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# Radiothérapie conformationnelle par modulation d'intensité des cancers de la cavité buccale et de l'oropharynx : analyse des résultats carcinologiques et des récurrences locales

Cécile Mione

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UNIVERSITE CLERMONT AUVERGNE  
UFR DE MEDECINE ET DES PROFESSIONS PARAMEDICALES

THESE D'EXERCICE

pour le

DIPLOME D'ETAT DE DOCTEUR EN MEDECINE

par

**MIONE Cécile**

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Présentée et soutenue publiquement le 8 avril 2022  
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**Radiothérapie conformationnelle par modulation d'intensité des  
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Membres du jury : Madame Nathalie PHAM DANG, Professeur  
Monsieur Michel LAPEYRE, Docteur  
Monsieur Julian BIAU, Docteur





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## **LISTE DES ABBREVIATIONS**

**CBCT** : Cone Beam CT

**CT**: computed tomography

**CTV** : Clinical Target Volume

**DFS** : Disease free survival

**ENE -** : positive node, without extranodal extension; **ECE +** : extranodal extension

**fd95%** : Dose received by 95% of the volume of failure

**GTV** : Gross Tumor Volume

**Gy** : Gray

**IMRT** : Intensity modulated radiation therapy

**LC** : Local control

**LRC** : Locoregional control rate

**MRI** : Magnetic Resonance Imaging

**N-** : none positive node

**ND** : not determined

**NR** : not reported

**OC** : oral cavity, **OP**: oropharynx

**ORN** : osteoradionecrosis

**OS** : Overall survival

**pCT**: planning CT ; **rCT**: recurrence CT

**PNI** : perineural invasion

**PTV** : Planned target volume

**R <5mm** : close margin, <5mm

**R1** : microscopic positive margin ; **R2** : macroscopic positive margin ; **R0** : negative margin

**RIR** : rigid image registration/ **DIR**: deformable image registration

**RT** : Radiation therapy

**SCC** : Squamous cell carcinoma

**TV** : Target volume

**UICC** : Union for International Cancer Control

**VMAT** : Volumetric modulated arctherapy

**V<sub>recur</sub>** : recurrence volume

## **I- AVANT-PROPOS**

Les cancers de la cavité buccale et de l'oropharynx sont un sujet majeur de santé publique. Il s'agit en effet de l'un des rares cancers dont l'incidence augmente, notamment chez la femme, dont la consommation de tabac et d'alcool s'accroît, mais également avec l'augmentation de cas viro-induits par HPV (Human Papilloma Virus) ces dernières années, pour les cancers de l'oropharynx.

La prise en charge de ces cancers est complexe et multidisciplinaire. Lorsqu'elle est réalisable, la chirurgie première est une des pierres angulaires du traitement. Cependant, lorsqu'il existe des facteurs de risque de récurrence (stade avancé, marges à risque, embolies lymphatiques, engainements périnerveux, adénopathies avec rupture capsulaire, etc...), une radiothérapie post-opératoire est indiquée, parfois potentialisée par de la chimiothérapie notamment en cas de marge R1 et/ou de rupture capsulaire.

La radiothérapie conformationnelle avec modulation d'intensité (IMRT ou RCMI), validée par l'HAS depuis 2003, et développée à Clermont-Ferrand, au Centre Jean Perrin, dans l'équipe du Dr Lapeyre en 2011, est aujourd'hui la technique d'irradiation de référence dans le traitement des cancers de la tête et du cou. Elle permet, par rapport à la technique conformationnelle en trois dimensions, de réduire la dose aux organes à risque tout en délivrant une forte dose aux volumes cibles. De nombreuses études ont effectivement rapporté les résultats de cette technique, notamment pour le maintien de la fonction salivaire. Cependant, cette technique, qui permet un fort gradient entre les structures, pourrait générer un risque accru de récurrence, dans les cas de volumes d'irradiation trop restreints. La délimitation ou contourage des volumes cibles est donc une étape essentielle, qui conditionne les résultats du traitement notamment en terme de contrôle locorégional, et exige une solide expérience de l'équipe médico-physique.

Les récurrences des cancers de la tête et du cou sont de mauvais pronostic et conduisent le plus souvent au décès. Il est donc nécessaire de déterminer leur étiologie, pour apporter des mesures correctives, et ce, malgré la complexité des méthodes pour les analyser.

Ce travail de thèse se donne donc l'objectif de contribuer à la compréhension des récurrences locales. Il s'inscrit dans une démarche d'analyse des résultats carcinologiques des patients traités par RCMi post-opératoire, entre 2011 et 2019, pour des carcinomes épidermoïdes, de la cavité buccale ou de l'oropharynx, en la complétant par un focus particulier appliqué à l'analyse des récurrences locales. Il poursuit un travail non publié, initié en 2015 par le Dr Martin, sous la direction du Dr Lapeyre. Ce travail de thèse se présente sous la forme de trois articles :

Le premier article décrit les résultats globaux en termes d'efficacité et de toxicité, après radiothérapie post-opératoire de patients traités pour un carcinome épidermoïdes de la cavité buccale et de l'oropharynx, entre 2011 et 2019. .

Le second article est une revue de la littérature est une revue de la littérature des différentes méthodes validées d'analyse des récurrences (Mione et al., *Cancer/Radiothérapie*, 2021).

Le troisième article décrit les sites de récurrences locales en fonction des méthodes appliquées.

Nous concluons en soulignant les difficultés d'interprétation et le besoin d'une méthodologie d'analyse standardisée, pour poursuivre la compréhension des récurrences et améliorer ainsi les pratiques thérapeutiques.

## **II- Outcomes of oropharyngeal and oral cavity cancer patients treated with postoperative volumetric modulated arctherapy**

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## **Introduction**

Surgery is one of the cornerstone treatment of oropharyngeal and oral cavity cancers [1]. Adjuvant postoperative radiation therapy is recommended for patients with adverse features including advanced disease and inadequate margins. The addition of concurrent chemotherapy is recommended, particularly for patients who have ‘high risk’ pathologic features which include extracapsular nodal extension (ENE) and/or a positive surgical margin [1,2].

Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arctherapy (VMAT) is nowadays the recommended radiation technique for the treatment of head and neck cancers [3]. IMRT/VMAT for head and neck cancers is a complex technique both for target volume delineation and dosimetry [4,5]. The delineation of the target volumes is therefore an essential step, which conditions the results of the treatment, particularly in term of locoregional control [6,7] and requires a solid training of the medical-physical team [8,9]. Presently, there are limited published series of postoperative radiation therapy for oropharyngeal and oral cavity cancers treated with an IMRT/VMAT technique.

The aim of this study was to assess the oncologic outcomes and toxicities of operated patients with oropharyngeal and oral cavity squamous cell carcinomas (SCC), treated with postoperative VMAT in our institution.

## **Material and Methods**

### **Patients**

The database maintained by the Department of Radiation Oncology at our institution was used to identify patients treated with postoperative VMAT for oropharyngeal or oral cavity SCC between May 2011 and December 2019. Patients with distant metastases or concurrent malignancies at time of diagnosis, other histology than SCC, R2 margins and/or a previously irradiated cancer of the head and neck were excluded. Our institutional review board guaranteed permission to conduct this retrospective study.

One hundred and sixty-seven patients were retrospectively reviewed. Patient characteristics are described in Table 1.

The initial location of the tumors was the oropharynx in 40% of cases (n=67) and the oral cavity in 60% (n=100) of cases. The median age of the patients was 60 years (20 - 94 years). One hundred and twenty-five patients were smokers (75%). The WHO performance status was assessed as 0 for 78 patients (46,7%), 1 for 73 patients (43,7%), 2 for 15 patients (8,9%) and 3 for 1 patient (0,7%). The TNM stage according to the 2009 International Union Against Cancer (UICC 2009) classification was based on clinical, radiological (cervico-thoracic CT and/or MRI; PET scan was sometimes performed), endoscopic and histological data (Table 1). There were 23 stages 2 (13.7%), 37 stages 3 (22.1%), 94 stages 4a (56.4%) and 13 stages 4b (7.8%).

**Table 1:** Patient and disease characteristics

<b>Characteristics</b>	<b>N (%)</b>
<b>Gender</b>	
Male	122 (73)
Female	45 (27)
<b>Median Age (range)</b>	60 (20-94)
<b>Site</b>	
Oral Cavity	100 (60)
Oropharynx	67 (40)
<b>T-stage</b>	
1-2	72 (43)
3-4	95 (57)
<b>N-stage</b>	
0-1	72 (43)
2-3	95 (57)
<b>UICC Stage 2009</b>	
I	-
II	23 (13,7)
III	37 (22,1)
IVa	94 (56,4)
IVb	13 (7,8)
<b>P16</b>	
Positive	24 (14)
Negative	38 (23)
Unspecified	105 (63)
<b>Smokers</b>	125 (75)
<b>WHO status</b>	
0-1	151 (90)
2-3	16 (10)
<b>Treatment</b>	
<b>Chemotherapy</b>	
Concomitant	72 (43)
Neoadjuvant	5 (3)
No	90 (54)
<b>Nodal surgery</b>	
Bilateral	90 (53.9)
Homolateral	77 (46.1)
<b>Tumor characteristics</b>	
<b>ENE+</b>	68 (42)
<b>Tumor differentiation</b>	
Well	74 (44)
Moderate	56 (34)
Poor	19 (11)
Unspecified	18 (11)
<b>Lymphovascular invasion</b>	
Yes	48 (29)
No	117 (70)
Unspecified	2 (1)
<b>Perineural invasion</b>	
Yes	70 (42)
No	91 (54)
Unspecified	6 (4)
<b>Margin</b>	
R2	-
R1	56 (34)
R0 close < 5mm	63 (37)
R0	41 (25)
Unspecified	7 (4)

## Treatment

The overall treatment strategies were individualized for each patient and recommended at multidisciplinary tumor board.

### - Surgery:

All included patients underwent surgery of the primary tumor associated with lymph node dissection (unilateral for 46.1% and bilateral for 53.9%). The operative technique depended on the location and initial extension of the disease.

Sixty-seven patients (40%) had a free flap inserted during surgical reconstruction.

### - Anatomopathology:

Sixty-three patients had a close margin (<5mm), 56 had microscopic positive margin, 70 had perineural invasion and 48 lymphovascular invasion. 121 had positive neck dissection, 68 of which had nodes with extranodal extension (ENE) (Table 1).

### - Radiotherapy:

Patients underwent radiotherapy in case of advanced tumors (T3-T4), close or positive margins, lymph nodes involvement with or without ENE, the presence of lymph-vascular space invasion, and/or perineural invasion [10,11].

The median interval from surgery to initiation of radiotherapy was 46 days (24 - 100).

All patients were irradiated with VMAT with simultaneous integrated boost (Rapidarc®, Varian Medical Systems, Palo Alto, CA, USA).

A planning CT-scan, supine, in the treatment position, was performed, with 2.5-mm-thick slices, and a personalized thermoformed mask with 5 points of attachment.

Preoperative imaging was merged with the planning CT scan to guide contouring of this surgically reshaped area.

Tumor target volumes and organs at risk were delineated according to the different expert recommendations and contouring consensus [12–17]. Three clinical target volumes (CTV)



were typically defined. CTV1 (59.4 to 60 Gy) was defined as the preoperative tumor bed with margin (1 to 2 cm), and manually adjusted according to anatomical barriers.

CTV2 (54 Gy) was defined as subclinical sites at risk not operated, according to the risk of tumor involvement following guidelines [14–16]. Prophylactic node was irradiated with this same dose, following guidelines [12,13,15]. CTV 3 (66 Gy) was occasionally identified, in cases of ENE and/or positive margin. Planned target volumes (PTV) related to positioning errors and movements were obtained by adding a 4 mm margin around the CTVs.

