THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1
sous le sceau de l'Université Bretagne Loire

Thèse en vue du

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

présentée par

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Née le 22 juin 1992 à Marseille

Faisabilité, tolérance et efficacité du Taxotère-Cisplatine-5FU (TPF) dans la stratégie de prise en charge des carcinomes épidermoïdes de la tête et du cou, en Bretagne et Pays de Loire.

Thèse soutenue à Rennes le 2 avril 2021

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Remerciements

Remerciements au Professeur Franck Jegoux qui me fait l'honneur de présider le jury de thèse, et au Docteur Joël Castelli. L'apport de vos spécialités placent la discussion d'aujourd'hui dans un champ multidisciplinaire, qui me tenait à cœur en choisissant ce sujet.

Remerciement au Docteur Damien Vansteene qui a permis la mise à disposition des données de l'Institut de Cancérologie de l'Ouest et me fait l'honneur de sa présence aujourd'hui. Merci pour l'éclairage de votre expertise nantaise et la considération que vous portez à ce travail.

Je remercie chaleureusement le Docteur Julien Edeline, pour son accompagnement dès le début du projet et sa présence dans le jury. Julien, merci surtout de ton soutien pendant l'internat, de tes conseils avisés et de ton appui universitaire. L'aboutissement de mon internat aujourd'hui leur doit beaucoup.

Je remercie le Docteur Elodie Vauleon d'avoir dirigé cette thèse. Merci Elodie de ton enthousiasme pour ce projet et de ta disponibilité. Ta personnalité de médecin a aussi marqué celle que je deviens et je suis heureuse que cela se concrétise par un projet commun.

Au moment de devenir oncologue, je me souviens et souhaite remercier les personnes qui m'ont conduite jusque-là par leur exemple et la beauté de leur engagement, en particulier le Professeur François Goldwasser et le Docteur Anatole Cessot dont les rencontres ont été déterminantes pour le choix de l'oncologie. Je remercie aussi les médecins et équipes qui m'ont accueillie pendant les semestres d'internat. Merci à chacun de votre confiance, du souci de la transmission et parfois de l'amitié que vous avez offerte. Merci du fond du cœur.

Chers co-internes de chaque semestre partagé, je suis heureuse d'avoir côtoyé de si belles personnes et des médecins si compétents. Merci de la solidarité qui rendait plus douce les difficultés, des liens presque familiaux soudés au quotidien. Je vous souhaite une belle route et espère la recroiser un jour.

Entre tous, merci à toi Lucie. C'était formidable de pouvoir gravir les étapes de l'internat avec le soutien de l'amitié. Merci des rires et larmes partagés : pourvu que ça dure !

Merci encore à vous tous qui avez soutenu, encouragé, accompagné ce parcours en médecine : famille, amis, colocs chéries. J'aurai aimé partager avec vous la joie du terme aujourd'hui et vous dire ma reconnaissance de vive voix.

François-Xavier, il faut plus qu'un merci pour te dire tout ce que te doit cette réalisation : les sacrifices qui l'ont rendu possible, ta prévenance, ton estime et ta lucidité. Pour l'amour qui nous lie, et à l'Amour qui a tout créé : merci.

A Elisabeth que j'ai portée en portant ce projet.

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Titre

Faisabilité, tolérance et efficacité du Taxotère-Cisplatine-5FU (TPF) dans la stratégie de prise en charge des carcinomes épidermoïdes de la tête et du cou, en Bretagne et Pays de Loire

Title

Taxotère-Cisplatin-5FU (TPF) as first-line chemotherapy in squamous cell carcinomas of the head and neck: feasibility, safety and efficacy in a real-life multicenter cohort.

Résumé

CONTEXTE – Pour le traitement des carcinomes épidermoïdes de la tête et du cou (CETEC) localement avancés, la chimiothérapie a montré un bénéfice en survie, qu'elle soit concomitante ou en induction d'une radiothérapie. Si l'association de Cisplatine-Docetaxel-5FU (TPF) est le traitement de référence en induction, ses indications ne sont pas validées aujourd'hui en dehors de la préservation laryngée (PL) pour les patients relevant d'une laryngectomie totale (LT).

METHODE – Nous rapportons les données d'une cohorte multicentrique de patients traités par TPF entre 2012 et 2016, en première ligne d'un CETEC localement avancé, non résécables ou relevant d'une LT et candidats à un protocole de PL. Le critère principal de jugement était la faisabilité du traitement, les critères secondaires : la tolérance et l'efficacité. L'analyse est conduite en population totale et dans un sous-groupe de patients relevant d'une PL.

RESULTATS – Sur 129 patients, 96 (74.4%) ont reçu au moins 3 cycles de TPF, dont 66 (51.1%) sans réduction de dose. Pendant le TPF, 12 patients sont décédés et 4 perdus de vue. 38% des patients ont subi un effet secondaire de grade 3 à 5. Le taux de réponse après TPF était de 61.2%, la survie globale médiane de 43.2 mois (IC95%, 26.4 - 59.9) et la survie médiane sans récidive de 14.5 mois (IC95 7.8 - 21.3). Dans le sous-groupe PL, on rapporte 78% de taux de réponse, 35% de survie avec larynx fonctionnel à 3 ans et une survie globale médiane de 50.2 mois (IC95%, 21 – 78).

CONCLUSION – La chimiothérapie d'induction par TPF réalisée hors essai thérapeutique garde une efficacité satisfaisante malgré une difficile faisabilité. Il est important de considérer la lourde toxicité de ce traitement qui n'a pas fait ses preuves hors PL.

Abstract

BACKGROUND – In locally advanced squamous-cells head and neck carcinoma (HNSCC), chemotherapy improves outcomes both with concomitant radiotherapy or for laryngeal preservation (LP). While combination of Cisplatin, Docetaxel and 5FU (TPF) is the best treatment in induction chemotherapy, all indications are not currently approved, except for laryngeal preservation.

METHODS – Data are reported from a multi-center cohort of 129 patients who received TPF between 2012 and 2016 in frontline of a locally advanced HNSCC, considered to be unresectable or were candidates for organ preservation. Primary endpoint is feasibility of the treatment. Secondary endpoints are tolerance and efficacy. The analysis was conducted in overall population and in a LP subgroup.

RESULTS – 96 patients (74.4%) received at least 3 cycles of TPF, of whom 66 (51.1%) without dose reduction. Grade 3 to 5 adverse events occurred in 49 patients (38%), febrile neutropenia and severe infection in 26 (20%). Overall response rate (ORR) after TPF chemotherapy was 61.2%, median overall survival (OS) 43.2 months (95% confidence interval [CI], 26.4 to 59.9), median progression-free survival (PFS) 14.5 months (95% CI, 7.8 to 21.3). For the 37 patients in LP subgroup, 13 (35%) patients were alive with a functional larynx after 3 years.

CONCLUSION - TPF induction chemotherapy, performed out of therapeutic trials, remains effective despite its poor feasibility. Heavy toxicity is to be considered, as this treatment has not been proven to be effective besides laryngeal preservation.

Keywords

Adult - Antineoplasic Agents - Antineoplastic Combined Chemotherapy Protocols - Carcinoma, Squamous Cell – Cetuximab - Chemoradiotherapy, Adjuvant – Cisplatin - Cohort study - Combined Modality Therapy – Deglutition – Fluorouracil - Head and Neck Neoplasms – Humans - Induction Chemotherapy - Laryngeal Neoplasms - Larynx preservation - Organ Sparing Treatments – Radiotherapy – Real life data - Retrospective Study – Speech – Surgery – Taxanes – 5-Fluoro-uracil

Abbreviations

CI: Confidence Interval

CRT: Concomitant chemo-radiotherapy

G-CSF: Granulocyte colony-stimulating factor

GORTEC: Groupe Oncologie et Radiothérapie de la Tête et Cou

GSTTC: Gruppo di Studio Tumori della Testa e Collo

Gy: Grey

HNSCC: Head and Neck Squamous-cells Carcinoma

ICT: Induction chemotherapy

LP: Laryngeal preservation

NCI – CTCAE: Common Terminology Criteria for Adverse Events of the National Cancer Institute

ORR: Overall response rate

PF: Cisplatin and 5-FU protocol

PFS: Progression or recurrence free survival

RECIST: Response Evaluation Criteria in Solid Tumors

RT: Radiotherapy

RTOG: Radiation Therapy Oncology Group

TL: Total laryngectomy

TPF: Docetaxel, Cisplatin and 5-FU protocol

UCNT : Undifferentiated Carcinoma Nasopharyngeal

Introduction

Head and neck squamous-cell carcinoma (HNSCC) account for 16800 new case in 2018, with a strong male prevalence(1). Tobacco and alcohol are the most important risk factors. Severity of this disease is due to locoregional or metastatic evolution, leading to death 4,770 patients per year (estimate 2018). Functional impairment is another problem, concerning phonation, swallowing and breathing, caused by tumor invasion or treatment itself.

A multidisciplinary approach is required, closely associating surgery, radiotherapy and chemotherapy. Therapeutic research for this disease has always aimed at both greater efficacy improving survival and better functional outcome.

Chemotherapy in locally advanced cancer has theoretical benefit of treating micrometastatic disease and thus reducing the risk of metastatic relapse. When performed in induction, i.e., prior to any local treatment by surgery or radiotherapy, reduction in tumor size improve local control. Chemotherapy sensitivity identifies different prognosis groups, whom depend subsequent treatments.

For resectable laryngeal or hypopharyngeal tumors, several decades of research resulted in a validation of a protocol called "laryngeal preservation" (LP). Primary chemotherapy with Docetaxel, Cisplatin and 5-FU (TPF) allows the selection of chemotherapy-responsive patients who are able to benefit from conservative treatment with radiotherapy, thus avoiding a total laryngectomy (TL) (2–11) .

In unresectable non-metastatic HNSCC, concomitant chemoradiotherapy (CRT) may improve locoregional control, with a greater benefit compared to induction chemotherapy (5,12,13). Since these results, introduction of Docetaxel has led to a renewed interest in induction chemotherapy. Several Phase III trials confirm the superiority of TPF over PF, for response, overall survival, and progression-free interval, without additional toxicity (14,15). However, clinical trials failed to prove a benefit of induction chemotherapy compared to concomitant CRT (16–20),which remains the standard of care for locally advanced HNSCC, except for LP.

