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Post-operative T1-2 N2b oropharyngeal squamous cell carcinoma: loco-regional control after ipsilateral or bilateral neck radiation

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UNIVERSITÉ de CAEN NORMANDIE

UFR SANTÉ

FACULTÉ de MÉDECINE

Année 2020/2021

THÈSE POUR L'OBTENTION

DU GRADE DE DOCTEUR EN MÉDECINE

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par

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Née le 13/06/1993 à AURAY

TITRE DE LA THÈSE :

Cancer de l'oropharynx T1-2 N2b opéré : contrôle loco-régional après radiothérapie unilatérale ou bilatérale

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Abréviations

TORS : Transoral Robotic Surgery

PRISMA : Preferred Reporting Items for Systematic Reviews and Meta-Analyses

BOT : base of the tongue

3D CRT : Three-Dimensional Conformal Radiation Therapy

IMRT : Intensity modulated radiotherapy

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Introduction

Les cancers oropharyngés sont en augmentation dans la population générale, touchant des patients de plus en plus jeunes, sans facteur de risque connu et sans autre comorbidité, avec une espérance de vie longue en cas de bonne réponse au traitement initial. Ces modifications épidémiologiques sont en lien avec l'augmentation de l'incidence de cas d'infection à HPV. Il est donc d'autant plus important de traiter efficacement en limitant au mieux les toxicités liées au traitement, qui peuvent avoir un retentissement sur la qualité de vie des patients. Alors que la radiothérapie cervicale bilatérale était le traitement standard, l'irradiation cervicale unilatérale a été utilisée. Elle a été validée pour des petits stades d'extension tumorale et ganglionnaire dès 2012. En effet, l'American Society of Clinical Oncology avait alors permis le traitement par radiothérapie unilatérale pour les cancers latéralisés, c'est-à-dire avec extension au palais mou inférieure à un centimètre et absence d'extension à la base de langue. Les stades concernés sont alors T1-T2 N0-N2a. Il s'agit de recommandations avec un faible niveau de preuve et donc sous conditions d'une discussion avec le patient concernant le risque de récidive. En 2017, l'American Society for Radiation Oncology modifie ces recommandations en incluant le stade N2b.(1) Cependant en pratique clinique de routine, l'irradiation cervicale unilatérale de ce stade aux présentations multiples, est très peu réalisée. Il s'agit donc de trouver un équilibre entre les toxicités radio-induites par la radiothérapie cervicale bilatérale et le risque de récidive ganglionnaire controlatérale en cas d'irradiation unilatérale. Il a tout d'abord été réalisé un travail de bibliographie afin de rassembler l'ensemble des connaissances sur le sujet existant dans la littérature afin de guider au mieux les études à venir. Dans un second temps, une étude observationnelle rétrospective au sein du centre François Baclesse a permis d'identifier les patients traités par irradiation unilatérale ou bilatérale, d'extraire, collecter et analyser les données relatives à ces deux populations pour évaluer la survenue d'une récurrence ganglionnaire cervicale controlatérale.

Systematic review : Unilateral radiotherapy in oropharyngeal cancer focusing on N2b disease : contralateral recurrence and toxicity

Introduction

Epidemiology of oropharyngeal cancer, especially in tonsillar fossa area is changing through the last decades. We indeed observe an increasing in the american and lately european population.(2) Patients profiles are changing, they are younger and potential long terms survivors, especially in the HPV positive area. (3) It has never been so important to find a balance between the risk of recurrence and toxicities especially late toxicities which will have a major impact on quality of life.

Nowadays, several treatment options exist : primary site surgery with or without Transoral Robotic Surgery (TORS), with or without ipsilateral or bilateral node dissection, surgery followed by adjuvant oncologic treatment, radiation or chemoradiation exclusively.

For now, it does not exist any randomised controlled study in the litterature concerning the treatment of the contralateral lymph node territory cN0 for patients with homolateral advanced nodal disease (≥N2b). These patients usually receive a bilateral radiotherapy to avoid contralateral recurrence and improve global survival.

Large radiation's field causes early and late toxicities. Therefore, the decision to exclude the contralateral neck from the radiation field is based on the balance between the risk of regional recurrence and expected toxicity from treatment. Decision of treatment is based on retrospective studies with limited evidence and therefore physicians experience. These studies have discrepitant results. However, some studies highlight that unilateral irradiation allows reducing toxicities while not worsening survival. The adjuvant situation is even more controversial as a few studies found pN status is an important prognostic factor to occult metastases. (4)

Current recommandations from American Society of Clinical Oncology in 2017 are « Unilateral radiotherapy may be delivered to patients with lateralized (< 1 cm of soft palate extension but without base of tongue involvement) T1-T2 N0-N2b tonsillar cancer without clinical or radiographic evidence of extracapsular extension, after careful discussion of patient preferences and the relative benefits of unilateral treatment versus the potential for contralateral nodal recurrence and subsequent salvage treatment ». Conversely, the American College of Radiology (ACR) recommended bilateral neck irradiation for tonsillar cancer with a nodal stage of N2b or greater in their 2012

guidelines.(5) It seems evident after all to develop a standardized protocol.
In this context, the aim of this review is to describe the outcomes concerning contralateral recurrence and toxicity after ipsilateral or bilateral neck radiation for patients with oropharyngeal squamous cell carcinoma already existing in the litterature. It will be a support to elaborate a prospective study comparing contralateral failure and toxicity between two populations of post-operative oropharyngeal squamous cell carcinoma T1-T2 N2b : one would receive unilateral treatment and the other one bilateral treatment.

Material and Methods

We performed a systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2015 checklist.

A- Search strategy

The National Institutes of Health « PubMed » database was searched for reliable citations published from 2000 to 2020 using the following MeSH terms and keywords : « Oropharyngeal Neoplasms » AND « Radiotherapy » AND « Neoplasm Recurrence »/« Local Recurrence » OR « Radiation injuries »/« Radiotherapy/adverse effects » OR « Lymphatic Metastasis » limiting in english publications in human. Using these terms, we identified 132 indexed references with interest.

B- Eligibility criteria

Of these 132 references, we identified 26 publications that appeared to respond to eligible criteria determined beforehand. Actually, original full-text were included if patients had oropharyngeal squamous cell carcinoma treated with unilateral and/or bilateral neck radiation in adjuvant or definitive treatment. We took into consideration all T stages and N stages but made a focus on N2b disease. We considered the studies which took contralateral neck recurrence into account.

C- Outcome mesures

Primary endpoint is contralateral recurrence in patients with N2b disease and secondary endpoint is toxicities induced by radiation.

D- Data extraction

Data of interest were :

- Publication year
- Study period of time and median time to follow-up
- Type : retrospective, prospective, multi or unicenter
- Inclusion and exclusion criteria
- Population : number, stages, HPV status
- Staging techniques
- Treatment techniques
- Outcomes : contralateral recurrence, overall survival, toxicities

Results

A- Contralateral Recurrences

1- Type of study

All studies are retrospective except the one by Rusthoven et al which is a prospective cohort of 20 patients from 2009.(6) In addition, only one study is multicentric : Kim et al.(7) Litterature's data has therefore not an high level of evidence.

2- Population

a- Cohort's size

The sample size widely varies between studies, ranging from 20 to 427 assessed patients. Cases of contralateral neck recurrence were mostly observed in larger studies although smaller studies did not often report contralateral neck recurrence.

b- Age

Median age of patients in the studies was similar, around 55 years. In the study by Huang, a statistically significantly older median age was found as compared with the HPV negative group (median age : 69 versus 57 years, p<0,001).(8) We know indeed that HPV positive population is younger than HPV negative population.(3) In Al Mamgani et al, they observed population was younger throughout the study period supposing HPV positive patients were increasing.(9)

In the study by Liu, we noticed that in the group lateralized tumors, patients treated with bilateral treatment were younger than those treated with ipsilateral treatment suggesting physicians are influenced by patient's age and would favour safest treatment. We could discuss this way to treat regarding a study which highlighted cancer induced by

radiation.(10)

c- Gender

In all studies, more than 70% of patients were male except in Cerezo et al (60%) and Vergeer et al (50%) studies.(11,12)

d- HPV status

HPV status/p16 status are not systematically determined. It is particularly important in our review to mention HPV status regarding the fact that small tumors with advanced nodal disease is specifically the phenotype of these tumors. Also, outcomes are known to be different in this specific population. In fact, we know response to treatment is better in HPV positive population.(13) Ye et al and Huang et al, compared outcomes in HPV positive and negative population.(8,14) The proportion of HPV positive patients in Huang et al was 71%. The proportion of p16+ in Ye et al was 78%. Some other studies have a population with an high proportion of HPV positive patients: Dan et al (44%), Maskell et al (92,5%), or p16+ as Gottumakala et al (74%) and Rackley et al (63%).(15–18)

e- Smoking history

Smoking status is usually registered in studies concerning head and neck cancer. Most of the studies notified smoking history, (based on report by patients) as former smokers, never smokers, current smokers or according to pack-year.

Studies with an high proportion of HPV positive patients have also high proportion of non or former smokers. Indeed, 36% of the population never smoked and 25% are former smokers in Rackley et al ; 26,4% and 49,1% respectively in Maskell et al, 44% and 44% respectively in Gottumakala et al.(16–18) Chronowski et al is also a study with an high proportion of non smokers as 46% never smoked but data concerning HPV status was mostly not available.(19) It suggests HPV positive patients could have been a significant part of this cohort. In Dan et al, conversely, 44% were HPV positive but 67% of the population smoked >10 pack-year.(15) As other studies registered an higher score of current or former smokers, it can be supposed that their population was mainly HPV negative.

f- Alcohol history

Only two studies picked alcohol data. Huang et al observed an excessive history of alcohol drinking in 59% in HPV negative group against only 26% in HPV positive group which was not significant.(8) In Wirtz et al, 28% of the population drank excessively,

25,9% had not known status and 37% never drank.(20) These 37% of patients could correspond to the HPV positive part of the population especially since 39% of the population never smoked or had unknown smoking status. Indeed, this corresponds to the phenotype of HPV positive status.(3) And HPV status was mostly unknown (73%) in this study.