Treatment was delivered in 30-33 fractions.

The planning system was Eclipse® (Varian Medical Systems), according to the recommendations of the International Commission of Radiation Units report n°83 [18] . The treatment was delivered using a Clinac IX® or Novalis TX® (Varian Medical Systems) linear accelerators delivering 6-MV photons, with daily position control by KV/KV beams or CBCT.

- Chemotherapy:

Seventy-two patients (43%) underwent concurrent chemotherapy. The main indications were R1 positive margins and/or ENE in patients under 70 years of age and in absence of contraindications [10,11,19]. The protocol used for concurrent radiochemotherapy was Cisplatin (100mg/m<sup>2</sup>) on weeks 1, 4 and 7 (n=55; 70.5%). Other concomitant treatment protocols included weekly Cisplatin (n=16; 20.5%). Three patients received induction chemotherapy with Taxotere-Cisplatin-5Fluoro-Uracile, one of whom received concomitant radiochemotherapy with weekly Cisplatin. One patient received induction chemotherapy with Carboplatin-5-Fluoro-Uracile-Erbitux.

## **Follow-up**

Weekly evaluations were done by the treating radiation oncologist for all patients during radiation treatment. The first posttreatment follow-up was at 3 months after radiation completion and then, every 3 months for the first and the second year alternating surgeon and radiation oncologist, and at least twice a year for up to 5 years, afterward yearly. A CT-scan was performed at 3 months and then annually.

## **Statistical analysis**

Groups defined by initial tumor localization were compared using Fisher's exact test and Wilcoxon-Mann-Whitney test. The Kaplan-Meier method was used to calculate survival curves. The last day of radiation therapy was used as time zero.

Comparisons between survival curves were made using the log-rank test. Median follow-up was estimated by the reverse Kaplan-Meier method.

Factors associated with survival were analyzed using univariate Cox regression models followed by penalized multivariate models, obtained by including all variables with a p-value < .05 in the univariate analysis and performing model selection by LASSO method.

All analyses were performed using R statistical software version 4.1.0 (R-Project, GNU GPL). P-values less than 0.05 were considered significant.

Factors associated with survival analyzed were: gender (Male/Female), tobacco use (Never/current or stopped), WHO stage (0/1-3), tumor status (T1-T2/T3-T4), number of pathological lymph nodes ( $\geq 3$ / $< 3$ ), tumor differentiation (well/moderate, poor), lymphovascular invasion, perineural invasion (PNI), extranodal extension (ENE), margin status (R0/close, R1), RT-treatment time and surgery-RT time.

## Results

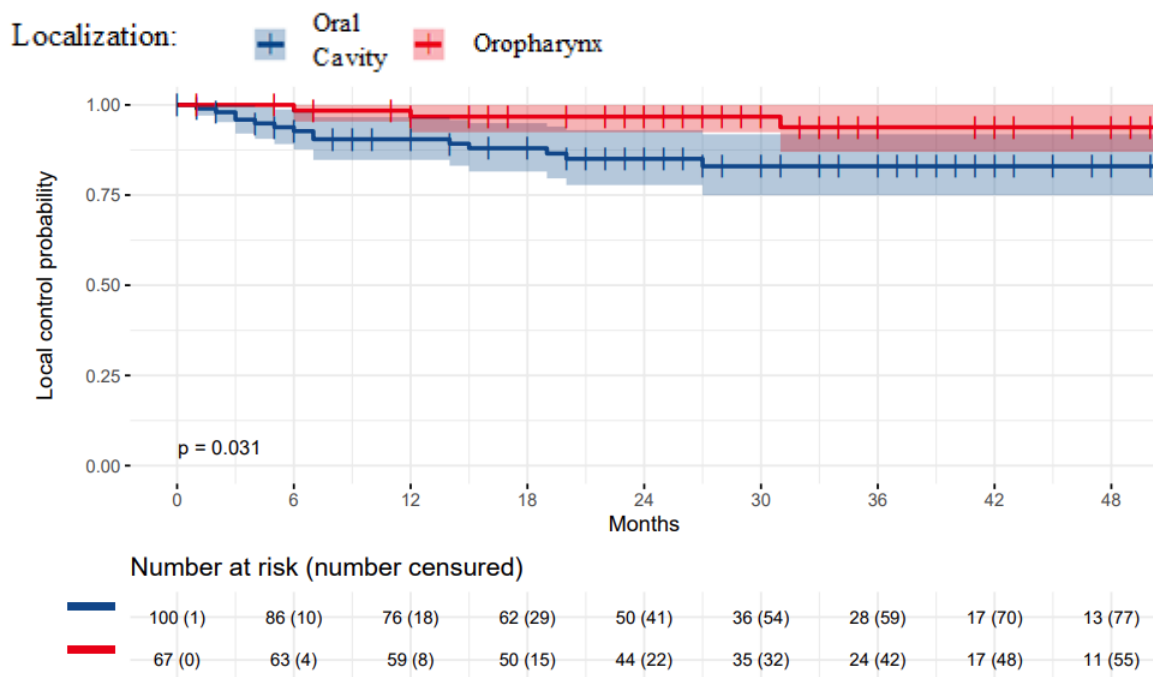
### Local, regional and locoregional control

The median follow-up was 33 months. During follow-up, 26 patients developed locoregional recurrences: 13 local, 9 regional, and 4 both local and regional.