We report retrospective data from a multi-center cohort of patients treated with TPF in frontline for HNSCC between 2012 and 2016. We aim to confirm feasibility of TPF in daily practice, evaluate its toxicity, measure its benefit, and assess the interest of TPF in laryngeal preservation.

Material and methods

PATIENTS

Among patients who received TPF protocol between 2012, September and 2017, December, we included those treated as a frontline for HNSCC. Non-inclusion criteria were: treatment for digestive cancer, thyroid cancer or UCNT. Patients who had previously received one or more lines of treatment for the same indication, and patients who never received TPF chemotherapy (died or loss of follow-up before the first treatment) were excluded.

Patients were recruited in three French hospital centers, in Bretagne and Pays de Loire, from chemotherapy prescribing software databases: University Hospital Center in Brest, Eugène Marquis Center in Rennes, and Institut de Cancérologie de l'Ouest René Gauducheau in Nantes.

Patients were informed by mail or online information. They had right to object to the processing of their data in the context of this study, under conditions defined by the EU Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data and free movement of such data (General Data Protection Regulation) and the law n° 78-17 of 6 January 1978 "Loi informatique et Libertés" modified. This study was approved by Ethics committee of Rennes.

A pre-defined analysis was performed in a subgroup of patients concerned by laryngeal preservation (LP) protocol. We included in LP subgroup patients meeting following criteria: T2 or T3 tumor of the larynx or hypopharynx initially operable by total laryngectomy (TL), decreased laryngeal mobility in direct laryngoscopy. Patients initially refusing surgery were excluded.

STUDY DESIGN

This retrospective study describes efficacy and safety of TPF chemotherapy in locally advanced HNSCC. Primary endpoint was feasibility of treatment, evaluated with rate of patients receiving complete treatment (3 cycles without dose reduction). Tolerance criteria were death per treatment, acute and chronic adverse events. We measured efficacy of TPF with Overall response rate (ORR), Overall survival (OS), Disease or progression-free survival (PFS). Same criteria and rate of living patients with functional larynx after 1, 2, or 3 years were explored in the LP subgroup.

In centers that signed the data sharing agreement, exhaustive list of patients who received TPF chemotherapy was extracted via the chemotherapy prescription software. Inclusion and exclusion criteria were verified from medical record data. Outcomes were extracted from medical correspondence, accessible in computerized patient records.

TREATMENT

TPF chemotherapy consisted of docetaxel, cisplatin (both 75 mg/m2 on day 1), and 5-fluorouracil (750mg/m2 by 24-hours continuous infusion for 4 days). Three cycles with a 21-days interval were usually planned. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) or antibiotic prophylaxis were prescribed according to physician's choice.

Tumoral response was clinically evaluated just before or after cycle 3. A computed tomography (CT)-scan could be performed after the end of chemotherapy.

After TPF chemotherapy, following treatment relied upon physician’s choice, initial indication and tumor response to chemotherapy. For patients with laryngeal cancer requiring total laryngectomy, a laryngeal preservation strategy could be proposed if the patient agreed before treatment to undergo TL in case of failure. In case of good or partial response to TPF, treatment was followed by radiotherapy with or without medical treatment. Patients who did not respond to induction chemotherapy underwent TL (with neck dissection), followed by radiotherapy with or without additional chemotherapy.

For non-resectable locally advanced HNSCC, planned treatment after induction chemotherapy with TPF was radiotherapy, with or without concurrent chemotherapy. Salvage surgery could be proposed in case of tumor progression at the end of radiotherapy.

ASSESSMENT OF OUTCOMES

With or after the last TPF cycle, tumor response was assessed in each center by clinical evaluation (using direct laryngoscopy in case of pharyngeal or laryngeal tumors), and / or computed tomography or magnetic resonance imaging of the head and neck. TPF response was defined by a clinical tumor reduction greater than 50% associated with a partial or complete radiological response according to RECIST 1.1 criteria (21). In LP subgroup analysis, tumor response was defined on the same criteria, to which was added recovery of normal laryngeal mobility. Tumor response was assessed the same way after radiotherapy.

OS was calculated from date of first specialist consultation to date of death (regardless of cause), and PFS was from date of first consultation until progression or recurrence (local, lymph node or metastasis recurrence). Survival analysis was conducted in overall population and in prespecified subgroups, with Kaplan-Meier method. Comparison between groups was made with log-rank test (Mantel-Cox method).

Tolerance analysis was conducted in overall population. We collected toxic effects described by physicians in medical reports during TPF (acute toxicity), and one year later (late toxicity and sequelae). Toxic effects were graded according to NCI-CTCAE v4.0 (22), and to RTOG for acute and late toxic effect of radiation (23).

Results

PATIENTS

188 patients were screened in three centers, of which 129 patients were included in this study (Rennes 19 patients out of 27 screened patients, Brest 7 out of 22, Nantes 104 out of 139). 61 patients were excluded for following reasons: TPF received for non-HNSCC cancer, mostly UCNT; TPF received for metastatic HNSCC after one or more lines of chemotherapy; when TPF had been prescribed but no cure was received by the patient (death before treatment or lost to follow-up). Cutoff date for analysis was May 31, 2020, corresponding to 30 months of follow-up for the last patient enrolled in the study. Table 1 shows demographic and tumor characteristics of the 129 patients included. More than 80% of patients were men, and predominant site of disease was hypopharynx. For 8 patients, disease could initially be graded as metastatic: 1 patient had contiguous bone damage, 3 had suspicious lung lesions, 2 had confirmed lung lesions, and 2 had liver lesions (one of them also had a bone lesion).

TREATMENT

Of 96 (74.4%) patients who received at least 3 cycles of TPF, 66 (51.1%) patients received 3 cycles of TPF chemotherapy without dose reduction (Table 2).

Dose reduction was applied from the first cycle for 12 (9%) patients: dose reduction of 5-FU for 7 patients (including 2 complete suppression of 5-FU), reduction of 3 drugs for 2 patients (-20%), reduction of docetaxel alone for 1 patient, cisplatin and docetaxel for 2.

38 (34%) patients received modified dose for second cycle. 26 additional reductions were applied compared to first cycle, including 14 dose reductions of 5FU alone, 4 dose reductions of the 3 drugs, 7 reductions of Docetaxel and 5-FU.

Treatment delay was applied for 18 patients: 3 at the first cycle, 12 at the second, and 5 at the third. Causes of interruption or delay of treatment were not available or not collected.

SAFETY

12 Patients died during the 9 first weeks of treatment, and 4 were lost to follow-up during this period of TPF treatment. In contrast only 3 patients died or were lost to follow-up between week 10 and week 20 after initiation of chemotherapy. Characteristics of patients who died during TPF are described in Supplementary table 1.

Adverse events are reported in Table 3. 102 patients (79%) had at least one adverse event. Grade 3 to 5 adverse events occurred in 49 patients (38%), including grade 3 or 4 neutropenia in 16 (12%) patients. Rate of febrile neutropenia and severe infection was 20% (26 events).

Asthenia was the most frequently reported grade 1-2 adverse event (18%), followed by digestive disorders (diarrhea 14%, nausea and vomiting 14%).

Regarding specific toxicity, 9 (7%) auditory toxicities and 6 (5%) renal toxicities were reported. Five cases of colitis, all grade 3-4, and one grade 3 coronary spasm occurred.

One year after treatment, 41 patients had late toxic effects, mainly induced by radiotherapy (skin fibrosis 15%, xerostomia or dysphagia 11%). Persistent auditive toxicity was reported for 2 patients, and 5 patients still had neurological sequelae. One episode of radionecrosis and one death by respiratory infection were reported.

EFFICACY

ORR after TPF was 61.2%, with complete response for 17 patients (13.2%). Evaluation was not available for 16 patients. Outcomes according to TPF response is described in Figure 1.

Of the 93 patients who received radiation therapy after TPF, 81 received the planned dose. Planned dose was 70 Gy for 87 patients, 66 Gy for 1, and 30 Gy for 3 patients. 46 (36%) patients received concomitant medical therapy using cisplatin (29), carboplatin and 5-FU (5), or Erbitux (10).

4 patients underwent surgery and adjuvant radiation therapy, all received the planned dose (70 Gy, 66 Gy for 2, 50 Gy).

After radiotherapy, 56 patients were in complete response and 15 in partial response, resulting in an ORR of 55% and complete response rate of 43 %.

At time of analysis, median follow-up was of 18.80 months (range 0.03 – 86.03). 63 patients died (48.8%) and 66 are alive (51.2%), including 40 in remission (31.0%). Median OS was 43.2 months (95% confidence interval [CI], 26.4 to 59.9) (Figure 2A). 54 of 63 deaths were due to cancer (41.9%).

Median OS between centers weren’t significatively different (p=0.635): Brest 16 months (95% CI, 0 to 38), Nantes 46 months (95% CI, 31 to 62) and Rennes 30 months (95% CI, 2 to 58) (Supplementary figure 1).

At date of analysis, recurrence had occurred in 56 patients. Median PFS was 14.5 months (95% CI, 7.8 to 21.3) (Figure 2B).

Rate of locoregional failure was 37% (48 patients). Median survival without locoregional recurrence was 25 months (95% CI, 13 to 36). Distant metastases occurred in 18% of the patients (24, including 18 with both locoregional and distant recurrence). Median survival without metastatic recurrence was 15 months (95% CI, 7 to 23) (Figure 3).

Impact of TPF dose intensity

For patients who received complete treatment (3 cycles without dose reduction), median OS was 49.6 months (95% CI, 23.8 to 75.5), compared to 10.2 months (95% CI, 0 to 24.5) for other patients (test Khi2 = 11.2, p = 0.001) (Figure 4). Median PFS were respectively 20.4 months (95% CI, 10.2 to 30.7) and 9.7 months (95% CI, 3.6 to 15.9) (test Khi2= 10.3, p=0.001).