3- Primary site

a- Localisation

All studies are focusing on squamous cell carcinoma of the tonsil except in Jensen et al (only 70% are), Cerezo et al, Vergeer et al (14% squamous cell carcinoma of the tonsil), Kagei et al and Wirtz et al whose 52% of the population correspond to oropharyngeal carcinoma.(11,12,20–22)

b- Tumor extension

1- Lateralization

Studies selected patients with lateralized tumors. According to different studies well lateralized means not crossing midline and furthermore >1cm to midline, no base of the tongue (BOT) or soft palate involvement or extension <1cm or <1/3, no extension to the posterior tonsillar fossa or posterior pharyngeal wall. Liu et al made a focus on lateralization.(23) They divided lateralized and non lateralized in two groups of 78 and 72 patients in an overall population of 167. In the first group, 47 patients were treated unilaterally whereas in the second group, only 7 patients received unilateral radiation. 18 patients had a loco-regional failure in the non lateralized group against 10 in the lateralized group (not mentioned if significant or not). As none of the lateralized patients treated with unilateral treatment failed in the contralateral neck, despite that 33% of them were N2 or N3, it could be suggested that primary tumor laterality may be a more important predictive factor than nodal disease for contralateral failure. Lynch et al also selected well lateralized patients, but 5% of the population had lateral soft palate involvement.(24) 28% of this subgroup failed in the contralateral neck approving this assertion. Therefore, Cerezo et al had a very lateralized population with precise exclusion criteria (<1cm of medial extension to the soft palate or the BOT, retromolar trigone, lateral alveolar ridge, cheek mucosa or lateral border of the tongue) and small stages (T1-T2 only) and none of the 20 patients failed in the contralateral neck.(11) Also, in Jensen et al 67% of the cohort of 139 patients had involvement of midline structures. (21) Most of patients (92%) who had involvement of midline structures received bilateral treatment. Patients eligible for ipsilateral treatment were selected only after primary tumor

characteristics and not nodal disease. For Jensen et al, there is no doubt that primary tumour extension to midline structures is the most important factor to consider before planning ipsilateral treatment since no patient without involvement of midline structures failed in the contralateral neck. Similarly, according to O'Sullivan, a high proportion (130/228) of patients had adjacent structures involvement : lateral, middle or medial palate/BOT involvement.(25) The lymph node failure occurred in one case in ipsilateral neck and one in contralateral neck for middle BOT involvement, 10 (26%) and 2(5%) for lateral BOT involvement. In case of palate involvement, 24%, 24% and 17% of ipsilateral neck failures were observed for respectively medial, middle and lateral involvement and 12%, 7% and 0% of contralateral neck failure. In the subgroup with both BOT and soft palate involvement, 21% failed in the contralateral neck. Contralateral recurrences are significantly influenced by these involvements. They recommend to use safely unilateral radiation for tumors confined to the mucosa and with ≤1cm of medial extension, reasonably when there is small extension to the soft palate or BOT. Anatomical localisation as tongue are known to have higher frequency of midline crossing lymphatic vessels and muscular contractions accelerates the flow. This highlights that tumors with extension to midline structures have ability to metastasize.(26,27) Thus, Chronowski et al excluded patients with BOT involvement in their study, as did Koo. In fact, they both reported great outcomes concerning contralateral recurrences, especially Koo who did not observed any failure.(19,28)

Vergeer et al had one of the highest rate of contralateral recurrence of the recensed publications, yet his study deals with a population who is not as well lateralized as the only exclusion factor is « crossing midline ».(12)

2- T stage

T1	≤2cm
T2	>2cm and ≤4cm
T3	>4cm or extension to lingual side of epiglottis
T4a	extension to mandible, hard palate, lingual muscles, medial pterygoid muscle or larynx
T4b	extension to around carotid artery, lateral pterygoid muscle, skull base, nasopharynx or pterygoid apophysis

Table 1 : 8th TNM : T classification for oropharyngeal cancer

Concerning the tumor extension, Lim et al highlighted advanced T stage, regardless of lateralization metastasizes more than small T stages (T1-T2 vs T3-T4 : p<0,05).(4) Olzowy et al also showed carcinomas of the tonsillar fossa starting with a T2 classification had an high frequency of bilateral metastases.(29) In that way some studies selected only patients with small T1 or T2 stages as Kennedy et al, Chronowski et al, Huang et al, Cerezo et al and Kim et al. Others had advanced T stages as Gottumakala et al whose population of 34 patients had 6% of T3 and 3%of T4 or in Wirtz et al whose 21,4% of the cohort was T3 or T4. However, patients who failed in the contralateral neck were T1 or T2 except one patient who was T4. In Jensen et al 13% and 21% of patients were T4 and T3 respectively. O'Sullivan et al had 37 patients T3-T4 in a population of 228 patients, 14 in the Kagei's cohort of 32 patients. Jackson et al also conducted a study whose T3 and T4 stages were well represented as 33 and 19 patients respectively were treated bilateraly and 52 and 9 unilaterally in a population of 271 patients.(30)

Tumor extension including lateralization and T stage is major prognostic factor to lymph node recurrence.

4- Nodal extension

N1	unique lymph node ipsilateral ≤3cm
N2a	unique lymph node ipsilateral >3cm and ≤6cm
N2b	multiple lymph nodes ipsilateral ≤6cm
N2c	bilateral or contralateral lymph nodes ≤6cm
N3a	lymph node >6cm
N3b	extra capsular extension

Table 2 : 8th TNM : N classification for oropharyngeal cancer

Nodal involvement was more or less extended from one an other studies. We made a focus here on N2b disease as this stage is challenging regarding the plurality of its presentation.

a- Number of node(s) involved

Cerezo et al excluded patients with more than 2 involved nodes >2cm. In Gottumakala et al as well, the number of nodes involved is notified. 41% had one involved node, 29% two and 29% had several nodes involved (3, 4, 5 or 12). In Wirtz et al they attested number

of involved nodes is a prognostic factor associated with contralateral recurrence and so pN2b and pN3 should receive bilateral treatment as in Lynch et al. However, there is no significant association with contralateral recurrence highlighted in the study. According to Vergeer et al, the number of nodes involved in the ipsilateral neck was, in the univariate and multivariate analyses, the only prognostic factor of contralateral recurrence.
Regarding to Cerezo et al and Gottumakala et al, number of involved nodes is a criterion associated for an increased risk for recurrence as it has already been demonstrated.

b- Level of involvement

According to Chronowski et al in 102 patients, we found 22 N2b who had nodes involved only in level II or III. In fact, anatomical studies had already demonstrated level II and III are the first involved levels for oropharyngeal cancer.(27,31)

c- N2b disease

An interesting proportion of studies in this review had a high rate of N2b disease. In Kennedy's study, a high proportion of patients had an advanced nodal disease since 34% out of 76 were N2b.(32) We noticed patients in the cohort had lateralized primary tumor and small T stage suggesting again that T extension is a higher risk than N disease to fail. N2b stage represented 56% of Gottumakala's population and no patient were N0. Kim et al and Maskell et al are both focusing on N2b stage. N2b represents most of the population (62% of all population, 45% for subgroup unilateral and 71% for subgroup bilateral) in Kim et al. In Maskell's study, 28/53 are N2b and treated unilaterally and the rate of relapse in this subgroup was significantly higher so they perform a second study with N2b stages only treated with bilateral treatment and observe no recurrence here. Differences between the two groups are developped lately in the review. In Dan et al as well, almost half (31/61) of the 61 patients of the population treated with unilateral radiotherapy are N2b. In Rackley et al also, N2b represented a major part of the population as 59% in a population of 81 patients. This is one of the largest cohort of N2b disease. Furthermore, 27% of the population had extra capsular extension and 45% had nodes involved >3cm. None of the patients failed in the contralateral neck in this surgical cohort of lateralized and T1-T2 population contributing to promote unilateral radiation despite these criteria of advanced nodal disease.
In Lynch et al also, 40% of the population was N2b and all patients received unilateral radiation. Similarly to Lynch et al concerning the outcomes, Wirtz et al, in a cohort of 197 patients treated unilaterally, counted a proportion of 34,6% patients N2b.
On the contrary, some studies had few cases of N2b disease as in Al-Mamgani et al

whose N2b represented only 17% of this ipsilaterally treated cohort of 185 patients. The same proportion of N2b disease is found in Vergeer et al : 22% (27 patients) of the cohort of 123 patients. And they were all treated with unilateral radiation as well. Liu et al, had also a proportion of 16% (27/167 patients) who were staged N2b and 4 of them only were treated with ipsilateral treatment. In Jackson et al, only 23 patients (8,4%) were N2a, N2b or N3 treated with ipsilateral treatment.

Dealing with the study of Huang, in the ipsilateral cohort of 96 patients, 8 were N2b. In these 8 patients, it is interesting to notice : one patient had 2 nodes involved in one level, 2 patients had 2 nodes involved in 2 levels, 4 patients had 3 nodes involved in 2 levels and 1 patient, 7 nodes in 2 levels. But N2b disease usually received bilateral treatment as there were 193 patients in the bilaterally treated population of 281 patients. 170 of them were HPV positive knowing HPV positive population treated with bilateral radiation had 240 patients. We know in fact HPV positive population has higher prevalence of N+.(33)

In Ye et al, in the p16+ population of 142 patients, 11 N2b patients were treated with unilateral radiation and 36 with bilateral radiation.

We do not have information concerning N2b stage in Kagei et al and Jensen et al.

d- Extra capsular extension

The statistical analysis found in Lynch et al extra capsular extension as prognostic factor of failure. Extra capsular extension concerned 22% of the population. In Wirtz et al also 23,4% of extra capsular extension was found after ipsilateral neck dissection. Lynch et al suggested so to treat with bilateral treatment patients with extra capsular extension. They mentioned in Al mamgani et al that 18% of the 80 neck dissection realised had extra capsular extension but it was not analysed in the statistical analysis so not proved as a prognostic factor of failure. In Vergeer et al, it is interesting to notice that 14 patients so 52% of N2b patients has extranodal spread. Extra nodal spread was not statistically influencing contralateral recurrence but we may suggest that association of involved node and extra nodal spread is a criteria of recurrence as demonstrated in Bernier.(34)

5- Imaging

a- Techniques

Imaging techniques were not homogeneous between studies.

Certain used techniques which are not recommanded anymore in oropharyngeal's cancer as Rackley et al which practiced partly echography to stage the neck.(35) Vergeer et al did not practice imaging of the contralateral neck for 14 patients in a cohort of 123 so the

contralateral recurrence could have been contralateral disease not detected at diagnosis. Most of the studies followed recommandations : head and neck CT, chest CT and MRI +/- FDG-PET scan. In fact recently FDG-PET scan became a very reliable technique to detect occult metastases.(35–38) It improves nodal staging and would assists physicians to select eligible patients for unilateral radiation to avoid the lack of treatment to the contralateral neck in case of occult metastases. Thereby Al Mamgani et al, Kim et al and Maskell et al used FDG-PET scan only when staging was challenging. Rusthoven et al, Hu et al (39) and Gottumakala et al used FDG-PET scan for all patients. Others used FDG-PET scan for most of the population as Dan et al (51/61 patients had a FDG-PET scan) and Cho et al (32/49). Nevertheless, Dan et al found 1/61 contralateral recurrence at only 6 months after treatment which could have been a contralateral involved node not detected at diagnosis. As well, Huang et al had two contralateral relapses at 6 months to treatment. Unfortunately they used FDG-PET scan occasionnaly after 2013, so we attest that these failures could have been nodal disease at diagnosis.

Chin et al used FDG-PET scan only after 2000, Liu et al only for 31 patients in a 167 patients cohort.

No information about staging were found in Kennedy et al, Kagei et al and Chronowski et al. Unfortunately they found in Chronowski et al 2 contralateral recurrences less than a year after treatment and without knowledges concerning the staging's method we can't exclude the fact that it could have been occult nodal disease at diagnosis.

b- TNM

Staging was made from the 7th edition of the American Joint Committee on Cancer (AJCC) in most of the studies. We did not have the information for a limited number of studies and some of them used older edition like Liu et al which staged after the 5th edition. Vergeer et al and O'Sullivan et al staged after 1997 classification of AJCC, and Jackson et al after 1974 revised in 1987 classification.

6- Treatment

Jouhi et al is an interesting study from 2017 comparing outcomes and especially regional recurrence in a population treated either with oncologic treatment, either with surgery +/- adjuvant treatment.(40) No significant difference was observed irrespective of the treatment strategy. In 1976, Perez et al found out the same outcome : no difference in survival comparing radiotherapy alone and surgery then radiation.(41)

a- Surgery

Not all studies were post operative : Kagei et al, Jensen et al, Al-Mamgani et al, Maskell et al, Hu et al,Huang et al, O'Sullivan et al and Murthy had a population who did not have surgery.

1- Primary site

In the post-operative studies, patients had surgery on the primary site consisting in tonsillectomy or oropharyngectomy with or without Transoral Robotic Surgery (TORS).