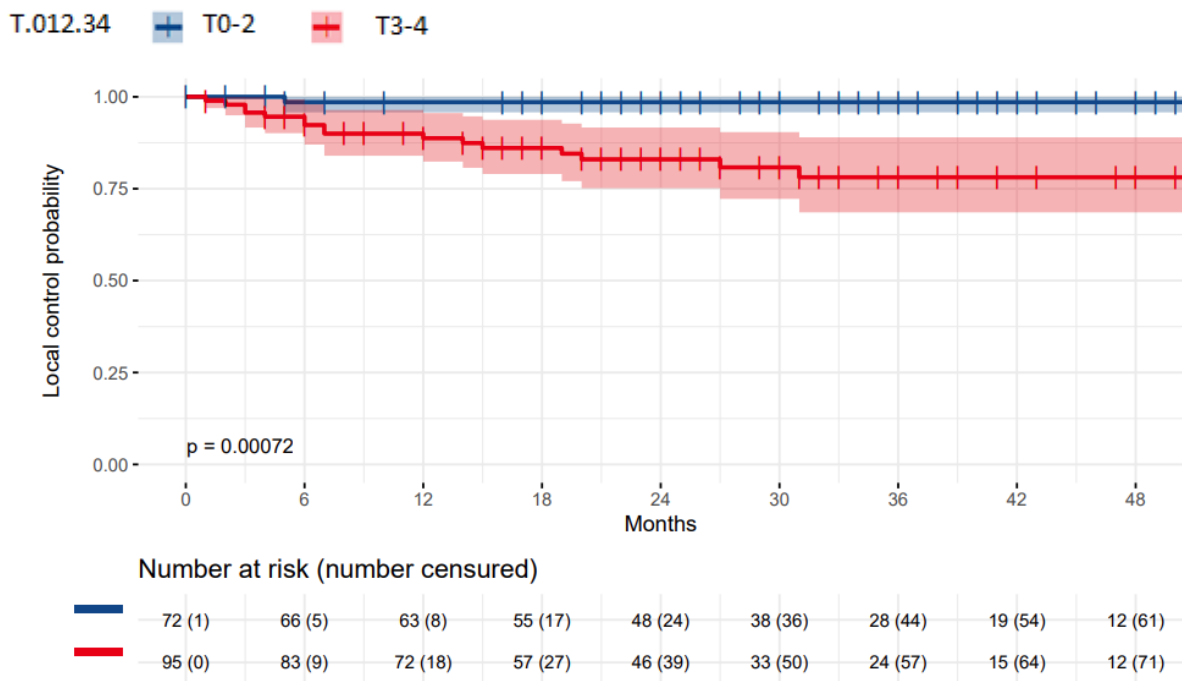
The actuarial 1 and 2-year local control rates were 93% and 90%, respectively, for the all population. For oral cavity cancers, 2-year local control rate was 85.1% vs 96.7% for oropharyngeal cancers ( $p=0.031$ ) (Fig. 1).

Higher tumor stage (T1-2 vs T3-4;  $p<0.001$ ) and presence of PNI ( $p<0.001$ ) were predictive factors of lower local control in univariate and multivariate analysis ( $p=0.03$  and  $p=0.01$  respectively) (Table 2, Fig.2, Fig.3).

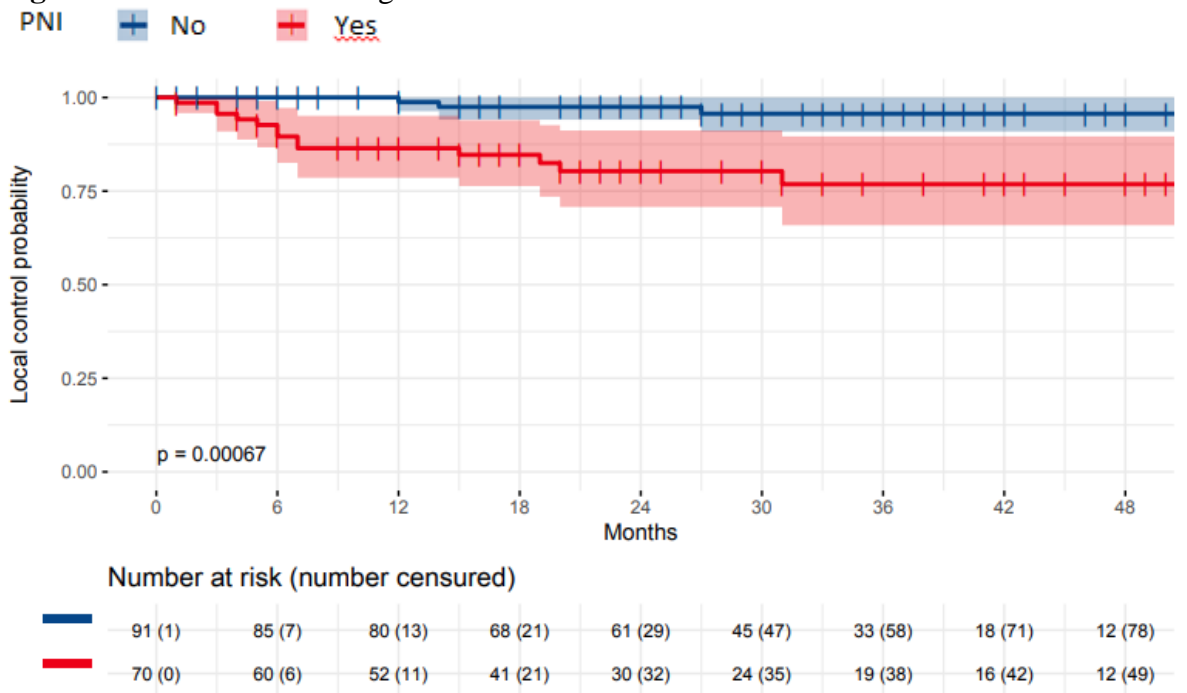
**Fig. 1:** Local control according to tumor site