Predictive and prognostic impact of response to TPF

For TPF responder patients (N=79), ORR after RT (or CRT) was 75.9 %. Whereas for TPF non-responder patients, ORR after surgery and/or RT (or CRT) was 35.3%. Final ORR after TPF complete response (N=17) and radiotherapy were 82.3 %, including 13 complete responses (76.5 %).

For TPF responder patients, median OS was 65 months (95% CI, 43 to 86), versus 18 months (95% CI, 11 to 25) for TPF non-responder patients (P=0.025) (Figure 5).

LARYNX PRESERVATION

Among patients treated for laryngeal or hypopharyngeal tumors, 53 were considered by physician to be part of a laryngeal preservation strategy. Among them 34 met all criteria defined above for LP subgroup, 16 patients initially had a mobile larynx, 2 patients had a T4 tumor, 2 refused surgery. In contrast, 3 patients not described by the clinician as undergoing LP met all the criteria and were included. TPF indications and their distribution by center are described in Supplementary figure 2.

In this 37-patients population, mean age was 61 (range 42 to 74). Tumor characteristics are described in Table 4.

20 patients (54 %) received complete TPF treatment without delay or dose reduction. 28 patients (75%) received 3 cycles.

After TPF, 4 patients were not evaluable and did not receive additional treatment (deaths under TPF). 3 patients had tumor response of less than 50%, and 1 patient had a tumor response of more than 50% without recovery of laryngeal mobility. 29 patients were in clinical and radiological response with recovery of laryngeal mobility, resulting in a 78% response rate. Treatment according to response is described in Figure 6.

Among 4 non-responder patients, 2 patients underwent total laryngectomy: 1 was in incomplete resection and received no additional treatment, second was treated with adjuvant radiotherapy (66Gy). 1 patient received post-operative radiotherapy (70 Gy without chemotherapy), followed by salvage surgery. None were alive with a functional larynx after one year of follow-up.

Radiotherapy for LP was performed in 27 of 29 responder patients (73.0% of the LP subgroup). Planned dose was 70 Gy for all patients, 2 patients discontinued treatment at 58 and 66 Gy. 7 patients received concomitant medical treatment (Cisplatine for 2 patients, Carboplatine and 5FU for 2, Cetuximab for 1, and 2 NC).

At the end of radiotherapy, 3 patients were in radiological partial response, 2 of them underwent salvage surgery, 3 were in radiological progression, 2 of them underwent surgery. 21 patients were in clinical and radiological complete response after radiotherapy, for an overall complete response rate of 57%.

In this subgroup, median OS was 50.2 months (95% CI, 21 to 78). Median PFS was 30.2 months (95% CI, 5 to 54). (Figure 7)

10 patients experienced a relapse. Rates of locoregional failure and metastatic relapses were 16% and 14% respectively.

One year after treatment, 21 (57%) patients were alive with a functional larynx, 18 (49%) at 2 years, 13 (35%) at 3 years. 22 (59%) patients were alive with functional swallowing at one year of treatment, 18 (49%) at 2 years and 13 (35%) at 3 years.

Discussion

CONTEXT

Chemotherapy's contribution to localized HNSCC

Research around induction chemotherapy (ICT) for CETEC was initiated with the objective of laryngeal preservation as an alternative to total laryngectomy (TL). It sought preserving a functional larynx without impairing survival. This therapeutic sequence is based on the rational that chemosensitivity predicts radiosensitivity, addressed as early as the 1980s with the results of 2 series of patients(24,25). In the 1990s, 3 randomized Phase III trials evaluated ICT with 3 cycles of Cisplatin and 5-FU (PF), followed by radiotherapy if there was a good response to chemotherapy(2–4). TL and post-operative RT were performed in poor responders. Patients in comparative arm received standard of care: no chemotherapy, TL followed by post-operative irradiation. Two of these trials conclude to a non-inferior survival, allowing 59 to 64% laryngeal preservation. A meta-analysis of these trials, published by Pignon in the Lancet in 2000, show a non-significant trend in favor of the control arm with a proportion of patients alive at 5 years of 45% versus 39% in the LP arm, of which 23% were alive with their larynx (HR 1.19, 0.97-1.46)(5).

Induction chemotherapy with PF followed by radiotherapy became a standard of care for treatment of resectable laryngeal cancer, as an alternative to TL. In RTOG 91-11 trial published in 2003, this treatment was compared to Cisplatin CRT or radiotherapy alone(6). This study confirms the benefit of adding chemotherapy for survival without laryngectomy either induction or concomitant, but rate of laryngeal preservation and locoregional control was greater with Cisplatin CRT(10).

Meanwhile, question of chemotherapy in unresectable locally advanced HNSCC cancers is raised. Pignon's main meta-analysis, initially published in 2000 and updated in 2009, evaluated the addition of chemotherapy to a locoregional treatment based on 87 trials conducted between 1963 and 2000, involving 16,485 patients. The study concludes to an absolute benefit of 4.5% at 5 years (HR of death 0.88, $p<0.0001$). Benefit was greater for concomitant CRT than for ICT(5,12) which was therefore not validated in this indication.

TPF versus PF

Development of Taxanes has renewed interest in induction chemotherapy for both resectable pharyngeal cancer and non-resectable locally advanced HNSCC. In 2007, 2 trials were published in the New England Journal of Medicine evaluating TPF versus PF in ICT(14,15). In TAX-323, published by J. Vermorken, patients with unresectable stage III or IV disease without metastasis received 4 cycles of ICT followed by radiotherapy alone. Results were in favor of TPF, both for PFS (HR 0.72, $p=0.007$), its primary endpoint, and for OS(15). In TAX-324 trial published by M. Posner, patients with stage III or

IV disease, or candidates for laryngeal preservation, were treated with 3 cycles of ICT followed by weekly Carboplatin CRT. An improvement in OS was shown with TPF, which was the primary endpoint (HR 0.70, p=0.006). There was no significant difference in incidence of metastasis but better locoregional control in TPF arm(14).

In 2009, Y. Pointreau published a trial for laryngeal preservation, comparing 3 cycles of TPF to 3 cycles of PF. Patients responding to chemotherapy received radiotherapy with or without chemotherapy. Non-responder patients underwent TL followed by radiotherapy with or without chemotherapy. Primary endpoint was the laryngeal preservation rate at 3 years, significantly higher after TPF than after PF (70.3% and 57.5%, p=0.3). No significant differences were found in overall survival and disease-free survival (p=0.57 and p=0.11, respectively)(8). Because of these significant results, long-term confirmed in G. Janoray's publication(11), TPF became a standard of care in LP.

Benefit of TPF compared to PF was confirmed by a meta-analysis of MACH-NC published in 2013, including 1772 patients from 5 trials with both resectable and locally advanced cancers. ICT with Taxane-PF provided an OS benefit of 7.4% at 5 years (HR 0.79, p<0.001), a decrease in local and metastatic relapses. Compliance was better with TPF than PF, and rate of CRT after TPF was higher(13).

ICT vs RCT

However for unresectable tumors, ICT with TPF has not proven to be superior to CRT, which remains the standard with a high level of evidence(12). Several Phase II-III trials, published between 2013 and 2018, compared an ICT followed by CRT or Cetuximab - Radiotherapy to exclusive CRT, with no proven benefit(16–20). Two of these trials focused on disease with advanced nodal spread (N2, N3), for which a benefit of ICT had been suggested by the Tax-PF meta-analysis(13). The DeCIDE trial, published in 2014, did not conclude by lack of inclusion(17). The GORTEC 2007-02 trial also failed to prove a benefit in PFS of TPF followed by Cetuximab-Radiotherapy compared to Carboplatin-5-FU CRT(20). But there was a decrease in the occurrence of distant metastases in the TPF arm, suggesting a better micrometastatic disease control.

Results of the GSTTC Phase II-III trial were presented at ASCO in 2014 with a significant but debated benefit. Based on double (2x2) randomization, it evaluated contribution of ICT for unresectable HNSCC, then compared the addition of Cetuximab or Cisplatin- 5-FU with radiotherapy(19). About the first question, M. Ghi’s publication concludes that ICT provides a benefit for OS (primary endpoint) and PFS. With an ORR to ICT of 76%, complete response rate after radiotherapy was 42.5% after ICT versus 28% in the control arm. There was no significant difference in metastatic recurrence rate (13% vs. 16%, p=0.274), but a borderline benefit for locoregional relapse after ICT. Compliance and tolerance were similar in both arms.

In summary, while ICT with TPF has been validated for laryngeal preservation as an alternative to total laryngectomy, it has not shown any benefit for treatment of unresectable localized HNSCC. In this context, risk of ICT is to compromise radiotherapy in case of progression under TPF, or the addition of concomitant chemotherapy in case of limiting toxicity. Tolerance of such a treatment raises the question of feasibility in daily practice, while benefit is uncertain.

ABOUT OUR RESULTS

Feasibility and Toxicity

From our cohort data, TPF induction chemotherapy seems a difficult-to-complete and toxic treatment. Only 74% of the 129 patients received 3 cycles of TPF, and 51% without dose reduction, compared to 81-94% in trials evaluating TPF(14–20). Mortality rate during induction chemotherapy was 9.3%, 12% including lost to follow-up, which is significant and higher than in mentioned trials (3.4% deaths under TPF in the TAX323 trial, of which 2.3% were toxic deaths, and 2% toxic deaths in TAX 324(14,15)). Causes of death are not always known, sometimes occurring outside hospital.

Most frequent grade 3-4 toxicity is infection (14%) to which can be added febrile neutropenia (8%). This risk is well known since first TPF trials, with febrile neutropenia rates up to 27%, despite use (unsystematic, sometimes after amendment) of G-CSF and / or antibiotic prophylaxis with fluoroquinolone(14–20).

High prevalence of co-morbidities in HNSCC patients is known to expose to more severe complications. Early management of locally advanced tumors is also complicated by compressive or hemorrhagic event. Such toxic chemotherapy should therefore be considered only in selected patients, after eradication of infectious sites and introduction of nutritional support. It is highly recommended to ensure early and optimal management of complications. Primary prophylaxis with G-CSF and/or antibiotic prophylaxis had been shown to be effective(18).