2- Ipsilateral neck dissection

Neck dissection could be associated with surgery on the primary site and planned before or after radiation. Ipsilateral neck dissection is commonly done. Patients with nodal involvement are commonly those eligible for ipsilateral neck dissection as observed in Dan et al (34/61), Vergeer et al (102/123), Al-mamgani et al and Rackley et al (67/81). In Lynch et al, patients with nodal disease ≥N2 only were operated (76/136). In Rusthoven et al 14/20 had planned neck dissection whose 4 patients for N2a disease or large (>3 cm) N2b disease. Positive microscopic margins was the other criterion required to practice neck dissection. In Liu et al, only patients with N3 disease were eligible to neck dissection before treatment and planned after if partial response to treatment was observed : 5 and 3 patients respectively were concerned. We do not have informations about reasons to practice neck dissection in Chronowski et al but it is interesting that 60% of the population had surgery on the primary tumor and only 8% had neck dissection. Otherwise, 19% had excisional biopsy of cervical lymph node which could correspond to a sentinel lymph node detection which was not validated at that time. This method is enabled only in T1-T2 N0 patients with squamous cell cairnoma of the oropharynx.(42,43) We have already seen FDG-PET scan is used to search occult metastases and so Kennedy et al practiced neck dissection after 1995 if FDG-PET scan or head and neck CT found obvious lymph nodes after radiation treatment as described in Li et al.(44) They also practiced neck dissection before treatment, especially before FDG-PET scan era when more than 2 lymph nodes >1 cm were involved. 32 patients in this cohort of 76 received such treatment.

3- Bilateral/contralateral neck dissection

The controlateral neck dissection was rarely done except in Wirtz et al : 73% of the population had bilateral neck dissection and the 27% left, ipsilateral neck dissection only. No statistical association was found between contralateral recurrences and contralateral

neck dissection but we suggest it could have been a protective factor and in fact the rate of recurrence is the contralateral neck is low (6%) in this large cohort of patients with advanced nodal disease and advanced T extension. In Cho et al, they all had ipsilateral neck dissection and when the tumor was above T3 and/or when there were multiple lymph node metastasis in the ipsilateral neck, a contralateral neck dissection was also performed.(45) It happened in 24 cases on a cohort of 49 patients. Mendenhall et al also practiced bilateral neck dissection in 19 cases and ipsilateral in 179 cases.(46) The neck dissection was planned after radiotherapy when nodal involvement was important or when not enough regression was seen after treatment. In the multivariate analysis, it significantly impacted loco-regional control (p=0,0003). In Chin et al, 120/154 ipsilateral neck dissection were performed and 30 contralateral neck dissection when FDG-PET scan or CT found obvious contralateral nodal involvement.(47) In Kim et al, neck dissection was ipsilateral in 59 cases and bilateral in 55 cases in a population of 241.
Contralateral neck dissection is favored in recommandation when oropharyngeal carcinoma are extended to midline or involved posterior pharyngeal wall.(48)
Surgery is interesting in staging. Indeed it provides prognostic factors as lateralization, deepth invasion, presence of positive margins, number of nodes involved and/or extra capsular extension. It is helpful to stratify the risk and treat correctly to improve recurrence control and survival. However, as a reminder, there are no difference in outcomes found in Jouhi.(40)

b- Chemotherapy

T extension as positive microscopic margins and/or N extension as extracapsular extension are criteria in Chin et al, Rackley et al, Cho et al, Koo and Wirtz et al to administer chemotherapy according to EORTC recommandations. Wirtz et al considered these criteria as high risk of failure and so 30% of the population received concurrent chemoradiation after surgery. Al Mamgani et al reserved chemotherapy to patients with large T extension : T3. None of the patients who failed were concerned and so none received chemotherapy. N extension including precisely N2 and N3 disease are other criteria in Rusthoven et al, Dan et al, Lynch et al and Liu et al. So patients with N2b disease received mostly chemoradiation or adjuvant chemoradiation in case of surgery like in Chronowski et al. Whereas in Huang et al only one of the N2b patient treated unilaterally received chemoradiation, the 7 others received radiation alone despite the existence of a large serie supporting concurrent chemotherapy decrease risk of metastases in HPV positive oropharyngeal carcinoma with advanced nodal disease.(49) Kennedy et al whose 34% are N2b treated only 21 patients with chemoradiation in a

cohort of 76 patients, when extracapsular extension and/or > 2 nodes involved. One patient with >2 nodes involved failed. We do not know if he received chemoradiation. In contrary, in Gottumakala's study, 74% of this population with advanced disease received chemotherapy, whose 62% concurrent. It could partly explain the low recurrence's rate despite the advanced disease of the cohort. O'Sullivan et al did not use chemotherapy at all despite a few rate of extended primary tumors (191/228 patients were T1-T2) and 11 patients staged ≥ N2b. Three contralateral recurrences occured. In Vergeer et al also, patients did not receive chemoradiation and it is one of the highest score of contralateral recurrence.

Maskell et al administered chemotherapy according to 3 groups of risk of recurrence and each had a specific treatment (low risk : RT alone, intermediate risk : chemoradiation, high risk : induction then chemoradiation). Recurrence's rate is similar to Vergeer et al who did not use chemotherapy and Lynch et al who used chemoradiation when nodal disease ≥N2.

In Kim et al we can see chemotherapy was no administered equally regarding of the group of treatment : 32% in the bilateral one and 21% in the unilateral one, suggesting the population and especially the tumor's criteria of agressivity were more present in the bilateral group.

In Kagei et al 12/32 patients had concurrent chemoratherapy but criteria of administration are missing.

Data about chemoradiation administration was missing in Cerezo et al, Jensen et al, Hu et al and Jackson et al.

Cisplatin is the most commune systemic treatment administered.

c- Radiotherapy

1- Irradiation technique

Radiation techniques have changed through the years. Intensity modulated radiotherapy (IMRT) is the current reference method as it is more precise and reduce unintentional irradiation of the uninvolved tissue improving acute and late toxicities.(50,51)

Gottumakala et al as Chin et al used only IMRT. All other studies used IMRT and/or other techniques as Three-Dimensional Conformal Radiation Therapy (3D CRT). IMRT significantly reduces acute and late toxicity comparing to 2D/3D CRT but evidence regarding the superiority of IMRT over other techniques concerning survival outcomes has not yet been established.(52) It is notable in Chronowski et al, who selectioned patients retrospectively from 1970 to 2007, that techniques changed during the study period. They used from 1970 to 1988 appositional mixed-beam photon/electron

technique, then from 1988 to 2003 wedge pair technique with matched ipsilateral anterioreposterior supraclavicular field and finally IMRT from 2003. In Mendenhall et al also techniques were not homogeneous through study period (1964-2003). Patients uderwent throughout times interstitial brachytherapy boost to the primary site after external beam radiotherapy, intersitial brachytherapy, intraoral cone irradiation sing 250 kVp x-rays and finally IMRT for only 17 patients.

2- Neck Irradiation

All studies concerned the place of ipsilateral neck irradiation for patients with oropharyngeal squamous cell carcinoma.

Dan et al, Kennedy et al, Chronowski et al, O'Sullivan et al, Maskell et al, Vergeer et al, Al Mamgani et al, Gottumakala et al, Rusthoven et al, Cerezo et al, Koo, Rackley et al and Lynch et al used only unilateral neck radiotherapy while other studies used ipsilateral and bilateral radiation to compare the outcomes between the two different population.

3- Doses of radiation

Doses of radiation depends on different criteria : adjuvant or definitive treatment first. In Gottumakala et al median dose for definitive treatment is 69,96Gy against 64,56Gy in adjuvant. In Cerezo et al definitive treatment is determined as 66-70Gy whereas post operative treatment as 54-64Gy. Definitive treatment delivered higher doses of radiation. We could imagine patients with definitive treatment are more likely to develop acute and late toxicities.

It depends of technique as in Koo whose definitive treatment by IMRT delivered 67,5 Gy against 70Gy in 3DCRT. In post operative, it treated by respectively 63 and 66Gy. IMRT delivered less doses for reducing toxicities.(50,51)

It also depends on the risk. In fact, in Rackley's study, positive margins or extra capsular extension were considered as high risk of recurrence and these 8 patients received 66 Gy whereas the others received 60Gy. Vergeer et al treated with this exact same dose patients with extra capsular extension as well and also patients with nodal disease. While in other studies N0 neck and N+ were treated differently. In Hu et al and Lynch et al : N0 received 50 to 54 Gy and 50Gy respectively, N+ 66-70Gy and 65Gy respectively.

It is to be noticed in Vergeer et al, that post operative patients with large margins defined as ≥5mm received decreased doses compared to other patients.

We found also differences between ipsilateral and bilateral group in Ye et al particularly whose 66% of the unilateral treated group received ≤60Gy against 61-70Gy for 65% of the bilateral group ($p<0,01$). In Kim et al, radiation doses were higher in the bilateral group

and none of the patients treated bilaterally relapsed in the contralateral neck.
We have already seen N+ received higher doses, yet N+ are more likely to be treated with bilateral treatment beeing responsible for more severe toxicities.
Finally, Kennedy et al is remarkable for one of the higher median doses delivered in the study : 74,4 Gy. Also Mendenhall et al delivered respectively for once daily and twice daily 80 Gy and 81,7 Gy resulting in median doses of 66 and 76,8 Gy which is the higher of the review. In the contrary Maskell et al and O'Sullivan et al delivered the lowest doses as the maximum dose was 55 Gy in both studies.

7- HPV positive

HPV positive oropharyngeal cancer are a different population than HPV negative oropharyngeal cancer and we know they do not respond the same way to treatment, means they do not have the same outcomes concerning survival. 33 Indeed this is a younger population, non smokers or former smokers with a very few pack-year. They have small T extension as mostly T1-T2 and advanced nodal disease.(53–55)
Some very interesting data about this population are that they have a better survival and especially overall survival than HPV negative population but they do not have statistically different regional recurrence-free survival. 26 This is not the specific population we focalized on this review but we have to include data given that this population is growing becoming the most represented one in oropharyngeal cancer in united states and probably soon to be in Europe. 2
Ye et al is one study exploring the same primary outcome, contralateral recurrence, in HPV positive population. 78% of the population was p16+ and it appears that they had smaller T extension but bigger N diseases than p16-.
As Ye et al, Huang et al is a study concerning disease control in HPV population with small tumors (T1-T2) and nodal disease from N0 to N2b. 80% of the population was HPV positive. In Ye et al 78% of p16 negative were actual smokers when only 1/3 of the p16 positive were smokers and the 2 other third of the p16 positive population were non smokers or former smokers. Unfortunately, we do not know if the 4 patients who relapsed were smokers or not : we could make an hypothese that they are and so respond not as well as non smokers/former smokers to radiation and have more chance of relapse. It seems necessary to assess a study with population of p16 positive non smokers treated in unilateral way comparing to a population of p16 positive smokers. The outcomes should be likely to autorize unilateral radiation in p16 positive non smokers population. So the outcomes of Ye et al, the low rate of contralateral recurrence, seems to be explained by the high proportion of p16 positive in the study's population and that this population

concerns mostly non smokers-former smokers. As well, in Gottumakala et al we found out 44% of the population is not smokers at all and 74% are p16 positive, we know that p16 positive tumors are more likely to respond to chemo-radiation so it could explain the good outcomes of this study (1/34 contralateral relapse). Concerning the population we see the same difference in Huang et al than in Ye et al or Gottumakala et al concerning smoking status.