**Fig.2:** Local control according to T status



**Fig.3:** Local control according to PNI

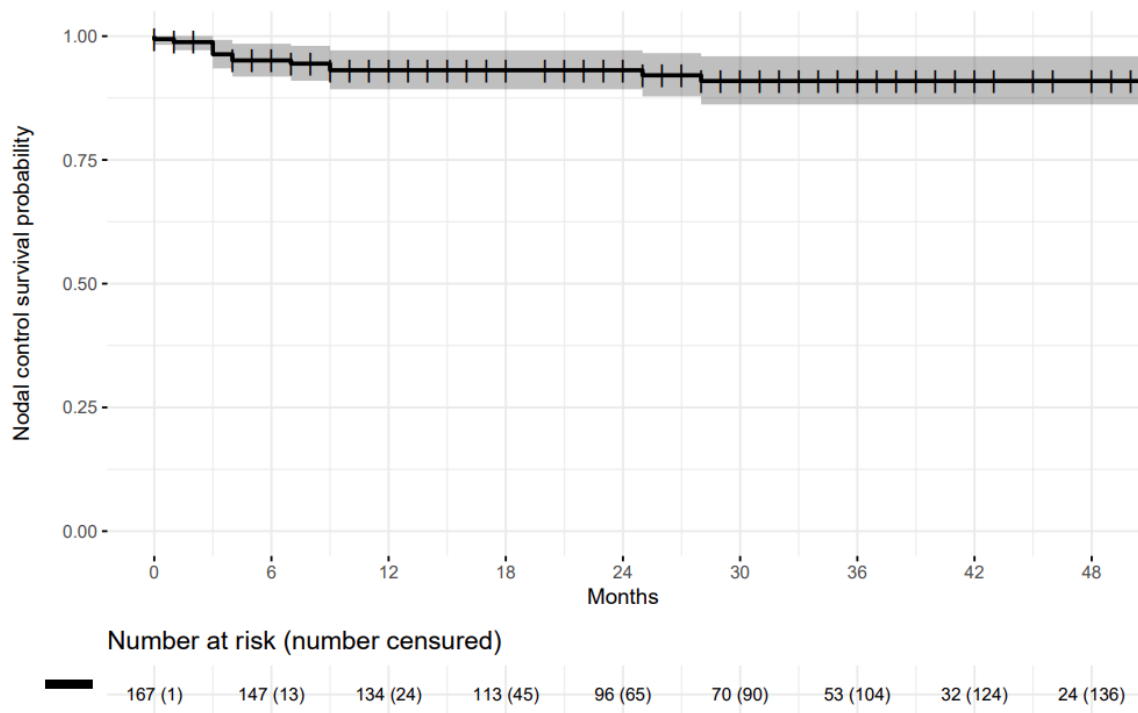


The actuarial 1-year regional control rate was 93.1% (Fig.4), including 90.6% among oral cavity cancer and 96.8% among oropharynx cancer. The actuarial 2-year regional control rate was also 93.1% (Fig.4), including 90.6% and 96.8% among oral cavity and oropharynx cancer

respectively (p=0.16).

Only a number of lymph node superior to 3 was a predictive factor of a lower regional control in univariate and multivariate analysis (p=0.009 and p=0.006 respectively) (Table 2).

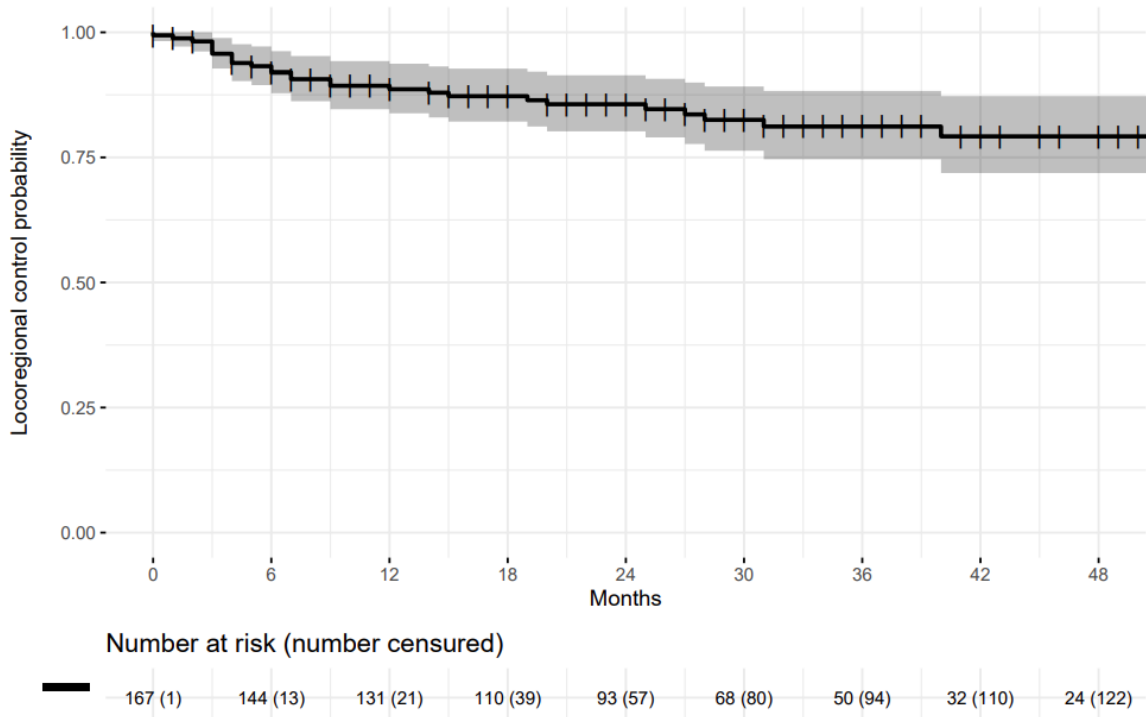
**Fig. 4:** Regional control for the all population