A "center effect" can also be discussed, by number of patients treated and available medical expertise, assuming that a greater habit of managing toxicities limits complications. Our results do not support this hypothesis: 14 patients died during treatment in Nantes for 104 patients included (13%), Rennes 2 out of 18 patients (11%) and none of 7 in Brest, where chemotherapy is prescribed by the ENT team and not oncologists.

After TPF, 93 patients (72%) received radiation therapy, which is consistent with studies like TAX 324 and GORTEC 2000-01(8,14,18), but lower than other similar trials(9,15,20). For 36% of patients, this radiotherapy was combined with concomitant chemotherapy: 20% Cisplatin and 8% Cetuximab.

Benefit of chemotherapy associated with radiotherapy after TPF is not proven, nor type of treatment, whether in laryngeal preservation or in non-operable cancers. Cetuximab in combination with exclusive

radiotherapy allow an improvement in locoregional control, overall survival and recurrence-free survival without deterioration of tolerance compared to radiotherapy alone(26). Phase II TREMPLIN trial showed comparable efficacy of Cetuximab or Cisplatin in combination with radiotherapy, in a laryngeal preservation protocol, and improved safety with Cetuximab(27,28). But studies published to date do not provide solid recommendations for treatment after TPF.

In our cohort, 32% of patients had at least one side effect after one year. We report 15% skin fibrosis and 11% dysphagia. These results are probably underestimated by retrospective analysis, but remain significant.

Efficacy

Despite mentioned toxicity, efficacy of induction chemotherapy appears to be maintained. Response rate to TPF is 61.2% with 13.2% complete response, which is consistent with TPF results in TAX 323 and TAX 324 trials(14,15). In GORTEC 2007-02 trial, which included locally advanced N2-N3 patients, ORR was 45.5% after TPF and RT-cetuximab(20). In our LP cohort, ORR was 78% after TPF, which is comparable to data of GORTEC 2000-01 trial, in TPF arm(8).

After CRT, ORR is 55%, with 43% of patients in complete response (respectively 82.5% and 56% of patients evaluable after CRT). In LP cohort, complete response rate after complete treatment was 57%. These data are consistent with those reported in literature(14,15,19).

In our cohort, median OS was 43.2 months and 50.2 months in LP subgroup. Median OS is highly variable across trials, depending on inclusion criteria and initial disease prognosis. In TAX 324 trial, only including patients with unresectable tumors, median OS was 18.8 months after TPF, while in Posner's trial, also involving operable laryngeal carcinomas for LP, median survival was 70.6 months(14,15,29). As a comparison, GORTEC's trial evaluating TPF in a LP protocol found a 5-year survival of 50.9%(11). An interesting result is prognostic impact of response to TPF and achievement of complete treatment with TPF. But this effect is overestimated by early deaths under TPF, worsening the prognosis of the control arm.

Median PFS after TPF is also highly variable in literature, depending on inclusion criteria: TAX 324 trial reports a PFS of 38.1 months, TAX 323 trial 11.0 months. GORTEC 2000-01 updated results report locoregional control rate of 46.6% at 5 years and disease-free survival rate of 42.4% at 5 years(11). In our cohort, median PFS was 14.5 months, and 30.2 months in the LP subgroup, which seems consistent with previous data.

Laryngeal Preservation

Analysis of the Laryngeal Preservation subgroup raises several questions.

First, inclusion criteria for such a protocol are not homogeneous across studies nor centers. We have chosen these inclusion criteria for LP subgroup: T2 or T3, with decreased laryngeal mobility. Patients initially refusing surgery were excluded. These criteria met only 64% of the patients considered by clinicians as undergoing a LP protocol. Moreover, these criteria are not strictly those of major studies of LP. For example, GORTEC 2000-01 trial included 13.6% T4 tumors, and had no criteria for laryngeal mobility(8). Second, there is no standardized definition of response to TPF. In GORTEC 2000-01 trial, response is defined as a clinical complete response or a partial response with laryngeal remobilization: response rate after TPF was 80%, but only 45.5% of patients recovered a normal laryngeal mobility(8).

In LP cohort, laryngeal preservation rate at 3 years is 35% of the overall population (and not alive population). This result appears to be lower than the data from the GORTEC 2000-01 trial. With a 70% laryngeal preservation rate at 3 years, and an overall survival rate of 60%, survival rate with functional larynx at 3 years seems to be 42%(8). Long-term analysis of the same trial reports a 5-year Larynx Dysfunction-Free Survival (LDFFS) rate of 67.2% in the TPF arm(28).

Limits

This study is subject to the biases of retrospective studies, such as under-reporting of side effects, lack of information regarding causes of death or treatment discontinuation. Some relevant information are missing, such as comorbidities and HPV tumour status, type of surgery, occurrence of second cancer, long-term functional recovery (tracheotomy dependence, gastrostomy).

Lack of a standardized evaluation of the response to TPF and after CRT, is to be highlighted. Lack of available data, either clinical or radiological response, has led to using a composite response criterion, especially for LP cohort.

Our data did not allow us to assess Laryngo-esophageal Dysfunction-free Survival, composite criteria recommended by an expert panel for laryngeal preservation trials. Events are death, local relapse, total or partial laryngectomy, tracheotomy at 2 years or later, or feeding tube at 2 years or later.

Conclusion

This cohort study suggests that TPF in frontline chemotherapy out of clinical trials is still effective, despite its poor feasibility. Toxicity is significant, with a high rate of death on chemotherapy. On the other hand, indications for TPF ICT are not strongly validated.

Studies comparing TPF induction chemotherapy to radiochemotherapy were conducted before development of IMRT in radiotherapy, or even Taxanes. To update these data, we are awaiting the results of SALTORL international multicenter trial in resectable laryngeal tumors, comparing cisplatin CRT to a LP protocol with TPF 3-cures, followed by radiotherapy alone in responders(30). At this time, benefit of a treatment associated with post-induction radiotherapy and role of Cetuximab have not been defined.

Prospect of improving survival while reducing treatment's toxicity is now based on immunotherapy, which has proven beeing effective for metastatic HNSCC(31). A phase 1 trial is ongoing, to evaluate safety of Durvalumab in combination with TPF ICT(32). The GORTEC recently published safety data for combination of Avelumab and Cetuximab with radiotherapy in locally advanced unresectable tumors, in phase III REACH trial(33). Study is closed and we are awaiting efficacy results(34). The MK-3475-689 phase III trial, still in progress, is evaluating Pembrolizumab in a neo-adjuvant setting prior to surgery for locally advanced tumors(35).

To conclude, data from a cohort of patients treated with TPF highlights the lack of robust recommendations based on recent studies, regarding TPF induction chemotherapy for locally advanced HNSCC. Although TPF is better validated for laryngeal preservation, treatment and assessment modalities remains heterogeneous. We hope that ongoing and future studies will provide answers to the many questions still open, and would improve both survival and functional preservation for patients.

Acknowledgments

Thanks to the clinical research departments of the Brest University Hospital, the Eugène Marquis Center in Rennes, and the Institut de Cancérologie de l'Ouest in Nantes, for their involvement in this project.

We especially thank Dr Julien Edeline for his support in statistical analysis, Hubert de Jacquelin and Charles Goislard for their kind and careful review.

The autors have no conflicts of interest to declare.

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List of tables

Table 1. Baseline characteristics of patients treated with TPF chemotherapy

Sex (N, %)		
Male	109	84,5
Female	20	15,5
Age (mean, range)	59 y	26 - 75
Center (N, %)		
Brest	7	5,4
Nantes	104	80,6
Rennes	18	13,9
Smoking (N, %)		
Active	69	53,5
Stopped	44	34,1
No	12	9,3
Chronic alcoholic intoxication (N, %)		
Active	50	38,8
Stopped	34	29,4
No	41	31,8
OMS Performans status (N, %)		
0	75	58,1
1	42	32,6
2	7	5,4
Site of primary tumor (N, %)		
Hypopharynx	44	34,1
Larynx glottic	14	10,8
Larynx sus glottic	20	15,5
Oropharynx	30	23,3
Oral cavity	12	9,3
Others *	9	7,0
Stage of primary tumor (N, %)		
T1	1	0,8
T2	20	15,5
T3	61	47,3
T4	45	34,8

Tx	2	1,5
Node stage (N, %)		
N0	29	22,5
N1	13	10,1
N2a	9	7
N2b	22	17,1
N2c	32	24,8
N3	24	18,6
Metastatic status (N,%)		
M0	121	93.8
M1	8	6.2

* Others sites: cup syndrome (2), maxillary sinus (2), ethmoidal sinus (1), sphenoidal sinus (2), nose (2)

Table 2. TPF: Dose modification and number of cycles received.

Cycles received	**N**	**(%)**	**With dose reduction (N)**
1	18	14,0%	0
2	15	11,6%	8 (53%)
>= 3	96	74,4%	30 (31%)
Total	129	100,0%	38 (30%)

Table 3. Acute toxicity of chemotherapy.

	Grade				
	1-2	3	4	5	Grade 3 - 5
Non-hematologic adverse events (n, %)					
Nausea-vomiting	18 (14)	2 (1)	-	-	2(1)
Diarrhea	18 (14)	6 (4)	1 (1)	-	7 (5)
Asthenia	24 (19)	3 (2)	-	-	3 (2)
Neuropathie	11 (8)	-	-	-	-
Hand-foot syndrome, oedema	10 (8)	-	-	-	-
Mucositis	9 (7)	7 (5)	1 (1)	-	8 (6)
Weight loss	7 (5)	7 (5)	-	-	7 (5)
Auditive	9 (7)	-	-	-	-
Colite	-	3 (2)	2(1)	-	5 (3)
Infection	6 (5)	11 (8)	3 (2)	4 (3)	18 (14)
Renal failure	2 (1)	3 (2)	1 (1)	-	4 (3)
Hematologic adverse event (n, %)					
Anemia	4 (3)	5 (3)	1 (1)	-	4 (3)
Neutropenia	-	5 (3)	3 (2)	-	8 (6)
Febrile neutropenia	-	5 (3)	3 (2)	-	8 (6)

Table 4. Tumor characteristic in Larynx preservation sub-group.