8- Contralateral recurrence : primary outcome

	Number of patients	Contralateral recurrence rate	Stage of contralateral recurrence
Dan	61	1,60%	T2N2b
Kennedy	76	3,00%	T1N2b
Lynch	136	5,90%	T3N0 T2N1 T2N2b (6)
O'Sullivan	228	3,50%	T2N1 (4) T3N1 (3) T4N1 (1)
Vergeer	123	5,70%	-
Al Mamgani	185	1,10%	T1N2b T2N0
Maskell	53	7,50%	T1N2b
Gottumakala	34	2,90%	T2cN1
Chronowski	102	2,00%	T2N0, TxN0
Wirtz	197	6,10%	T1N1 (2), T4N2a (1), T2N0 (1), T2N1 (3), T2N2b (2), T1N2b (3)

Table 3 : contralateral recurrences in studies with ipsilateral radiation only

	Number of patients	Contralateral recurrence rate	Stage of contralateral recurrence	Patient who relapsed in the group received ipsilateral radiation
Huang	427	2,10%	T2N1	Yes
Liu	167	0,60%	T2N2b	No
Jackson	271	1,48%	N0 (1) N1 (2)	Yes
Kim	241	1,24%	T2N2b (3)	Yes
Jensen	139	1,44%	-	Bilateral (1) Ipsilateral (1)
Mendenhall	503	3,40%	N0 (1) N2 (1)	Yes
Murthy	57	3,30%	T1-T2N2	Yes
Ye	182	2,20%	T1-T4 N0-N3	Yes

Table 4 : contralateral recurrences in studies with ipsilateral and bilateral radiation

a- Studies with contralateral recurrences

1-Ipsilateral treatment only

Dan et al found one contralateral recurrence in a cohort of 61 patients. Treatment was definitive and adjuvant. Population was at risk as 52% was ≥N2b, half of patients who had neck dissection had extra capsular extension. In the contrary patients had low T stage (97% T1-T2), well lateralized tumor with no involvement of the BOT, soft or hard palate, 33% were non smokers and 44% HPV positive, 89% of the population received systemic treatment when they had high-risk features. One patient staged T2N2b relapsed in the contralateral neck. He was HPV positive and treated with ipsilateral radiation. He failed only 6 months after treatment and it could have been an occult metastasis even if FDG PET scan was used when doubt. Regarding good outcome in this study they attest the safety to treat well lateralized oropharyngeal tumor with unilateral treatment despite nodal involvement. We notice almost half of the population is HPV positive, non smokers which is a protective factor to recurrence. (55–57)

In Kennedy's cohort of 76 patients only one failed at 37 months from end of treatment. He was staged T1N2b. Patients had agressive characteristics as 34% were N2b, very small proportion received chemoradiation, but they were all well lateralized with no involvement of the BOT or extension onto the soft palate. T stage was low : T1 or T2 exclusively. Also they used the highest dose of radiation in the review and neck dissection was realized when FDG-PET scan could not assure the staging. HPV data were limited and described for only 9 patients which consisted on an important lack of information to analyse the outcome. It could be a part of the explanation of the very good outcome of this study. They highlighted than all recurrences presented within 4 years of treatment. It suggest follow-up has to be at least 4 years to not underestimate recurrence rate.

Lynch et al registered one of the highest score of contralateral recurrence (5,90%) and seven of the eight patients who relapsed were N2b. It means 13% of N2b patients had contralateral recurrence against 5% of N1 and 0% for N0, N2a and N3. Lynch et al had well lateralized tumors, only 5% were not lateralized and 96% of the cohort is staged T1-T2. Patients ≥N2 were treated mostly with ipsilateral neck dissection and chemoradiation but 22% had extracapsular extension whose 20% failed in the contralateral neck. These difference were not significant as no statistic test were realized but it suggests extra capsular extension is a major prognostic factor of recurrence as already proved in litterature.(34,58,59)

O'Sullivan et al conducted a non post operative study on 228 patients. It is not mentionned wether chemoradiation was used or not. Furthermore doses of radiation were one of the lowest of the review. Population had a majority of T1-T2, very few rate of T3 and T4 but more than half of the population had adjacent structures involvement and in fact 4 of the eight who relapsed had palate involvement and 3 had BOT involvement. Also 3 of them were T3 and one of them were T4. The eight contralateral recurrences appeared for patients staged N1. None of the N2b or N3 patients failed even if they represent a small proportion of the global population of the study. It is interesting to notice time of follow up was 7 years, which let time to fail. In O'Sullivan et al, T extension is clearly influencing outcomes strengthen the idea of using unilateral radiotherapy only for patients with lateralized tumor.

Maskell et al was a non post operative study, using chemoradiation according to the risk of recurrence and with one of the lowest doses of radiation of the review. They registered one of the highest rate of recurrence : 7,5%. They observed all the contralateral

recurrences (4/53) were T1N2b and p16 positive. The contralateral nodal recurrence rate for N2b subgroup was 14,3%. The median time to recurrence was 29 months. So they switched for a bilateral treatment for N2b disease including a second study focusing on this stage. This second serie treated bilaterally had 23 patients staged N2b who did not present any contralateral recurrence. But the irradiation technique was different : the first group (unilateral) was treated with 3D CRT technique and the second (bilateral) with IRMT. Time of follow up of the second study was only 33 months against 68 in the first cohort. Also this serie was revealing that all contralateral recurrences were p16+ in a population with major proportion of HPV positive patients and non smokers or former smokers. These patients are supposed to have better outcomes but we did not know smoking status for the patients who relapsed. Also 2 of them presented invasion of the level 4 in the neck.
This study suggests that p16 positive tumors could be more likely to metastasize.(53,54) For now, it does not exist enough evidence in litterature to certifie that p16 positive is a major risk factor of nodal metastases and especially contralateral.

Vergeer et al had a population not well lateralized and 44% had extended tumor as T3 or T4, 22% of this cohort of 123 patients had extended nodal extension, staged N2b disease and half of them had extra nodal extension. Yet they did not use chemoradiation for advanced nodal disease as most of the study. On the other hand, they increased doses of radiation for patients with nodal extension and/or extra capsular extension and realised neck dissection in more than half of the population when nodal involvement. A few rate of patients had no imaging of the contralateral neck at diagnosis. Vergeer et al registered one of the highest score of contralateral recurrences. The 5 year contralateral nodal control is 88% for N1 and N2a and only 73% for N2b. Nodal involvement is statistically influencing contralateral recurrences (p=0,008). They conclude patients with multiple nodal involvement as N2b disease and especially when there was extra nodal extension should be treated with bilateral treatment or at least followed very frequently because they salvaged 71% of patients who failed.

In contrary in Al Mamgani et al only 2/185 patients (1,1%) failed in the contralateral neck. Unfortunately no statistical analysis was realised to highlight the predictive factor of recurrence especially contralateral. One of the patient was T1N2b treated by brachytherapy and failed 3months after treatment. The other patient was staged T2N0 and was treated by IMRT technique. Both of them did not receive chemotherapy as we explain earlier. This one failed 11 months after treatment. They both failed very early after

treatment suggering it could have been contralateral nodal disease at diagnosis detected neither by clinical examination or imaging even if FDG-PET scan was realised at any doubt of staging. Data were unfortunately missing for smoking status and HPV status and we know the influence of this characteristics on outcomes. The low rate of contralateral recurrence could be partly explain by the absence of T4 and N3 disease and low rate of T3 (7%) and N2 (a : 10%, b : 17%). The population who has been selectioned for the study had mostly small lateralized primary tumors and no nodal extension (N0 : 50%).

Gottumakala et al interested in a small cohort of 34 patients all treated with IMRT in adjuvant or definitive way. Staging was really precise as FDG PET scan was used for every case. This population was really interesting because it had advanced nodal disease probably due to the fact the population was mostly an HPV positive one.(33,53) Indeed 9% of the population is T3-T4 and 60% of the population had ≥ 2 nodes involved. None of the population was N0 and 56% was N2b, our specific stage of interest. 74% of the population was HPV positive and 88% non or former smokers, the exact population who is a very good responder to chemoradiation.(57) Indeed 74% of the population received chemotherapy. In these circumstances only one patient with no advanced nodal disease (T2N1) failed in the contralateral neck and he may have had contralateral nodal involvement at diagnosis as « PET/CT after surgery showed a contralateral borderline enlarged 2 lymph node with maximum SUV of 3.3 ». And the unique contralateral failure, developped only one year after treatment, was in the place of this previous suspicious lymph node. This was a small cohort, retrospective one but it is an example of a very reliable study as techniques used to diagnose and treat are conform to the recommandations and adapted to the population. It seems indispendable to detect HPV status, smoking status, staged patients with FDG PET scan to treat in consequences.

Wirtz et al assessed a post operative population of 197 patients with advanced T extension as more than 20% of the population were T3 or T4. HPV status was not known in most of cases unfortunately but 50% of the population was actual smokers so we could imagine they were HPV positive patients. They were all lateralized. Also nodal disease was extended as one third were N2b and more than 20% of them had extra nodal extension. Patients with positive margins and extra capsular extension who were considered at high risk, received concurrent chemoradiation and most of them bilateral neck dissection which was not found to be a protective factor statistically. They found 12 contralateral recurrences and 5 of them were staged N2b, only one of the 12 were T4, others had small T extension as T1 or T2. Regarding the high proportion of N2b disease

in the failure population, they proposed to treat contralateral neck when patients had involvement of this neck but also when patients were pN2b. On the other hand they clearly promotted unilateral neck radiation for head and neck cancer regarding the few rate of recurrence in this large cohort.

In Chronowski et al, there were 2 contralateral recurrences in a population of 102 patients whose 22 were N2b, all lateralized and with small T stage (T1-T2). Involvement of low neck disease (level IV) was an exclusion criteria so all N2b patients had involvement in the level II and/or III only and none patients were N3. Chronowski et al was a retrospective cohort whose patients were selected from 1970 to 2007. Techniques throughout this time changed and so were not homogeneous during the study period of time. Only 5 patients received chemotherapy whose 2 received induction only, 2 concurrent only and one induction and concurrent. They were all N2b. We did not have information concerning pathological risk factors as extra capsular extension or positive margins to determine if patients were eligible to concurrent chemotherapy regarding to ASTRO recommandations but comparing to the number of N2b disease, number of patients receiving chemotherapy seems small.(59) Nonetheless only two failed in the contralateral neck and they had low T stage (one unknown and one T2) and no nodal extension. Despite the number of N2b diseases, no IMRT for all, almost no chemoradiation, none of the 22 patients failed in the contralateral neck.

2-Bilateral and unilateral radiation

Mendenhall et al realized a large study of 503 patients whose the aim is to update outcomes for patients treated with definitive radiotherapy (305 patients) or definitive and neck dissection (198). They used ipsilateral radiation on lateralized primary tumor and neck for 58 patients and analyzed the loco-regional control. 56% of the population had ≥N2 disease whose 24% was N2b and 47% of the population had advanced T stage as T3-T4. We unfortunately did not know the proportion of advanced T stage in the unilaterally treated subgroup. In this subgroup, only two showed contralateral recurrence : one N0 who also failed in primary site and ipsilateral neck and one N2 who only failed in contralateral not irradiated neck. 63/503 developped recurrence in the neck without precision about ipsilateral or contralateral recurrence except those 2 from the ipsilateral treated subgroup. Control at 5 years was lower with the higher neck stage : N0 95%, N2b 84% but this was not evaluated in the multi variate analysis so not significantly proved. On the contrary, T stage and especially overall stage and neck dissection influenced significantly survival.

Murthy performed a study who selected retrospectively patients from 1965 to 1975 and compared loco regional control between ipsilateral and bilateral group.(60) This cohort is very interesting as 12 patients were T3 and 23 T4 meaning more than half of the population had extended primary tumor. Unfortunately we do not have informations about lateralization or positive margins which are pejorative criteria. Of these 35 patients with advanced T stage, 15 were treated with unilateral treatment. Nodal involvement were also extended as 13 patients were N2 and 11 were N3. They respectively treated 8 N2 in unilateral and 2 N3 in bilateral. It is remarkable that ipsilateral treatment for advance T or N stage was only before 1973, the difference providing from a physician preference. We do not have specific information about N2b stage. Only one contralateral recurrence was observed in the ipsilateral group. It was a T1-T2 N2 stage. Not counting the type of radiation : 9% of T1-T2 failed in the neck, same proportion for T4 and 16% for T3. Also, 8% of N0 failed in the neck and 23% and 9% for N2 and N3 respectively. Despite the advanced stages of this cohort of 57 patients only one failed in the contralateral neck in the subgroup ipsilateral which had 34 patients.