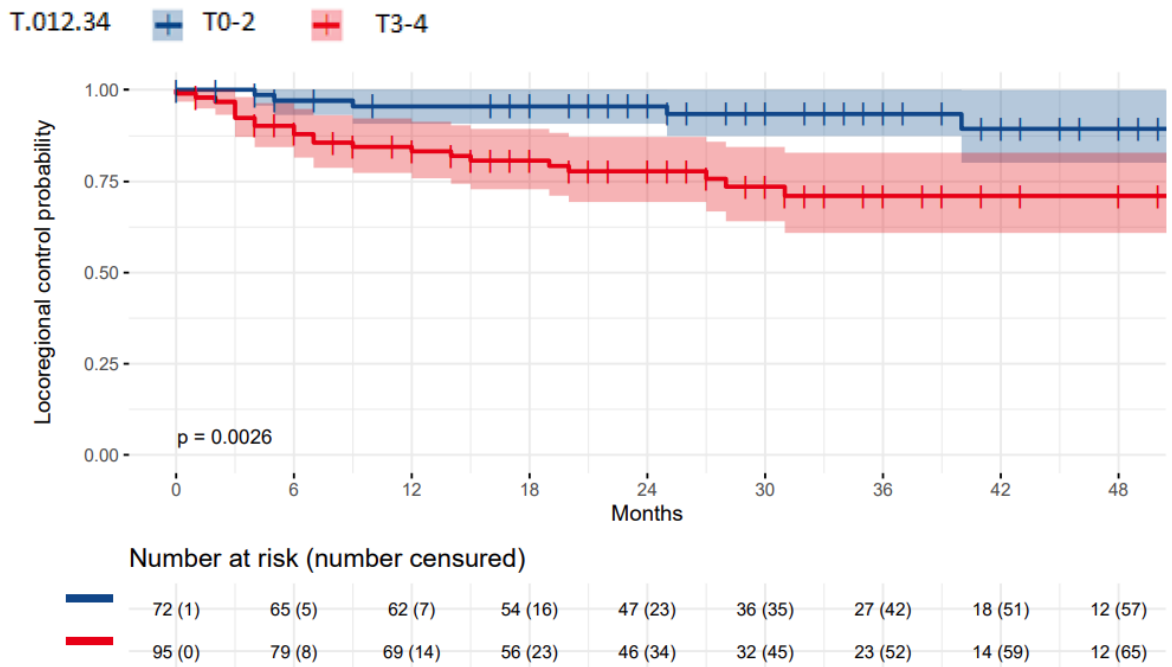
The actuarial 1- and 2-year locoregional control rate was 88.6% and 85.6% respectively (Fig.5), including 85.3% and 80.1% among oral cavity cancer and 93.6% and 93.6% among oropharynx cancer (p=0.022).

Higher tumor stage (T1-2 vs T3-4; p=0.002), presence of PNI (p=0.008) and time from surgery to initiation of VMAT (p=0.03) were predictive factors of lower local control in univariate and multivariate analysis respectively (p=0.02, p=0.04, p=0.02) (Table 2, Fig.6).