Site of primary tumor (N, %)		
Hypopharynx	20	54
Larynx glottic	12	32
Larynx sus glottic	5	14
Stage of primary tumor (N, %)		
T2	2	5
T3	35	95
Node stage (N, %)		
N0	14	38
N1	6	16
N2a	4	11
N2b	3	8
N2c	10	27

List of figures

Figure 1. Treatment received according to response to TPF.

RCT: radio-chemotherapy, RT: radiotherapy, CT: chemotherapy, LR: Locoregional

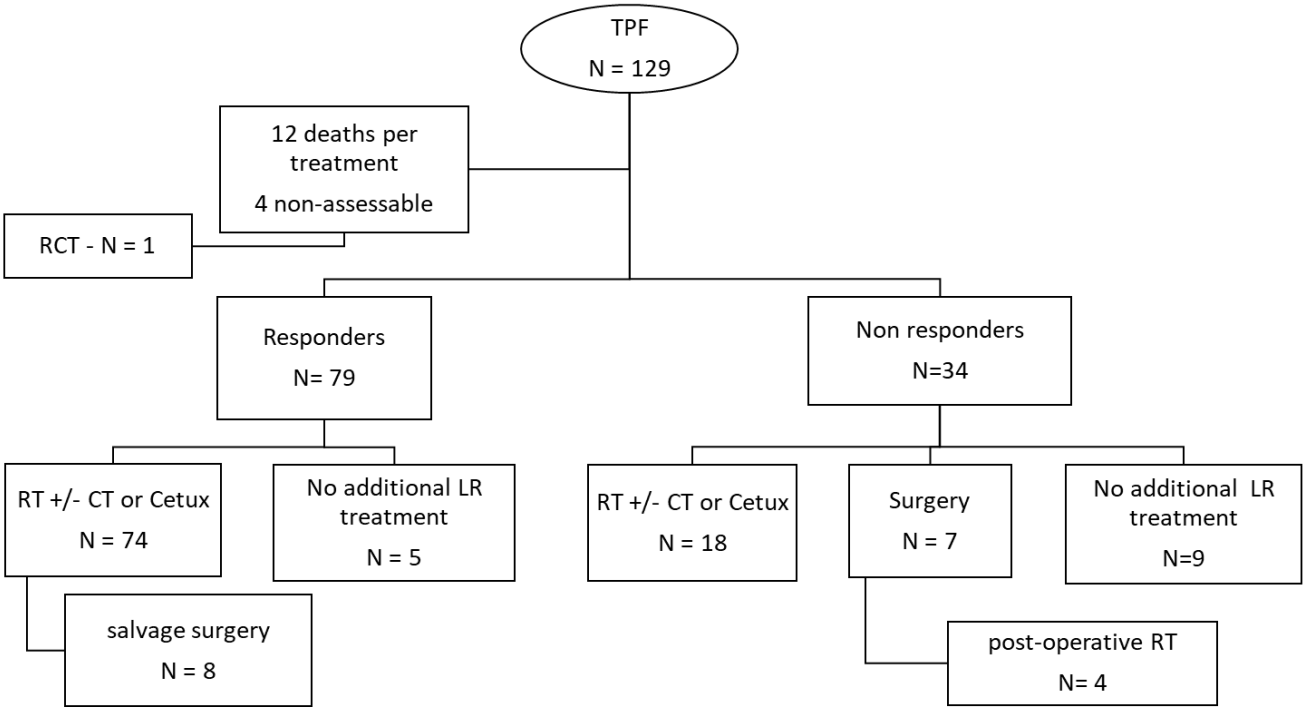


Figure 2. Overall survival (A), Recurrence or progression-free survival (B) in overall population.

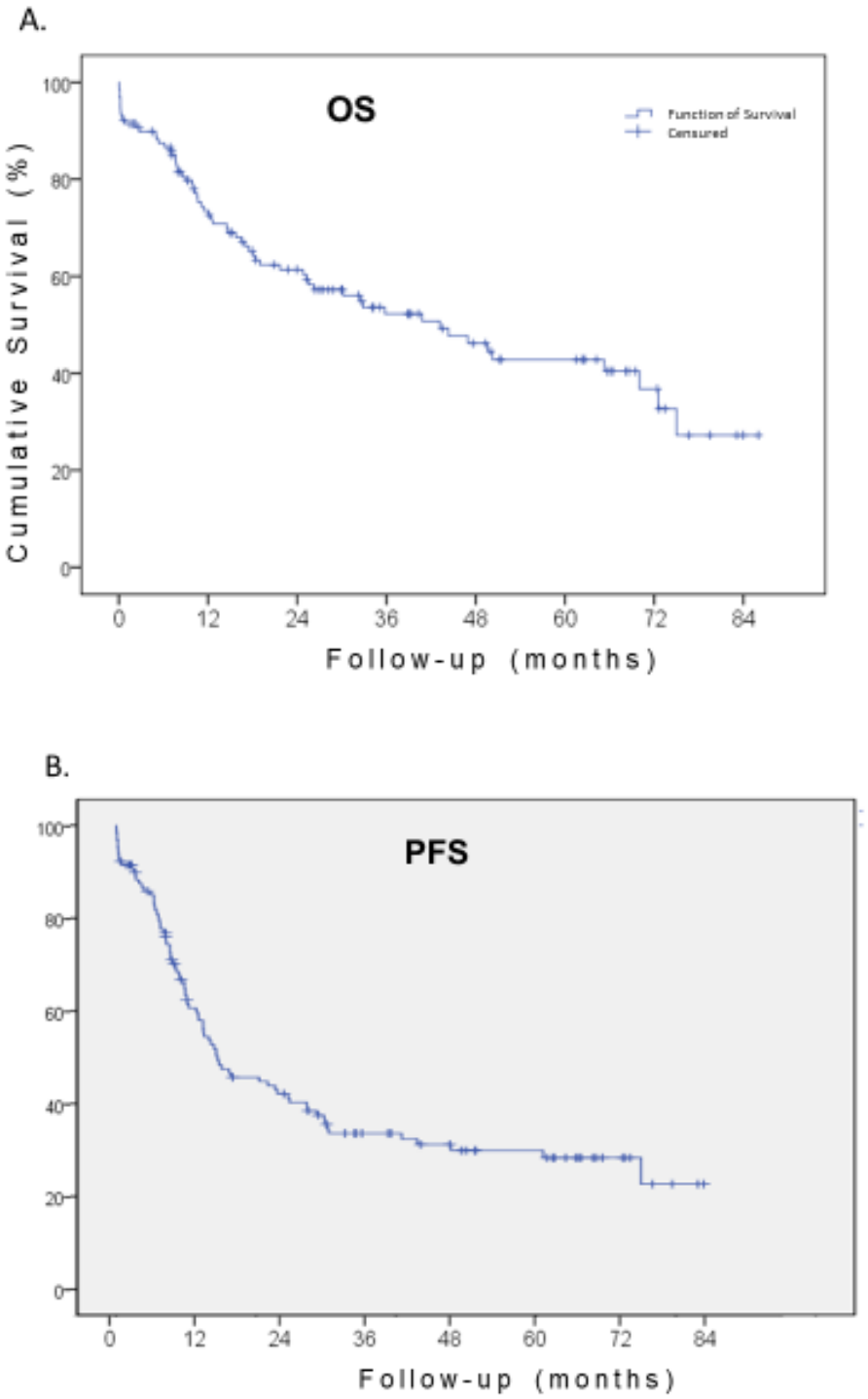


Figure 3. Loco-regional (A) and Metastatic (B) PFS in Overall Population.

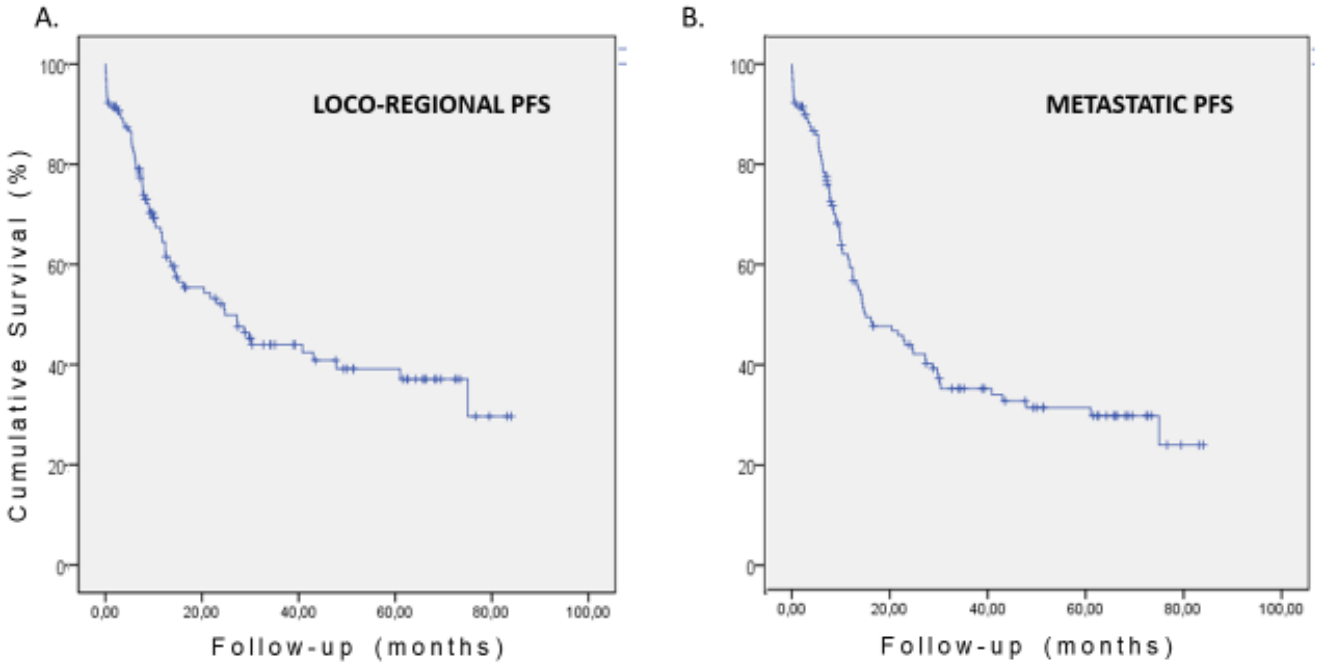


Figure 4. OS (A) and PFS (B) in patients who received complete or partial TPF treatment.