In the Liu's cohort of 167 patients whose 27 (16%) were N2b they treated 65% of them with bilateral treatment. Patients with N2b disease were treated with concurrent chemoradiation and did not have neck dissection. None of the patients with high nodal extension as N2 or N3, lateralized and treated with unilateral treatment failed on primary site or neck. There was more loco-regional failure in the group non lateralized than in the lateralized one but we do not know if this difference is significant. The unique contralateral failure (0,6%) is staged T2N2b, received bilateral treatment and data was missing concerning lateralization. We could afford that lateralized tumors, even if nodal extension is high can be treated with unilateral treatment. P16 status and smoking status were not influencing outcomes here but were not available for all patients so probably not reliable.

In Ye et al and Huang et al most of the population is HPV positive and non smokers or former smokers patients. They were mostly treated bilaterally. In Ye et al, doses of radiation were higher for HPV positive patients than for HPV negative patients. Patients with positive HPV status had small T stage but higher N stage. In Ye et al, 47 patients were N2b and 27 N2c-N3 in the p16 positive subgroup of 142 patients. All of the contralateral recurrences were in the p16 positive group treated unilaterally. In this subgroup the rate of recurrence is 7,5% (4/182) but 2,2% for the all population. It suggests that unilateral treatment in p16 positive population is less protective of contralateral

recurrences than bilateral treatment. Unfortunately we do not know how much patients N2-N3 were treated with bilateral treatment in p16 negative population who represented only 40 patients in the whole cohort. Control of the contralateral neck was not significantly different (p=0.63) between p16 positive and p16 negative population but significantly different (p=0.05) between unilateral and bilateral group. But no significant difference was shown for local control, loco-regional control, disease free survival, disease specific survival and overall survival between the two groups of treatment in this subgroup of p16 positive patients. Survival outcomes are not different partly because of efficacy of salvage treatment consisted in neck dissection.

As well in Huang et al, in the ipsilateral group of 96 patients whose 62 are HPV positive and 34 HPV negative, we noticed 2 contralateral failures : one in each sub-group. Both patients were T2N1. One relapsed after 2,5 years and the other after 6 months, which could correspond to an occult disease at diagnosis. The 8 patients staged N2b treated in the ipsilateral group did not fail despite the fact they had advanced disease. But only 4% of N2b were treated with ipsilateral treatment in each group (HPV positive group and HPV negative group). However N2b was a very represented group in this cohort as 58% of the HPV positive patients are N2b and 32% of the HPV negative patients. Regarding the few rate of N2b disease treated with ipsilateral technique after recommandations at this time,(5) Huang et al proposed studies focalised on that stage and could not recommand ipsilateral treatment for N2b stage.

In the 271 patients cohort, Jackson et al found out 4 contralateral recurrences in the group of 178 patients treated unilaterally. They had all N0 or N1 disease and one was T2. Data were missing for others. Indeed most of patients in the ipsilateral group had small nodal extension and small T extension as 65,7% of this subgroup were T1-T2 and 87% were N0-N1. So the rate of contralateral recurrence was very low for the whole population (1,48%) but higher in this specific subgroup of patient (2,6%). The study highlighted relationship between T stage and disease specific survival. Indeed patients with T1 had significantly better outcomes than other T stages and both T2 and T3 better than T4. They found the same results concerning N extension as N2 and N3 had significantly better outcomes than N0. Also N3 had better outcomes than N1. In this study patients seemed to be split in two groups regarding T and N extension concerning survival. T1-T2 N0-N1 and T3-T4 N2-N3. Whereas all patients who failed in the contralateral neck belonged to the first group with supposed better outcomes. In this specific ipsilateral group, 13 patients of the 155 N0-N1 relapsed in the neck without relapse in the primary site against 3 in the N2-N3 group of 23. And the majority of these relapses occurred in the radiation field. They

concluded that outcomes' improvement will come with more efficient radiotherapy in the field which is concerned but not with volume's increasing.

In Kim et al, the 3 contralateral recurrences occurred in the ipsilateral group. Only one of them failed in the contralateral neck only, both others failed in the primary site and one also in the ipsilateral neck. They were all staged T2N2b. They failed at distance from treatment, respectively 20, 22 and 51 months. Two of them received chemotherapy which was not given as much as in the bilateral group. It is notable than one of the patients who failed received very low dose of radiation consisted in 54Gy only while median dose was 63Gy for all other patients who relapsed. 63Gy was also the median dose to the bilateral group. More patients were treated with IMRT in the bilateral group than in the ipsilateral group of patients. In the whole population, 9 patients had loco-regional relapses. The loco-regional relapse free survival between bilateral and unilateral group was not statistically different (p=0,083). Also 5 year overall survival was not significantly different (p=0,985) between the two groups. It is very interesting that similar outcomes were seen for N2b sub-group concerning loco-regional control and overall survival with p lower than in the whole cohort suggering that with larger N2b cohort it could have been significant. They stay cautious about this stage which counted more loco regional relapses in this cohort.

Jensen et al found 2 contralateral recurrences in a large cohort of 139 patients treated mostly in bilateral treatment especially when T and/or N disease was advanced. One third of patients were T3-T4 and received bilateral treatment Patients with involvement of midline structures received as well bilateral treatment. 7 patients had involvement of midline structures but did not receive bilateral treatment cause of age, negative FDG PET scan or small involvement. 5 of them failed in the primary site, 4 in neck whose only one in the contralateral neck and one at distance. They all died of disease except one who died for other reason and one who was still alive. It is interesting that the one who failed in the contralateral neck was the one who received ipsilateral treatment despite he had involvement of soft palate. It confirms the fact that involvement of midline structures is a predicitve factor to recurrence.(29)
There was no significant difference between the two groups for loco-regional control and overall survival at 4 years.

b- Studies without contralateral recurrence

	Number of patients	Radiotherapy	Stages	Chemotherapy (number)	Technique (number)
Rusthoven	20	Ipsilateral	T1-T3 N1-N2b	18	3D CRT (11) IMRT (9)
Cerezo	20	Ipsilateral	T1-T4 N0-N2b	2	3D CRT
Re-I Chin	154	Ipsilateral Bilateral	T1-T4 N0-N3	76	IMRT (154)
Koo	20	Ipsilateral	T1-T3 N0-N2b	20	3D CRT (14) IMRT (6)
Cho	49	Ipsilateral	T1-T4 N0-N3	31	-
Kagei	32	Ipsilateral	T1-T4 N0-N3	12	-
Rackley	81	Ipsilateral	T1-T2 N0-N2b	27	3D CRT (-) IMRT (-)
Hu	37	Ipsilateral	T1-T3 N0-N2b	30	3D CRT (5) IMRT (29) Unknown (3)

Table 5 : no contralateral recurrence

In 8 studies there were no contralateral recurrences.

These studies selected only lateralized tumors. But we noticed in Chin et al a non lateralized group. This group only received bilateral radiotherapy. In contrary in Cerezo et al, the inclusion criteria required very lateralized tumors.

Cerezo et al, Koo, Cho et al and Kagei et al had small T stage and mostly not advanced nodal disease. In Cerezo et al patients were only T1-T2 and N0-N2b with almost all of the population who is N0 (55%) against 25% of N2. And not all the N2b stage were included because patients with more than 2 lymph nodes involved and/or lymph node >2 cm were excluded. Similarly Kagei's population was 70% of N0. Only one patient was T3 in Koo, all others were also T1-T2. In this same study 80% of the population was N1 or N2b equally. Cho et al is a study with similar proportions of N0, N1 and N2b.

The others had mostly advanced disease. In particularly Rusthoven et al had small T stage as 55% of the population was T1 but advanced nodal disease as 65% of the population was N2b. We find the same proportion in Hu et al and Rackley et al whose 57% and 60% respectively were N2b. In Rackley et al it is interesting to notice that 36% had ≥ 3 involved neck nodes and/or nodes ≥ 3cm. Chin et al is this large cohort of 154 patients with the most advanced disease. Indeed, 25% of the population was T3 or T4, 55% is N2b and 14% had a bigger stage than N2b.

Staging was often realized with FDG-PET scan in these 8 studies except in Cerezo et al who did not use this technique at all. All patients received FDG PET scan in Rusthoven et al and Hu et al, about 70% in Cho et al and Koo. It could have helped detected occult contralateral metastasis at diagnosis and so treated consequently. Chin et al used it after 2000 for staging and performed bilateral neck dissection when they had doubts concerning contralateral lymph nodes : 20% of the population had bilateral neck dissection. In Cho et al all patients had ipsilateral neck dissection and half of them contralateral neck dissection when patients were T3 or had multiple ipsilateral involved nodes. The results are interesting : 24% cN0 were pN+ in the ipsilateral neck but none in the contralateral neck and 12% of cN1-N2b were pN+ in the contralateral neck. The only significant predictive factor of contralateral occult metastase was degree of differenciation.

P16 status was unknown for 5 studies here but in Chin et al, Hu et al and Rackley et al we can see most of the population, respectively 71%, 62% and 63% were p16 positive. We know p16 positive tumors are more likely to have a better response to concurrent chemoradiation. Taberna et al could explain the better outcomes of these studies.(3,53)

Concerning treatment most of the studies were post operative. In Cerezo et al 60% of patients had surgery before, 70% in Koo et al and Rusthoven et al. They all had surgery on T in Rackley et al and Chin et al and 80% of them on ipsilateral neck as well. None had surgery in Kagei et al.

Chemotherapy was administered for all patients except one in Rusthoven et al, even if patients did not have advanced nodal disease. We find the same proportion in Hu et al whose 81% of the population received chemotherapy. In contrary half of patients received chemotherapy in Chin et al. It is interesting to see that in the group lateralized/N0-N2b treated with unilateral radiotherapy, 54% received concurrent chemotherapy against only 37% in the same group treated with bilateral radiotherapy. The non lateralized group or N2c-N3 received also in 60% of cases concurrent chemotherapy. The difference was non significant. The same proportion is found in Kagei et al and Rackley et al (38% and 33% respectively). Chemotherapy was administered when tumors had extra capsular spread

and positive surgical margins in Rackley et al and Cho et al which are indeed known to be pejorative prognostic factors to recurrence.(34) Most of patients did not receive chemotherapy in Cerezo et al and Koo. These studies had mostly not advanced disease (55% N0 in Cerezo et al and 40% N1 in Koo).

Radiotherapy was for all ipsilateral only except for Chin et al whose 69% of the population received bilateral treatment. One group of lateralized tumors/N0-N2b and one with non lateralized tumors or N2c-N3. We can notice in the lateralized tumors/N0-N2b group treated bilaterally that positive margins or close margins are present in 60% of cases against only 40 in the ipsilaterally treated one. It was not significant. Both of the population were very close concerning their characteristics. The difference was the period of treatment : before 2007 the recommandation were to treat bilaterally and after 2007 it was allowed to treat these patients unilaterally. They were all treated with IMRT technique. Only Hu et al and Chin et al used only IMRT, other studies used either IRMT or 3D CRT.

Finally time to follow up was very different from one an other study. In Rusthoven et al the median time to follow-up was only 19 months while in Chin et al or Rackley et al it was 5,5 and 5,7 years respectively. The time to detect outcomes is so much longer and it could partly explain that no recurrence was found in Rusthoven et al.

9- Contralateral recurrence's treatment and survival

Most of patients who failed in the contralateral neck were salvaged by neck dissection. In Kennedy et al the unique contralateral relapse was salvaged and was disease free during five years and did not died of disease.

In Huang et al, both patients who relapsed were salvaged and disease free at last follow up. In Ye et al, patients who failed were salvaged by neck dissection and also survived.