**Fig. 5:** Locoregional control for the all population



**Fig.6:** Locoregional control according to T status

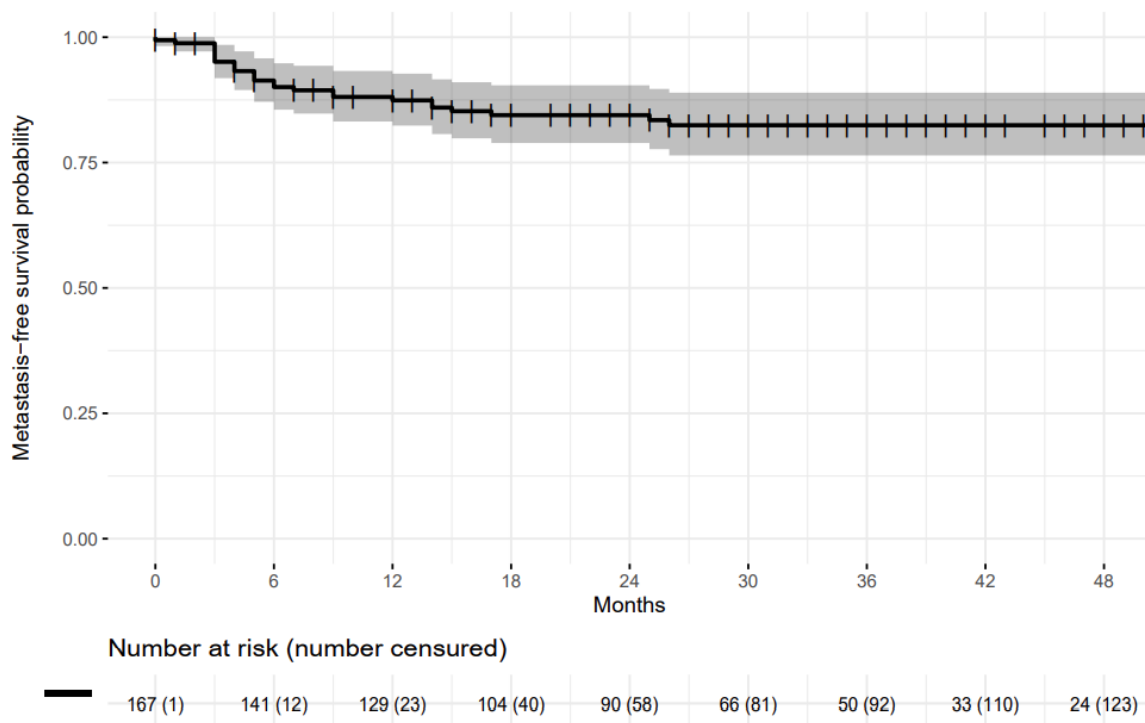


## Metastasis

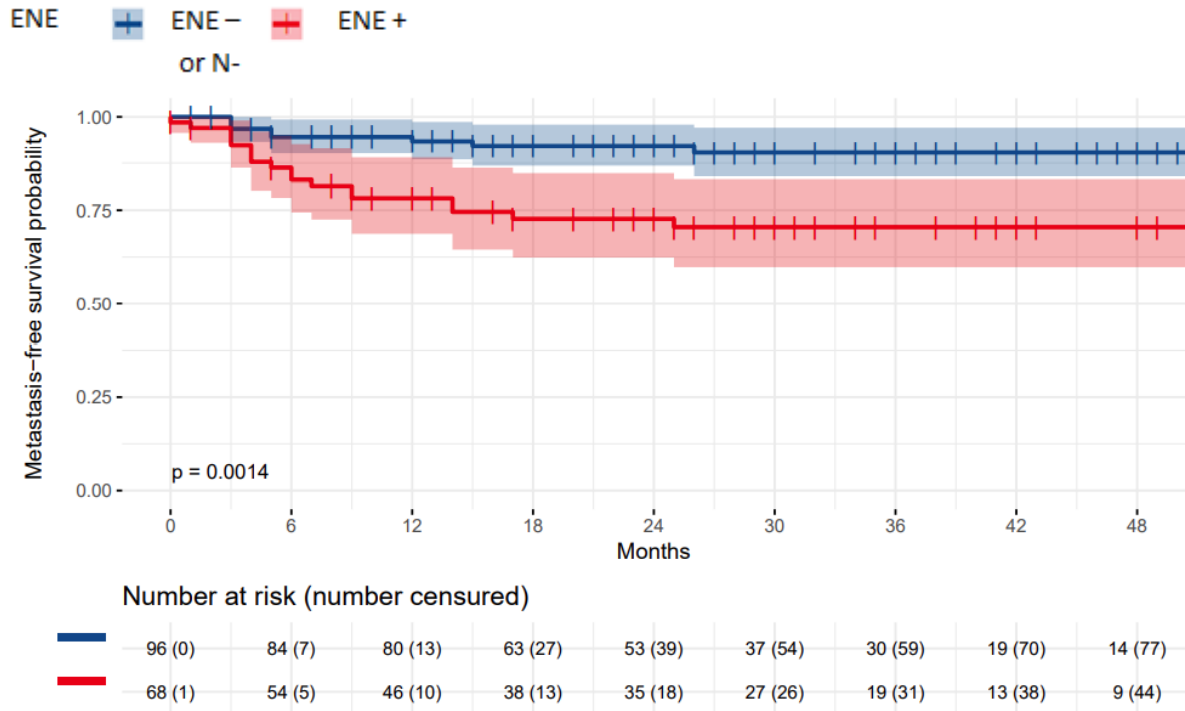
During follow-up, there were 26 metastatic events (15.6%) with a 2-year metastasis-free survival probability of 84.5% (Fig.7). Ten patients treated for an oropharyngeal cancer (2-year probability of metastasis-free survival = 85.9%) and 16 patients treated for an oral cavity tumor (2-year probability of metastasis-free survival = 83.3%) developed secondary localizations (bone, lung, cutaneous and liver) with no difference according to the initial tumor location ( $p=0.74$ ).

In univariate analysis, perineural invasion and ENE were associated with a poorer metastasis free survival. In multivariate analysis, only ENE remains significant (Table 2, Fig.8).

**Fig.7:** Metastasis-Free survival for the all population



**Fig.8:** Metastasis-Free survival according to ENE



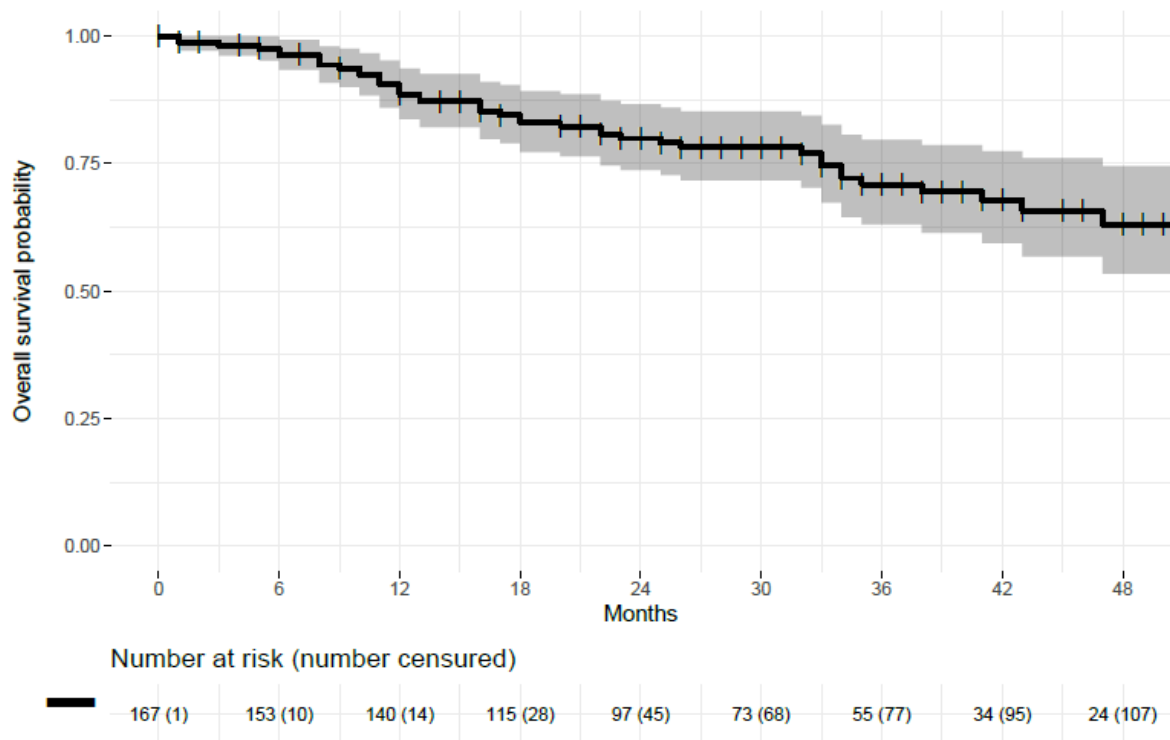
## Survival

Forty-two patients (25%) died during follow-up. The OS rate was 88.6% at 1 year and 80% at 2 years (Fig.9). The 2-year OS was 83.8% for oropharyngeal SCC and 77.3% for oral cavity SCC (p=0.27).