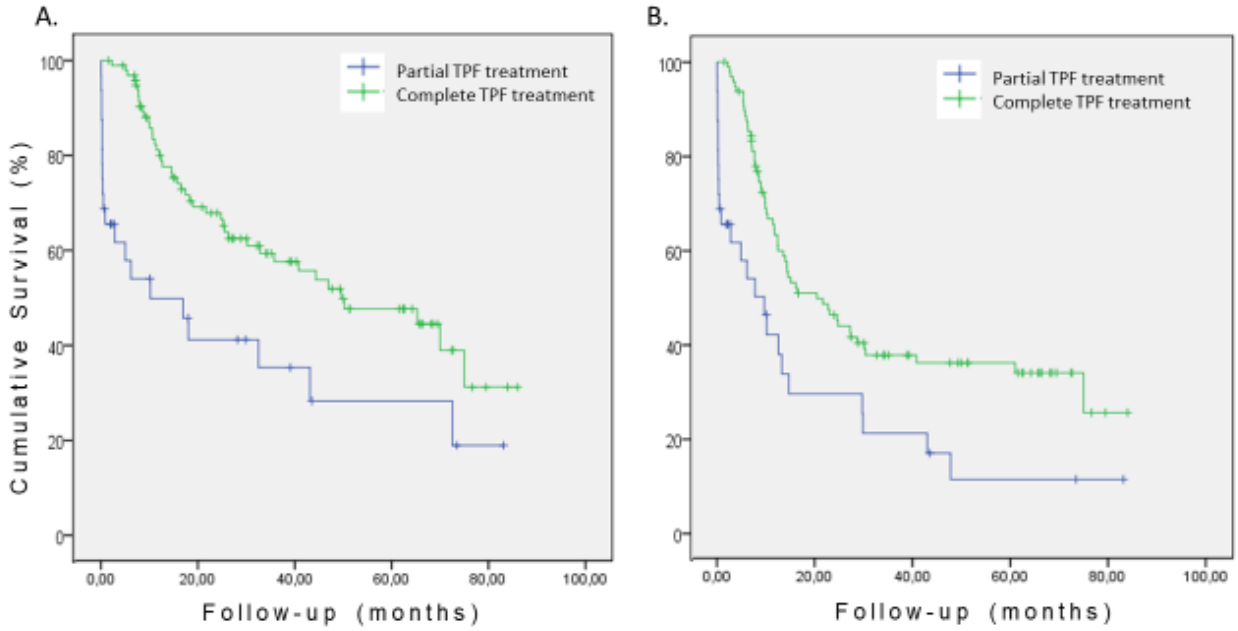


Figure 5. Overall survival in TPF responder patients and TPF non-responder patients.

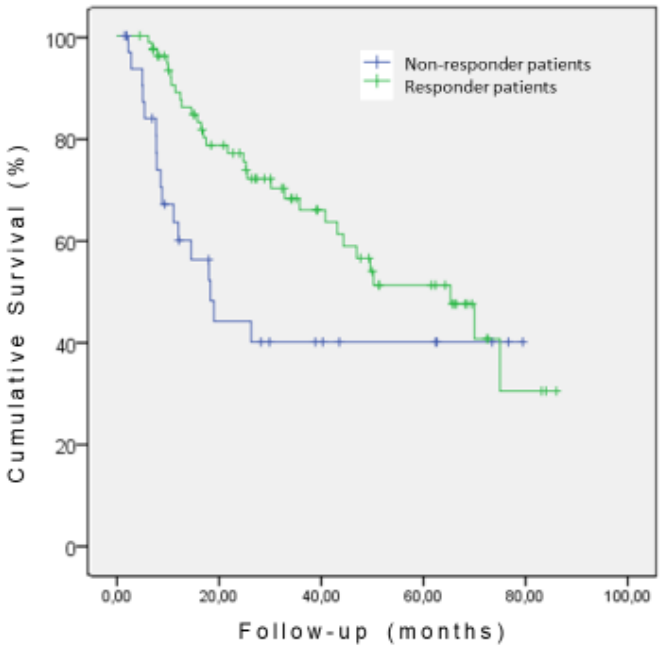


Figure 6. Treatment received after TPF, in Laryngeal preservation sub-group.

RT: Radiotherapy, CT: Chemotherapy, CRT: Concomitant chemoradiotherapy, LR: Locoregional.

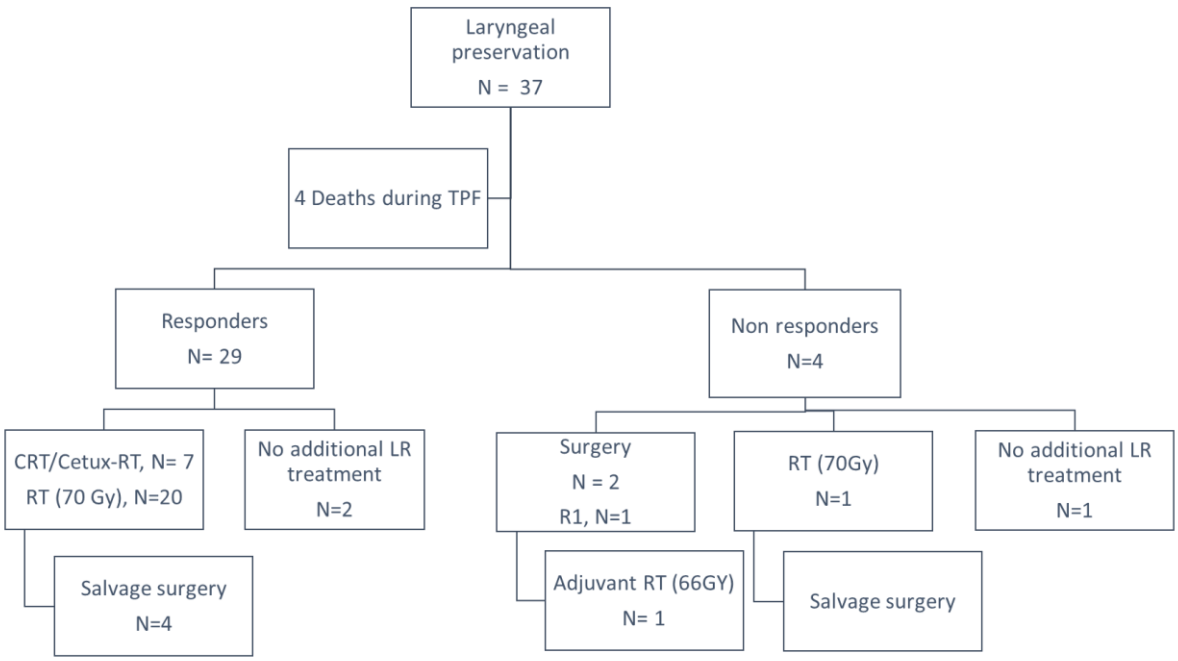
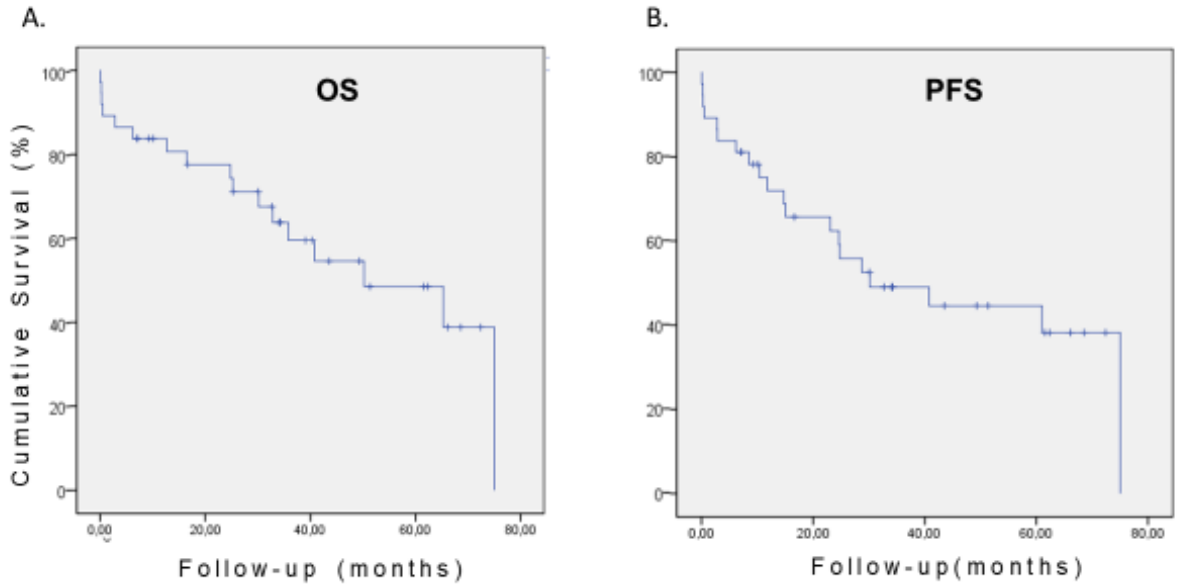


Figure 7. Overall survival (A) and Disease or Progression-free survival (B) in Laryngeal preservation population.