In Kim et al one patient was treated with surgery, re-irradiation and chemotherapy and had a complete response then, one did not receive any treatment and his survival data was missing and one was salvaged by surgery and had also a complete response to treatment. In Jackson et al 2/4 were salvaged by surgery. In Vergeer et al successful salvage could be performed in 71% of patients with contralateral metastases. In Dan et al, the contralateral recurrence was salvaged by neck dissection and post operative radiotherapy and the patient was disease free at 50 months of follow up. In Lynch et al, all of those who developed contralateral recurrence alone (6/8) were successfully salvaged with surgery and post-operative radiation. And in Al Mamgani et al, the N2b patient who relapsed was salvaged but not the one who had N0 stage.

B- Toxicity

	Late xerostomia : grade 2 ≥ grade 3	Osteoradionecrosis	PEG tube dependent at last follow-up	PEG tube placement
Rusthoven	5,00% 0	No information	0	No information
Dan	8,00% 0	3,00%	0	15,00%
Chin	No information	No information	25% bilateral group 2% unilateral group	49% bilateral 18% unilateral
Chronowski	No information	No information	No information	9,00%
Huang	No information	9,4% unilateral 6,4% bilateral Significatif ?	0 unilateral group 4,3% bilateral group at 12M of follow up	10% bilateral 5% unilateral
Kennedy	No information	13,10%	2,60%	17,00%
Lynch	No information	7,00%	0 (6M of follow up)	6,00%
O'Sullivan	No information	No information	7,00%	No information
Cerezo	12,5%-18,7% 0-0	No information	No information	No information
Koo	5% 0	No information	No information	No information
Vergeer	17,10%	6,00%	No information	No information
Al-Mamgani	7% 0,5%	No information	0	11,30%
Hu	0 0	No information	0	No information
Gottumukkala	No information	No information	3,00%	29,00%

Kim	4,3% ipsilateral group vs 25,7% bilateral group 0% ipsilateral group vs 2,9% bilateral group p<.001	No information	No information	No information
Rackley	13% No information	9,80%	1% at 6M 0% at 12M	No information
Kagei	9% 0%	3,30%	No information	No information
Mendenhall	No information	2,90%	3,50%	No information
Wirtz	63,4% (all xerostomia)	No information	No information	20,8%

Table 6 : Toxicities

Most of the present studies had toxicity as secondary outcomes. In fact radiotherapy treatment of oropharyngeal cancer is responsible of xerostomia and dysphagia among others.

Xerostomia is one of the most frequent and tough late effect of radiation. Patients suffered with buccal pain, difficulties to speak, chew and swallow. Dysphagia, already caused by pharyngeal mucosa fibrosis is then increased and patients could require a PEG tube during treatment and sometimes lifetime.(61) In addition, it is responsible of dental and buccal infections. Quality of life seriously decreases so.

Modern technique as IMRT reduces toxicity and improves quality of life by sparing salivary glands but it could be really achieved by excluding the contralateral neck from the irradiated volume. In fact, Jellema et al reported a faster recovery for patients treated with unilateral treatment versus bilateral treatment.(62) Also in the litterature it was proved salivary flux two years after ipsilateral treatment was coming back to a pre-treatment quality.(63) Contralateral salivary gland counterbalance the lack of saliva.

In the review we registered the data concerning toxicity. Table 6 registered the most common criteria : late xerostomia, late bone complication as osteoradionecrosis and PEG tube placement during treatment then dependency at long term. Not all studies registered

late toxicity, we also have informations about acute toxicities. Acute toxicities are less reliable data cause they do not represent long term quality of life. They represent only the treatment period.

In Chin et al, they showed that acute toxicities as xerostomia, mucositis and weight loss were significantly lower in unilateral treated group than in bilateral treated group. The difference was not significant. Chin et al not only registered acute toxicities, the study reported xerostomia measured by the University of Michigan Xerostomia Questionnaire from the end of treatment to 27 months after the beginning of treatment and it showed significant differences between the unilateral and bilateral treated group. The questionnaire was self reported by patient, the data were only subjective. It was indeed more scientificly interesting to report objective data such as salivary-flow for xerostomia like in Cerezo et al. They collected these subjective xerostomia grades using CTCAE3.0 scoring system and objective salivary flow was also reported : there were no grade 3 xerostomia, almost same number of grade 2 (12,5% and 18,7% in subjective vs objective group respectively) but the difference between the objective and subjective sub-group was important (31,2% vs 81,2%). This suggest that the salivary flow values do not always correspond to the level of symptoms reported by patients and that both subjective side effects questionnaires and measurement of the saliva should be included in the xerostomia evaluation.

Wirtz et al also registered acute toxicities and registered very high proportion of xerostomia (73,6), dermatitis (93,9%), mucositis (79,2%) and dysgueusia (73,1%). Concerning late toxicities : 62.4% of the population had xerostomia and 35% had dysgueusia. It could be explained by the fact that most of the population was treated by 3D CRT and 2D CRT, only 12.2% of the population was treated with IMRT.

Concerning xerostomia, we can see Rusthoven et al, Dan et al, Al Mamgani et al, Kagei et al, Koo, Cerezo et al, Rackley et al and Vergeer et al found almost the same rate of grade 2 xerostomia (5% to 17,1%). They all treated ipsilateral neck only except Kagei et al who treated 8 patients with bilateral radiation. No grade 3 were registered except in Al-Mamgani et al.

We also observed osteoradionecrosis which was higher in unilateral treated group in Huang et al (not significantly proved). Rackley et al and Kennedy et al showed high rate of oestoradionecrosis, 9,8% and 13,1% respectively. In kennedy et al it could be explain by the high dose of radiation. Following this hypothesis, the incidence of late grade 3-4 toxicities was 17% while most of studies did not registered grade 3 late toxicities at all. It was unilateral neck radiation only but mostly with conventional techniques. In Rackley et

al 8 patients received surgery as mandibulotomy with a free flap which could explain the high number of osteoradionecrosis. Material and surgery are factors which could weak the bone and cause oestoradionecrosis.

We were interested about the PEG tube placement and long terme dependence. This is an important aspect representing patient's quality of life. Most of series registered none patient who were PEG tube dependent at last follow up but 3 series showed interesting data. First Chin et al divided his serie in 3 groups (1 for lateralized primary tumor and N0-N2b treated unilaterally by IMRT, 2 for lateralized primary tumor and N0-N2b treated bilaterally by IMRT and 3 for non lateralized primary tumor or N2c-N3 treated bilaterally by IMRT). The difference of long term PEG tube was significant between the 3 series. In fact 2% of group 1 needed long term PEG tube against 20% of group 2 and 30% of group 3. They also found that xerostomia, mucositis, pharyngitis and weight loss were significantly higher in the bilaterally treated group which renforce the idea that bilaterally treated patients are more likely to need PEG tube placement. Yet they showed that group 2 and 3 received higher doses of radiation ($p<.01$). Doses and bilateral radiation seems to be tighly correlated with PEG tube dependency.
Gottumakala et al showed a very high score of PEG tube placement. We can see first that 10/34 had an invasive surgery as transoral resection and neck dissection and 6/34 had transoral dissection alone. These patients probably received a PEG tube at the end of the surgery. And then 25 patients were treated with induction or concurrent chemotherapy which could have caused second effects as mucositis responsible of PEG tube placement or PEG tube dependence during treatment. Whereas the population was treated with unilateral radiation and with IMRT which is known to be responsible of less side effects.
Dan et al also showed a high score of PEG tube placement but none were long term. It could be relative to the high number of patients who received concurrent chimiotherapy. Most of patients 59/61 received chemoradiation (5 induction and 54 concurrent) and it could have caused mucositis during treatment. Kennedy et al showed almost the same proportion than Dan et al but most patients din't receive chemotherapy. Most were treated by former technique of radiation and doses were very high (median 74,4Gy). This could explain side effects as mucositis or pharyngitis which could cause dysphagia.

Discussion

We already know invasion of midline structures are pejorative prognostic factor to recurrence.(29,64) We indeed see in these studies it has impact on recurrence. O'Sullivan et al and Jensen et al had both extension to midline structures. In Jensen et al they were treated with bilateral radiation except 7 of them who received unilateral treatment and 5 of them who had loco-regional failure. One was contralateral. But loco-regional control and overall survival was not significantly different at 4 years. In O'Sullivan et al, on the 8 contralateral recurrences, 7 of them had involvement of midline structures and this cohort used only unilateral radiation. They were all N1 meaning nodal extension was not the predictive factor of recurrence. In Liu et al patients who had not lateralized tumors had significantly higher rate of contralateral recurrence and in Vergeer et al, which is a study with one of the highest contralateral recurrence rate, the population was not lateralized. In the contrary populations like in Cerezo et al, which did not experience any contralateral failure, were very lateralized as we already seen. In Chin et al, which did not experience any failure as well, patients with no lateralized tumors were considered at high risk of failure and received bilateral treatment and concurrent chemoradiation. We could suggest regarding these results to treat patients with midline structures involvement, regardless to nodal extension, with bilateral treatment.

T extension is also a predictive factor to recurrence as T3-T4 stages are significantly more likely to be responsible of nodal involvement and even bilateral neck involvement.(4,29) In our review we can easily see studies which did not experience any contralateral failure had small T extension. In the contrary Vergeer et al had a significant proportion of T3-T4 (44%) treated unilaterally and they registered an high rate of contralateral recurrence despite the high doses of radiation used. We unfortunately do not know T stage of patients who failed in the contralateral neck. As a reminder they almost did not use chemoradiation. Similarly in Wirtz et al, also treated unilaterally, 20% of the population was T3-T4 and lateralized and they experienced 12 contralateral recurrences. However only one of these recurences had T4 stage, others had small T stage. But they all received chemoradiation and bilateral neck dissection which could have helped the great outcome for these patients with extended tumors. In Mendenhall et al also T3-T4 were well represented (47%) but only a few part of the population received unilateral treatment and indeed only 2 contralateral failure occured in this sugroup of patients. We unfortunately do not know T stage of the 2 patients treated unilaterally who failed in the contralateral neck. In Murthy more than half of the population was T3-T4 and more than half of the

population received unilateral treatment. Only one patient failed in the contralateral neck and had small T stage. In Jensen et al, T3-T4 disease, who represented one third of the population, received bilateral treatment and only 2 patients failed. Similarly patients in the unilateral group in Jackson et al had small T stage. We can see T3-T4 disease were treated with bilateral treatment or if not, like in Wirtz et al they received chemoradiation and bilateral neck dissection. Indeed Beitler et al recommend to use chemoradiation when T3-T4 disease, the great outcome in Murthy could suggest that unilateral treatment is safe even in case of T extension but we need to realise a more recent randomized study to confirm.(65)

In Bernier et al positive margins were found to be risk factor for poor outcomes.(34) In Wirtz et al there was an high proportion of positive margins and population was treated unilaterally anyway but with chemoradiation as recommanded in Bernier et al. We unfortunatelly do not have status for patients who relapsed but rate of recurrence was relatively high. For post operative study it seems essential to extract data about positive margins to highlight the impact of this factor and treat consequently.

N2b stage is our stage of interest and it is not clear how to treat patients with such nodal disease.

In the review we observed N2b represents a large part of contralateral recurrence. In Lynch et al, treated unilaterally, 7 of the 8 contralateral failures were staged N2b but 20% of them had extra nodal extension which is well known to be risk factor of poor outcomes.(34) In Kennedy et al, only one patient relapsed and was indeed staged N2b but N2b represented 34% of the population who was treated unilaterally. The patient was furthermore salvaged and disease free at the end of follow-up. It stays very good outcome. In Kim et al also the 3 contralateral failures in the unilateral group were N2b. Less use of IMRT and chemoradiation in this group comparing to bilaterally treated group could explain this outcome. However IMRT is not known to have better outcomes than 3D CRT so it would not have changed outcomes.(50) Concerning chemoradiation we know for extended nodal involvement chemoradiation is recommanded, it could have changed outcome in this study.(65) A well in Vergeer et al they almost did not use chemoradiation despite 22% of N2b with half extra nodal extension. Contralateral recurrences rate was high but we do not know unfortunately N stage of these patients. In the contrary Hu et al, who had 57% of N2b in the population treated ipsilaterally only used chemoradiation and in fact did not experience any relapse. The same observation is made in Rusthoven et al. Also in Chronowski et al patients with N2b disease received chemoradiation and none of them relapsed despite only unilateral radiation in this cohort.

