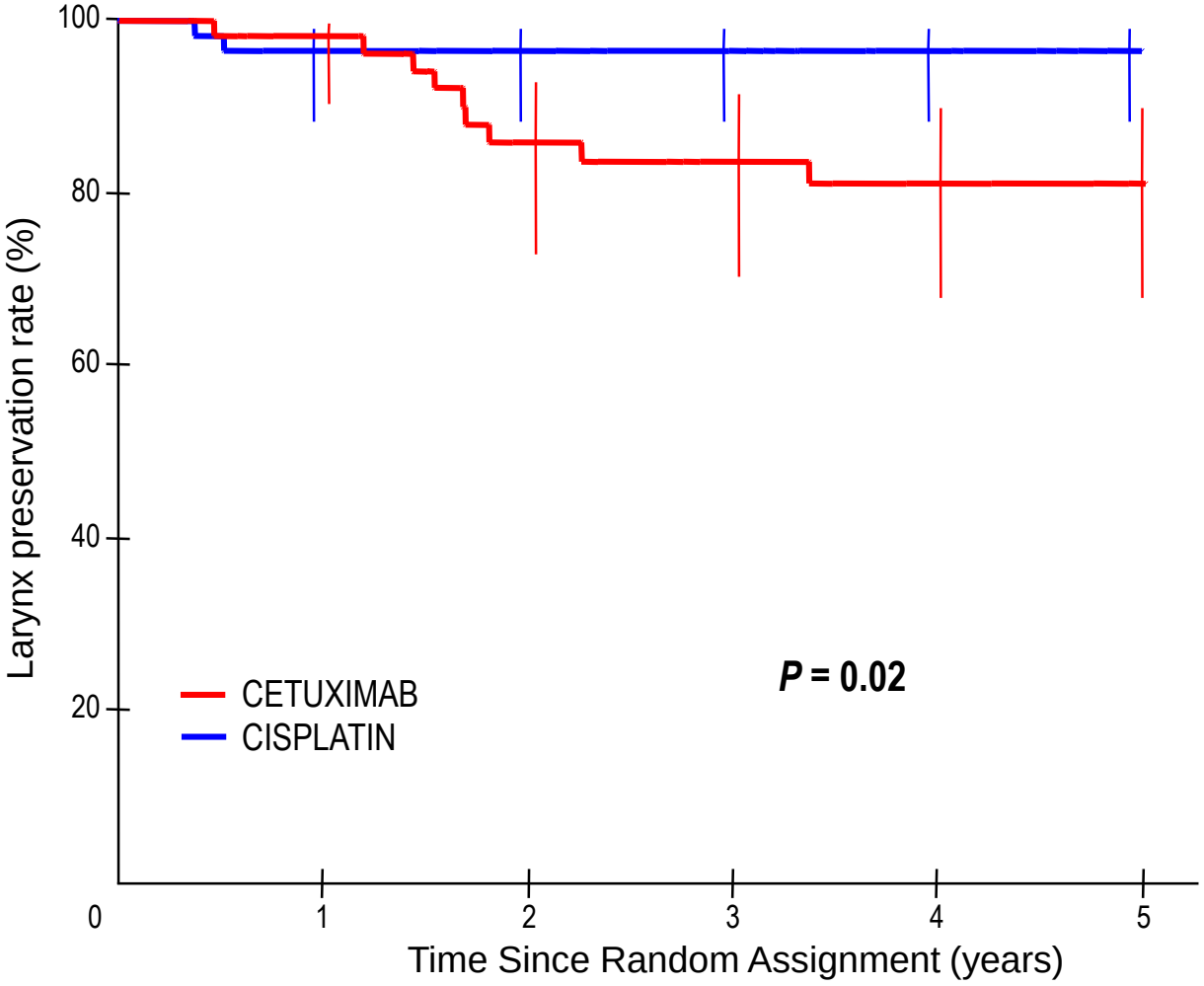
CISPLATIN	60	55	48	43	37	30
CETUXIMAB	56	50	39	33	30	28



CISPLATIN	27	25	24	22	17	15
CETUXIMAB	20	19	13	11	11	11



CISPLATIN	27	24	22	20	16	15
CETUXIMAB	20	19	13	11	11	11



Number at risk						
CETUXIMAB	56	51	39	33	30	27
CISPLATIN	60	55	51	47	39	31