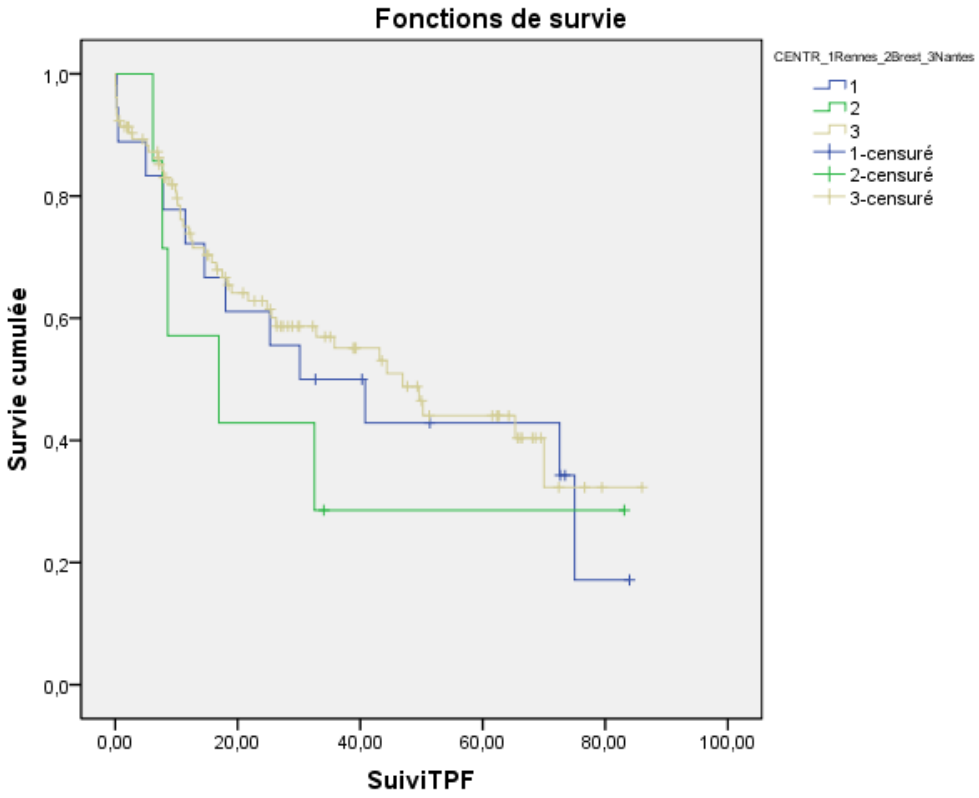


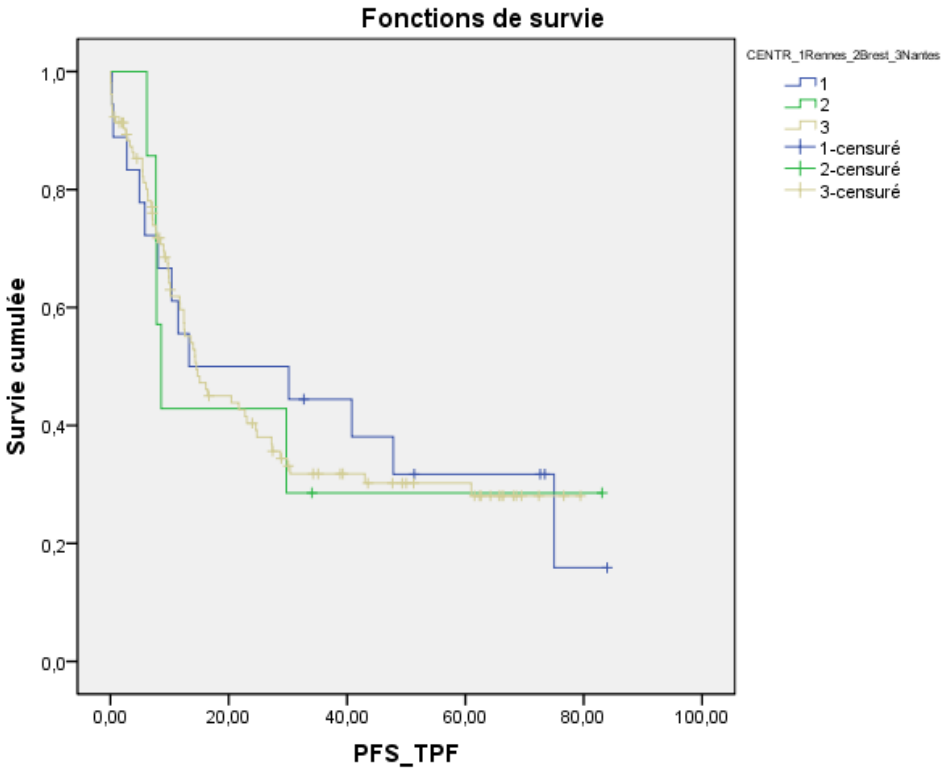
Supplementary material

Supplementary table 1: Baseline characteristics of patients who died during TPF

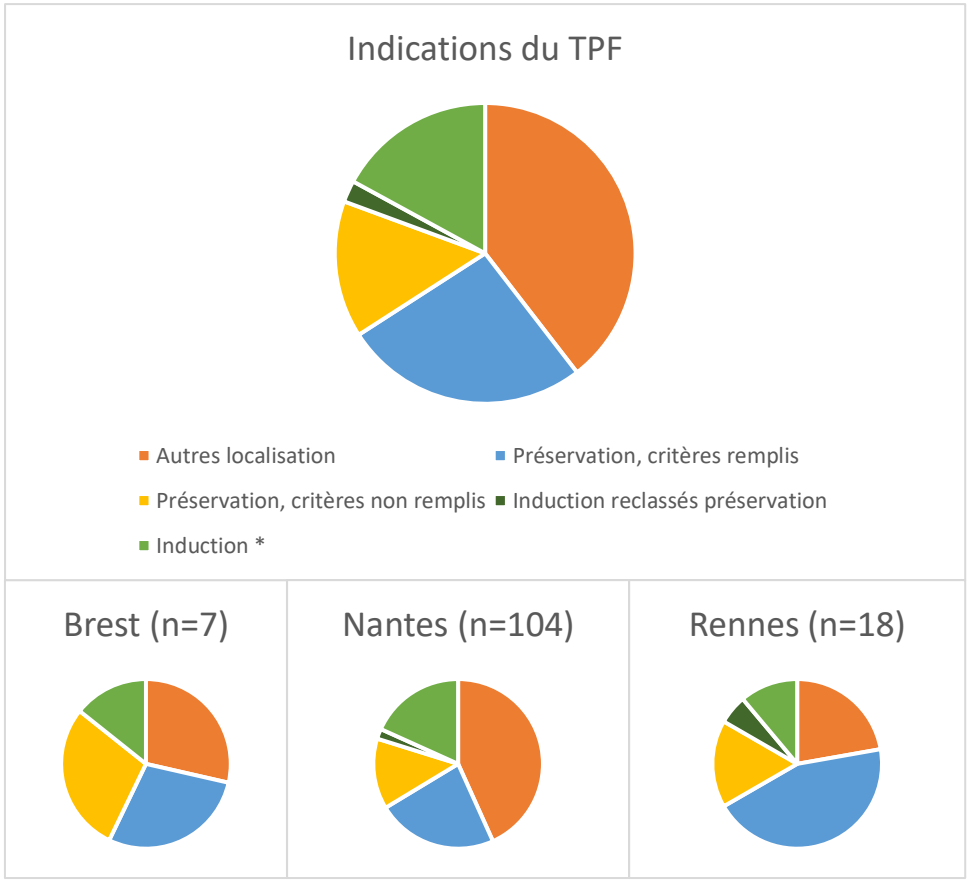
	N (total N=16)
Age	
<50 years	3
50-65 years	9
> 65 years	4
Performance status	
0	11
2	3
Center	
Nantes	14
Rennes	2
Localization	
Larynx - Hypopharynx	7
Including laryngeal preservation	3
Others	9
Toxic addiction	
Active smoking	9
Active chronic alcoholic intoxication	7
Both tobacco and alcoholic chronic intoxication	4