None of the N2b patients in Cerezo et al failed as well however they did not receive chemoradiation but none of them had more than 2 nodes involved and none of the nodes involved were >2cm. So unilateral radiation seems safe if concurrent chemoradiation is used for patients with N2b disease.

In Liu et al, N2b patients who failed in contralateral neck were treated with bilateral treatment, lateralization was not known and it could have been the reason of failure. Size and number of nodes involved seems to have an impact on recurrence and should be registered in each study and integrated in multi variate analysis.

Regarding the fact that HPV positive population has more advanced nodal disease, N2b stage is common in these population. Shoushtari et al found p16 positive population are more likely to metastasize in contralateral neck.(66) However in the review, Dan et al who treated its population with unilateral radiation, found only one contralateral recurrence. It was indeed a N2b disease but it was only 6 months after treatment and we suppose it was an occult diease at diagnosis. In Maskell et al, also an unilateral treated cohort, 2 of the 4 contralateral recurrences were N2b but 2 of them had involvement in IV level which is not common in oropharyngeal cancer and is an agressive characteristic. Furthermore all patients who relapsed were p16 positive and smoking status was unknown, yet we know patients with HPV positive status but smoking history do not respond as well that those with no smoking history.(55,56) It could explain outcomes in this study. Indeed in Gottumakala et al, none of the N2b p16 positive patients treated with unilateral radiation only, failed in the contralateral neck and they all had no smoking history. Finally Rackley et al did not registered failure in the N2b disease population despite the fact that 60% of the population was N2b, treated with unilateral radiation and most of them had >3 nodes >3cm. P16 positive population with no smoking history have great outcome concerning contralateral recurrence when treated with unilateral radiation only.(3,57) Furthermore this population is younger with less comorbidities, it is essential to treat them and avoid at most side effects which could have a major impact on quality of life.

Conclusion

Randomized controlled study needs to be established to confirm these hypothesis and help manage international recommandations.

We realized in our center a retrospective study to observe contralateral recurrence and toxicity of a post-operative oropharyngeal squamous cell carcinoma cohort with N2b disease. The aim of this study will be to observe outcomes and especially contralateral recurrence after unilateral treatment despite N2b disease in a post operative population

of oropharyngeal squamous cell carcinoma.

Post-operative T1-2 N2b oropharyngeal squamous cell carcinoma : loco-regional control after ipsilateral or bilateral neck radiation

Introduction

We have already seen in the litterature that current recommandations allowed unilateral radiation for oropharyngeal squamous cell carcinoma with nodal extension staged N2b if the tumor is lateralized (<1cm of soft palate and without extension to the BOT) and without evidence of extra-capsular extension. Furthermore they recommend to discuss carefully with the patient since benefits of unilateral treatment versus bilateral treatment concerning contralateral recurrence risk is relative. It does not exist any randomized controlled study concerning unilateral treatment for oropharyngeal squamous cell carcinoma and only one is prospective but with a small cohort of 20 patients. Furthermore none of them pertains to stage N2b. Prospective studies with larger cohort and controlled randomized studies has to be established, focusing on N2b stage.
This stage has in fact plurality of presentation.

This study is exploring outcomes in a cohort of 21 patients treated in our center from 2013 to 2018 with ipsilateral or bilateral post-operative radiation for an oropharyngeal squamous cell carcinoma staged T1-T2 N2b. We studied post-operative cases to homogenize as much as possible our population and especially because patients eligible to surgery have smaller T stage.(65) Patients with T3 or T4 extension have higher risk to relapse so it is less questionable.(4)
Primary outcome is contralateral recurrence and survival and secondary outcome is toxicity. The aim is to reduce toxicity and improve quality of life without compromising survival.
Purpose of our study is describing, in our center, contralateral recurrence and toxicities in a serie of 21 T1-T2 N2b patients to guide the establishment of a large prospective study.

Materials et methods

A- Population

This study is a retrospective, uni-centered one.

With electronic medical records, 21 patients were identified. They all had primary tonsillar squamous cell carcinoma treated by surgery and adjuvant radiation or chemoradiation. The population was treated in François Baclesse cancer center from january 2013 to june 2018.

The inclusion criteria were small T stages : T1 or T2, nodal extension staged N2b, well lateralized as no involvement of the pharyngeal wall, posterior tonsillar pillar and not crossing midline and curative intent.

Exclusion criteria was history of cancer and especially history of head and neck cancer.

Population's characteristics are shown in table 7. We can see most of the population was men, with a median age of 66 years, most of them had smoking history >10 pack-year. Indeed 14 patients smoked >10 pack-year whose 10 smoked at least 40 pack-year. 7 of these patients had an excessive alcohol history. One patient of the population had also an excessive alcohol history but was not a smoker and for one, information was missing about alcohol history. 12 others did not consume alcohol or only occasionally. Most of the population was staged T2 which correspond as a reminder to primary site tumor >2cm and ≤4cm. Tumors were mostly not well lateralized. In fact 8 patients had involvement of BOT and we know this is a major prognostic factor of recurrence especially contralateral recurrence. Indeed muscles contractions increase the flow in BOT's vessels.(26,27,29) Furthermore 2 had soft palate involvement which is also a prognostic factor to metastasize in the contralateral neck.(29) Nevertheless none crossed midline. Crossing midline is a predictive factor for contralateral neck recurrence.(64) 8 of them had positive margins which is also a risk factor for poor outcomes.(34) Also perineural invasion and angiolymphatic invasion were respectively present in 6 and 7 patients whose 4 of them had both. It has been proved that they are common in HPV positive patients, we unfortunately do not know the HPV status of the patients concerned. In addition the presence of at least one of these criteria is significantly associated with worse survival outcomes.(67)

They were all staged N2b as it was our stage of interest. Number of nodes involved was important. Only 4 patients presented with 2 nodes involved, all 17 others had 3 or more nodes involved. Most of them were in II and III level, only 2 presented nodal extension in level IV. We do know II and III are levels involved preferentially in oropharyngeal squamous cell carcinoma.(26,27,68) 15 of them had extra-nodal extension which is well known to be a pejorative factor for survival outcomes.(34)

Finally and unfortunately p16 status was mostly unknown in this cohort. Indeed data was missing for 14 patients. We do know populations are different according to p16 status and in fact response to treatment. We do know p16 positive patients are likely to have small

T stage but advanced nodal disease which fit perfectly to our population. We could so, assume that our population may be mostly p16 positive. However we have seen most of patients had a major smoking history and excessive alcohol history which does not correspond to a p16 positive population.(3,13,53,54,56,57)

	Number (%)	Ipsilateral (N)
Sexe		
- Men	17 (81)	4
- Women	4 (19)	2
Age (median)	66	67,1
Smoking status		
- unknown	1 (4,5)	
- No history of smokin	5 (24)	1
- <10 PA*	1 (4,5)	
- >10 PA	14 (67)	5
Excessive alcohol history		
Yes	8	3
No	12	3
Unknown	1	
T classification		
- T1	3 (14)	2
- T2	18 (86)	4
Involvement of adjacent structures		
- posterior pillar	6 (28,5)	1
- anterior pillar	3 (14)	
- retromolar region	1 (4,5)	1
- BOT**	8 (38)	
- soft palate	2 (9,5)	
- crossing midline	0	
Vascular embolisms		
Yes	7 (33)	1

No	3 (14)	2
Unknown	11 (52)	3
Perineural infiltration		
Yes	6 (28,5)	2
No	2 (9,5)	2
Unknown	13 (62)	2
Positive margins		
Yes	8 (38)	3
No	13 (62)	3
Number of nodes involved		
- 2	4 (19)	1
- 3	7 (33)	4
- 4-5	1-2 (4,5-9,5)	1
- 7-8	1-1 (4,5-4,5)	
- ≥10	3 (14)	
ECE***		
- yes	15 (71,5)	2
- no	6 (28,5)	4
P16 status		
- positive	6 (28,5)	2
- negative	1 (4,5)	
- unknown	14 (67)	4

Table 7 : Population characteristics for all population and ipsilateral group

*PA : pack-year

**BOT : base of the tongue

***ECE : Extra-capsular extension

B- Staging

To stage we did for all : clinical examination including nasopharyngoscopy, endoscopy under anesthesia, neck and thorax CT and MRI according to recommandations. Unfortunately most of patients did not have FDG-PET scan. FDG-PET scan was used for 7 patients.

Then tumors and neck dissection were staged by experienced anatomopathologists. This final stadification is the one used in the study according to the 7th TNM.

C- Surgery

All patients were first treated by surgery practiced throughout the study period by two different surgeons.

Oropharyngectomy was practiced in 20 cases which 5 were robot assisted. One patient was treated with bucco-pharyngectomy and mandibulectomy. 7 of them had reconstruction, 6 of them by pectoralis flap and one by ante-brachial free flap.

Concerning neck dissection, they all had ipsilateral neck dissection. Only one patient had a picking in the contralateral neck because he had an only node which was finally not involved. 4 had neck dissection of II-IV area, 1 of I-V, 13 of I-IV and one had a radical neck dissection with section of intern jugular vein. Number of nodes (involved or not) in the neck dissection were 14 to 48. We did not have data for two patients.

D- Radiotherapy

Techniques used during our study were IMRT in 19 cases and 3D CRT in 2 cases.

19 patients received 70Gy on the primary site and levels where nodes were involved or at risk of involvement. One patient received 60Gy and one 66 Gy. Median dose of radiation is 68 Gy and average dose of radiation is 59,03 Gy. Most of patients were treated daily during 7 weeks, without radiation during the week-end, in 35 sessions.

Mean dose to contralateral neck is 22.8 Gy.

Ipsilateral radiotherapy was delivered in 6 cases and bilateral in 15 cases. Population treated with ipsilateral treatment is described in Table 7. It is interesting to note that none had midline structures involvement as none had BOT or soft palate involvement, most did not have extra-nodal extension and number of nodes involved are 2-4 only in level II and III. They seem to have a less extended disease than bilateral population.

E- Chemotherapy

Only 4 patients were not treated by concurrent chemotheradiation. 17 others received 3 cures of cisplatin but 8 patients presented side effect and 7 of them did not receive the 3 cures. Side effects were aplasia in two cases, kidney failure in three cases, ionic disorders resulted of vomiting in one case and others reasons were not available.

We do know that concomitant cisplatin improves outcome when patients have pejorative factor as extra-nodal extension and/or positive margins.(34,58) It explains among others the high rate of concurrent chemoradiation and it could be an explanation to the good loco-regional control.
However concurrent chemoradiation is responsible for increasing toxicity.(59)

F- Statistics and outcomes

Primary outcome is contralateral recurrence and loco-regional control.
Secondary outcomes are toxicity and overall survival.
Statistical analyses for quantitative variable used Wilcoxon Mann Whitney or Student test and for qualitative variable we used Chi2 test or Fisher test.
Median follow-up is 5 years.