Supplementary figure 1: OS and PFS by Center

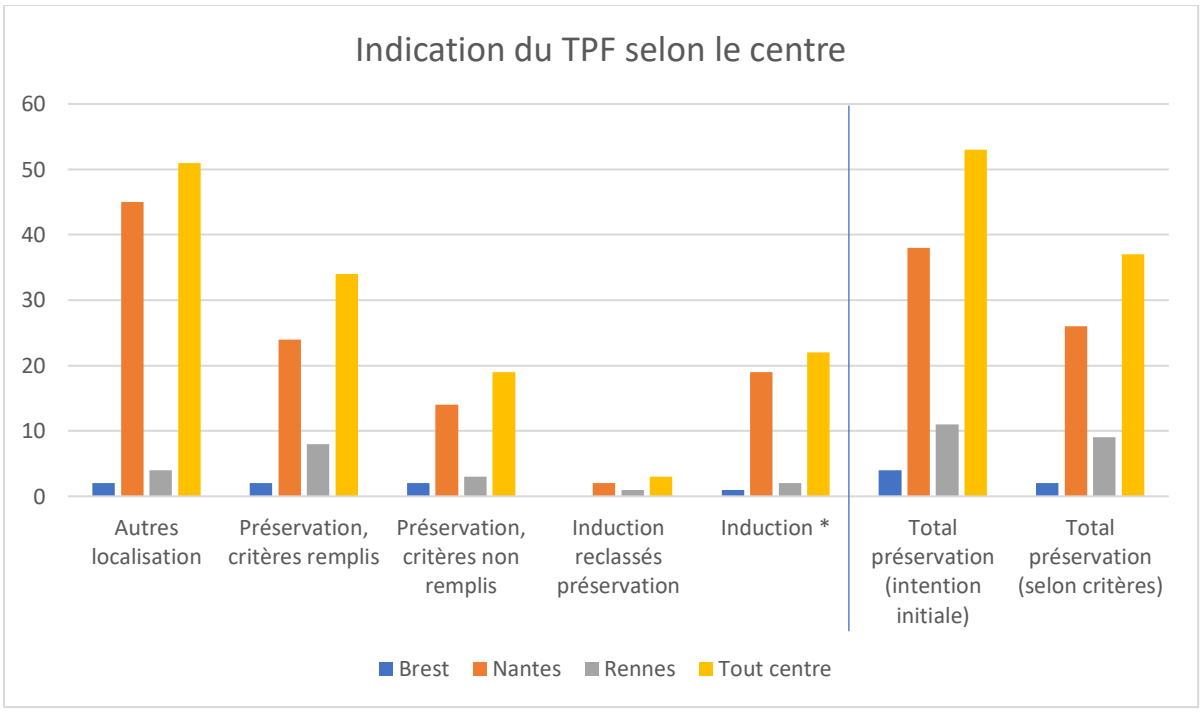




Supplementary figure 2: TPF indication and distribution according to the centers

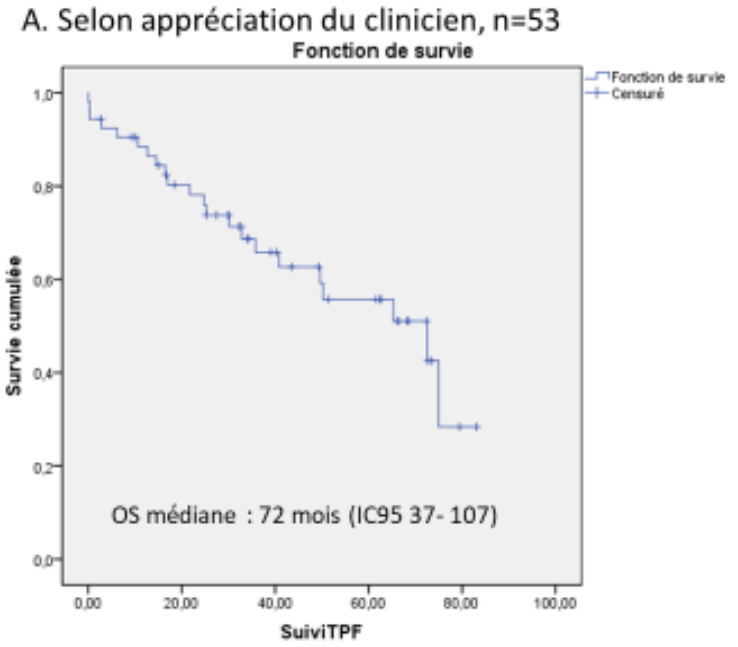


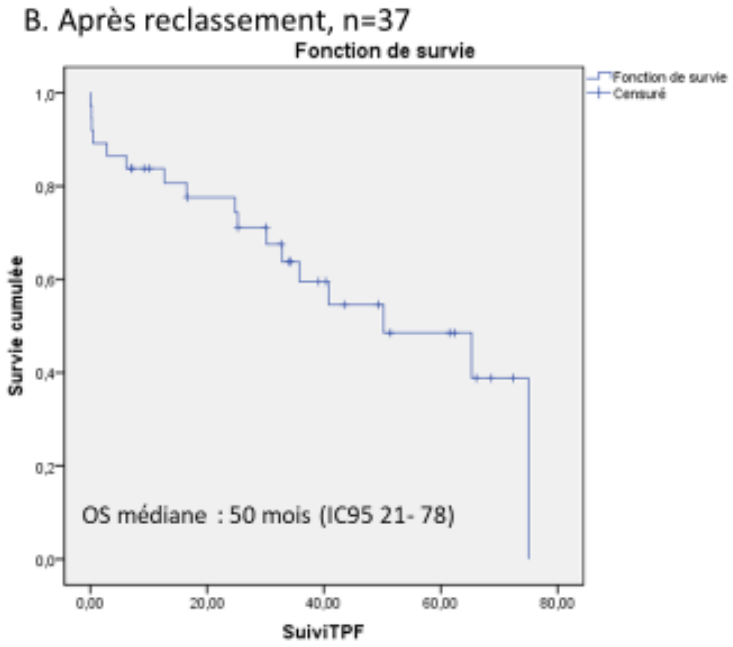
* Induction : localement avancés non opérables et/ou métastatique et/ ou refus de chirurgie



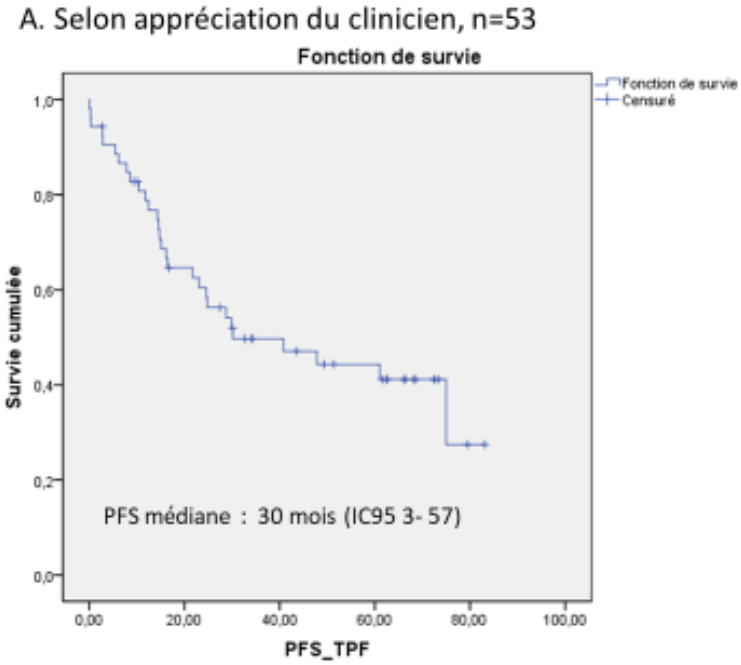
Supplementary figure 3: Survival according to indication, as describe by clinician or investigator.

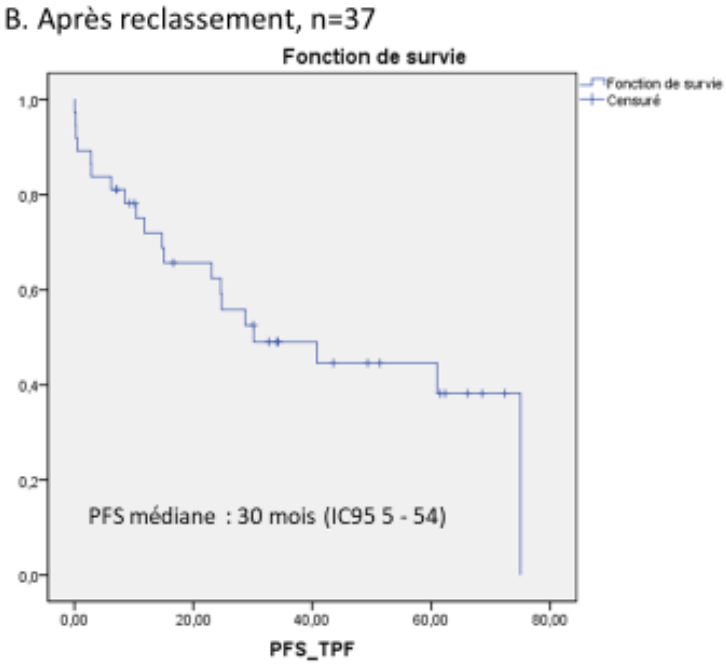
1. Overall Survival (OS)





2. Recurrence or Progression free – survival (PFS)





U.F.R. DE **MEDECINE** DE RENNES

N° 40-2021-

GOISLARD de MONSABERT, Camille – épouse CONNEN

Faisabilité, tolérance et efficacité du Taxotère-Cisplatine-5FU (TPF) dans la stratégie de prise en charge des carcinomes épidermoïdes de la tête et du cou, en Bretagne et Pays de Loire.

43 feuilles., 10 graphiques., 5 tableaux., 30 cm.-

Thèse : (Médecine) ; Rennes 1; 2021 ; N° .

Résumé français

CONTEXTE – Pour le traitement des carcinomes épidermoïdes de la tête et du cou (CETEC) localement avancés, la chimiothérapie a montré un bénéfice en survie, qu'elle soit concomitante ou en induction d'une radiothérapie. Si l'association de Cisplatine-Docetaxel-5FU (TPF) est le traitement de référence en induction, ses indications ne sont pas validées aujourd'hui en dehors de la préservation laryngée (PL) pour les patients relevant d'une laryngectomie totale (LT).

METHODE – Nous rapportons les données d'une cohorte multicentrique de patients traités par TPF entre 2012 et 2016, en première ligne d'un CETEC localement avancé, non résécables ou relevant d'une LT et candidats à un protocole de PL. Le critère principal de jugement était la faisabilité du traitement, les critères secondaires : la tolérance et l'efficacité. L'analyse est conduite en population totale et dans un sous-groupe de patients relevant d'une PL.

RESULTATS – Sur 129 patients, 96 (74.4%) ont reçu au moins 3 cycles de TPF, dont 66 (51.1%) sans réduction de dose. Pendant le TPF, 12 patients sont décédés et 4 perdus de vue. 38% des patients ont subi un effet secondaire de grade 3 à 5. Le taux de réponse après TPF était de 61.2%, la survie globale médiane de 43.2 mois (IC95%, 26.4 - 59.9) et la survie médiane sans récidive de 14.5 mois (IC95 7.8 - 21.3). Dans le sous-groupe PL, on rapporte 78% de taux de réponse, 35% de survie avec larynx fonctionnel à 3 ans et une survie globale médiane de 50.2 mois (IC95%, 21 – 78).

CONCLUSION – La chimiothérapie d'induction par TPF réalisée hors essai thérapeutique garde une efficacité satisfaisante malgré une difficile faisabilité. Il est important de considérer la lourde toxicité de ce traitement qui n'a pas fait ses preuves hors PL.

Rubrique de classement :	[ONCOLOGIE]
Mots-clés :	Chimiothérapie anticancéreuse – Traitement néo-adjuvant – Préservation laryngée – Carcinome épidermoïde – Carcinome de la tête et du cou – Chimiothérapie d'induction – Radiothérapie – Chirurgie – Etude rétrospective
Mots-clés anglais MeSH :	Adult - Antineoplasic Agents - Antineoplastic Combined Chemotherapy Protocols - Carcinoma, Squamous Cell – Cetuximab - Chemoradiotherapy, Adjuvant – Cisplatin - Cohort study – Fluorouracil - Head and Neck Neoplasms – Humans - Induction Chemotherapy - Laryngeal Neoplasms - Larynx preservation - Organ Sparing Treatments – Radiotherapy – Real life data - Retrospective Study – Speech – Surgery– Taxanes

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