Results

A- Loco-regional control

None failed in contralateral neck during our study period.
None failed in primary site or ipsilateral neck.
However one patient had a FDG-PET scan which found tracer on primary site. Endoscopy was not realized as the patient received only paliative chemotherapy. We do not know if he failed in the primary site. He could correspond to a local failure but was not considered as one due to the absence of evidence. An other patient failed in BOT a year and a half after end of treatment. He failed in the same side than oropharyngeal squamous cell carcinoma. Again we could suggest that this correspond to a local failure but time to relapse seems long and we registered this as a second localization.
Concerning diistant control, 5 patients developped distant metastases. 4 of them developped lung disease, one brain, one liver and two had mediastinum nodes relapse.
Concerning overall survival, 5 patients died during study period of time. Only one did not die of disease indeed he died two years after treatment and reason of death was not available. 4 others patient died of disease as they had distant metastases.
Contralateral recurrence free at 5 years is 100%.
Loco-regional control rate at 5 years is 100%.
Overall survival at 5 years is 76%.

B- Toxicity

We were interested in toxicities data. Indeed unilateral radiation has its interest in improvement of toxicity and quality of life. We know head and neck radiotherapy is responsible for side effect which has a major impact on quality of life. A cohort of 25 oropharyngeal squamous cell carcinoma showed quality of life was mostly related to the ability to eat however 80% of the population still had dry mouth 3.5 years after treatment and 40% did not regain weight loss.(61) Several studies showed sparing contralateral parotid gland provide better control of xerostomia. In fact mean dose to contralateral parotid gland is the only responsible for xerostomia and after 2 years of unilateral treatment contralateral parotid gland function is retained.(62,63)

Dysphagia, hyposialia, agueusia, weight loss, epidermitis, mucositis and PEG tube placement and dependency are criteria of interest. They are described in table 8. Median weight loss was 5kg for the whole study, from none to 43.5kg. The patient who lost 43.5kg had hyperthyroidism among others medical disease and it was responsible for this important weight loss.

Other side effects we observed in our study was nausea grade 2 for 3 patients treated with concurrent chemoradiation and treatment was bilateral, 2 patients had grade 1 nausea who one of them received ipsilateral treatment and the other bilateral treatment.

Ostoradionecrosis was observed for 2 patients whose one received unilateral and the other bilateral treatment. Both patients who developped osteoradionecrosis had fibula free flap at distance to treat.

	Bilateral radiation (15)	Ipsilateral radiation (6)
Dysphagia Grade 1 Grade 2 Grade 3	 3 6 2	 1 0 2
Xerostomia	10	5
Agueusia Dysgueusia	8 4	4 1
Epidermitis Grade 1 Grade 2 Grade 3	 3 5 3	 2 3 0
Mucositis Grade 1 Grade 2 Grade 3	 2 8 1	 1 2 2
Osteoradionecrosis	1	1
PEG tube placement	5	2
PEG tube at the end of radiation treatment	4	2
PEG tube long term dependency *	1	0

Table 8 : Toxicities data for both group of treatment

*long term dependency means here : present at the last follow-up

We realized as well a statistical analyses to compare toxicities between ipsilaterally treated and bilaterally treated population. Results are shown in table 9. We can see hyposialia was the only criteria significantly different in our study. However our cohort is small and both group are not homogeneous particularly concerning the size of the group. We may suggest dysphagia would be significantly different if cohort was larger as p=0.14 is close to significant result.

	Bilateral	Unilateral	P
Hyposialia	15	6	0.05
Agueusia	15	6	0.55
Epidermitis	15	6	0.82
Mucositis	15	6	0.36
Dysphagia	14	6	0.14
PEG tube placement	4	2	1

Table 9 : statistical analyses concerning toxicities according to bilaterally and unilaterally treated population

Discussion

Because of the retrospective nature of the study and the small cohort of 21 patients, our results must be interpreted with caution.

Furthermore our population was not homogeneous. Indeed primary tumors were not homogeneous concerning lateralization : 13 patients had involvement of adjacent structures. T stage was also not homogeneous but they all had T1 or T2 extension and we know they have similar outcomes.(4)

Nodal extension was also not homogeneous as extra-capsular extension was only present in a part of the population, 15/21, number of nodes involved was different from one an other but they all had N2b disease which was the stage of interest.

Concerning treatment, all patients did not receive the same treatment. First 6 received unilateral radiation while others received bilateral treatment but it was protocol of the study to select unilateral and bilateral treatment. Furthermore 4 patients were not treated with concurrent chemoradiation.

Finally p16 status, smoking and alcohol history were also not homogeneous. Indeed p16 status was mostly unknown, 28.5% were p16 positive and 4.5% p16 negative. Yet we know HPV positive tumors are exactly the phenotype of our population : small T stage but advanced nodal extension.(33,53) So we could imagine our population was a majority of p16 positive patients which could explain our great outcomes knowing they have a better response to treatment.(13,53,54) Though most of them had excessive alcohol history and current smoking status which is not supporting this hypothesis. However we know regional recurrences rate are not significantly different between p16 positive and

p16 negative population meaning our primary outcome would have not be different.(40) However it would have been interesting to know HPV status. It seems essential in HPV era to determine HPV status to treat patients with the most adapted treatment.

An other bias in our study is that not all patients had 5 years of follow up regarding the fact that 5 patients died of disease whose 2 very soon after treatment. Yet recommandations encourage to follow tightly during 5 years, time during which recurrence's risk is higher.

Our study presents a population with advanced disease. First of all half of patients had extension of midline structures as soft palate and BOT but none was crossing midline. The other half had extension to adjacent structures but not midline structures. However they all had small T stage : all population was T1 or T2 as in Cerezo et al, who did not experience any contralateral failure as well. Furthermore nodal disease was extended by the N2b stage first but also cause of the high proportion of extra-nodal extension (71.5%) and 14% had more than 10 nodes involved. And there were others pejorative prognostic factores present in high proportion : 38% of the population had positive margins, 28.5% had perineural invasion and 33% vasculars embolisms. Despite these characteristics none failed in the primary site or neck and especially none failed in the contralateral neck. But 5 had distant metastasis and 4 of them died of disease.

It is true our unilateral treated population is very small however 4 of the 6 patients had involvement of adjacent structures whose one of the BOT and they did not fail. In other studies like in Liu et al, patients from the group non lateralized tumors received bilateral treatment. In the litterature outcomes are opposing concerning extra capsular extension and association with recurrence as in Vergeer et al, which did not find significant influence of extra nodal spread on contralateral recurrence while Lynch et al, found signicant impact on failure when patients had extra capsular extension. These studies had around 20% of patients with extra capsular extension while in our cohort 71% of patients had extra nodal spread. This is however proved that extra capsular extension is a prognostic factor to recurrence.(34)

Regarding disease's extension in our population we understand why 81% of our population received chemoradiation. As in Kennedy et al, according to prognostic factors almost all patients received concurrent chemoradiation improving outcomes and

especially loco-regional control but increasing toxicity.(59) It could explain toxicities data in our study regardless of side radiotherapy. Indeed there was no difference except for hyposialia regarding radiation treatment. However a larger cohort could help to highlight significant differences.

Conclusion

In our population, any patient failed in the contralateral neck but our study was small. Prospective study with larger cohort needs to be planned to help to establish international recommandations and finally support an homogeneous management in contralateral neck treatment for patients with advanced nodal disease and especially N2b disease.

Conclusion

Il existe à ce jour, encore peu de données dans la littérature concernant le traitement adjuvant du cou controlatéral pour les patients atteints d'un cancer oropharyngé avec extension ganglionnaire classée N2b.

L'étude réalisée ne permet pas de mettre en évidence de différence significative concernant la récidive ganglionnaire et la toxicité entre une population de patients traités, pour un cancer oropharyngé de petit stade tumoral (T1-T2), par radiothérapie cervicale unilatérale ou bilatérale.

Le projet de cette étude rétrospective est de guider la réalisation d'une étude prospective au sein du centre, d'analyser statistiquement les résultats concernant la récidive ganglionnaire controlatérale dans une exacte même population. L'une des limites et difficulté de réalisation de cette étude à venir, au sein de notre centre, sera de sélectionner une population suffisamment grande afin d'avoir des résultats statistiques fiables.

Il parait encore difficile, étant donné l'absence de toute étude randomisée et l'existence d'une seule étude prospective dans la littérature, d'écrire des recommandations sûres concernant la prise en charge du cou controlatérale chez ces patients. Mais l'ensemble des données de cette revue et de l'étude laisse à penser qu'il s'agit d'une technique tout à fait envisageable, d'autant plus que la population atteinte de cancer oropharyngé tend à être de plus en plus jeune et qu'un point essentiel de leur prise en charge est le contrôle des toxicités notamment tardives qui ont un impact majeur sur la qualité de vie future de ces patients. Les techniques de pointe de surveillance comme le FDG-PET scanner permettent également d'envisager un suivi rapproché de ces patients afin de traiter le plus rapidement et efficacement possible des récidives possibles à venir en cas de traitement unilatéral. Le bénéfice quotidien de l'absence de toxicité tardive en comparaison à une récidive ganglionnaire controlatérale détectée à un stade très précoce et traitée par curage ganglionnaire suivi plus ou moins par un traitement adjuvant semble être une balance dont il faut discuter dans un premier temps en Réunion de Concertation Pluridisciplinaire entre spécialistes et médecins référents du patient, prenant en compte l'ensemble des données de ce dernier et notamment son âge et ses comorbidités et enfin avec le patient lui-même, principal acteur de sa prise en charge.

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ANNEE DE SOUTENANCE : 2020/2021

NOM ET PRENOM DE L'AUTEUR : OLIVIERO Agnès

TITRE DE LA THESE : Cancer de l'oropharynx T1-2 N2b opéré : contrôle loco-régional après radiothérapie unilatérale ou bilatérale

RESUME DE LA THESE EN FRANÇAIS :

Il existe actuellement des données de la littérature contradictoires et insuffisantes pour déterminer la prise en charge par radiothérapie cervicale des cancers oropharyngés avec extension ganglionnaire classée N2b. Il s'agit de trouver un équilibre entre toxicités tardives qui affectent la qualité de vie des patients de façon importante et risque de récidive cervicale controlatérale. Ainsi une revue systématique de la littérature a été réalisée afin de rassembler les données existantes actuelles.

Nous avons ensuite réalisé une étude observationnelle rétrospective au sein du centre François Baclesse avec pour but de mettre en évidence la présence de récurrence controlatérale cervicale et les toxicités présentes chez les patients traités par radiothérapie cervicale unilatérale et bilatérale. 6 patients ont été traités en unilatéral et 15 en bilatéral. Aucun des 21 patients n'a présenté de récidive controlatérale. Le contrôle loco-régional est de 100%. La survie globale de 76%.

Nous avons enregistré les données concernant les toxicités les plus fréquentes : dysphagie, xérostomie, perte de poids, agueusie, nécessité de nutrition entérale et ostéoradionécrose.

MOTS-CLES : Cancer oropharyngé, Radiothérapie, T1-2, N2b, post-operatoire

TITRE DE LA THESE EN ANGLAIS : Post-operative T1-2 N2b oropharyngeal squamous cell carcinoma : loco-regional control after ipsilateral or bilateral neck radiation

RESUME DE LA THESE EN ANGLAIS :

Actually litterature's data are opposing and not sufficient to decide if post-operative radiation is safe enough to be as efficient as bilateral treatment concerning contralateral neck failure in oropharyngeal squamous cell carcinoma with N2b nodal disease. It is necessary to find balance between late toxicities providing by bilateral radiation and loco-regional control.

We first collected data that were already existing in the litterature and wrote a review. Then we established a retrospective study in François Baclesse center and registered outcomes concerning contralateral recurrences and toxicities in a population of patients with T1-T2 N2b disease. 6 patients received unilateral treatment and 15 received bilateral treatment. None of the 21 patients failed in the contralateral neck and so loco-regional control at the end of the study was 100%. Overall survival was 76%. We collected data concerning the most common toxicities as agueusia, dysphagia, xerostomia, osteoradionecrosis, loss of weight of PEG tube.

KEY WORDS : Oorpharyngeal cancer, radiotherapy, T1-2, N2b, post-operative