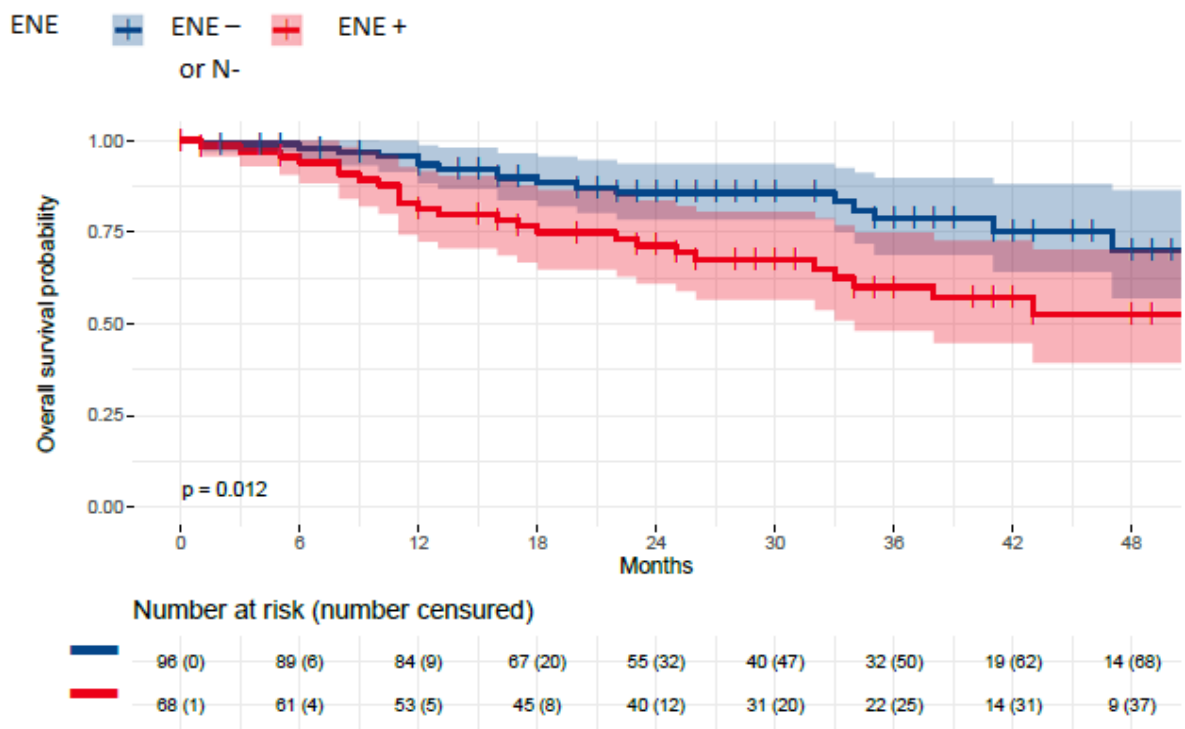
In univariate analysis, WHO stage  $\geq 1$  (p = 0.03), presence of ENE (p = 0.01) and T3-T4 tumors (p=0.004) were statistically associated with a decrease of the OS. In multivariate analysis, only the presence of ENE and T3-T4 tumors were independent predictors of OS (Table 2, Fig.10, Fig.11).



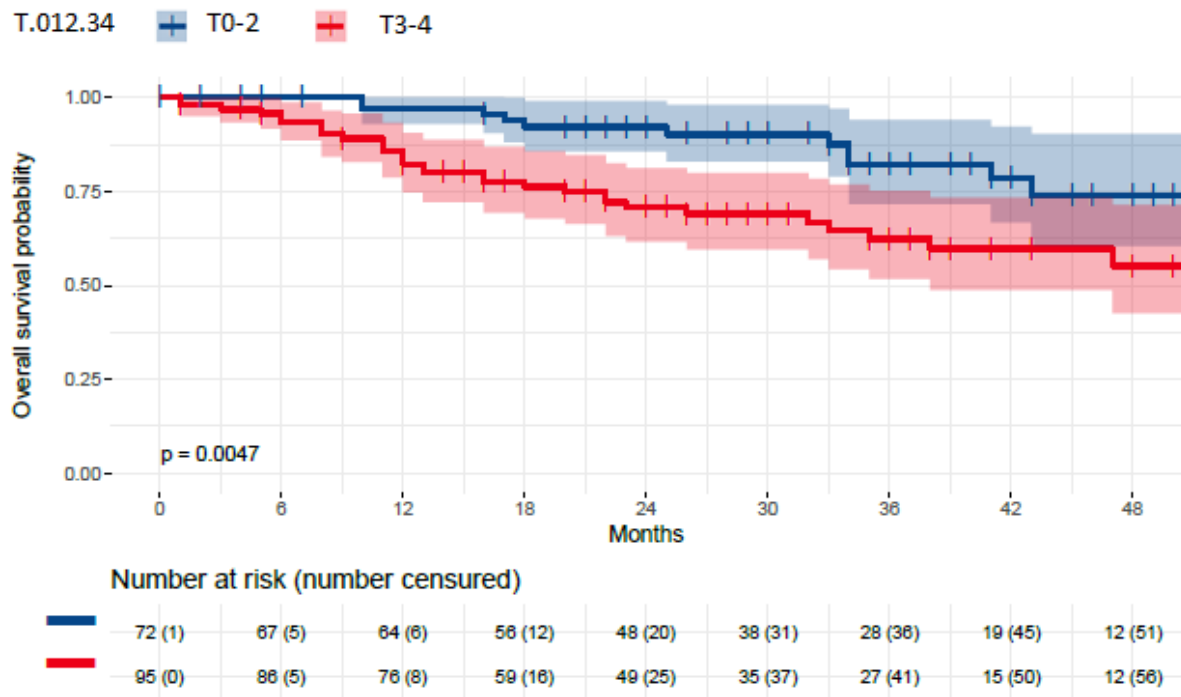
**Fig.9:** Overall survival for the all population



**Fig.10:** Overall survival according to ENE

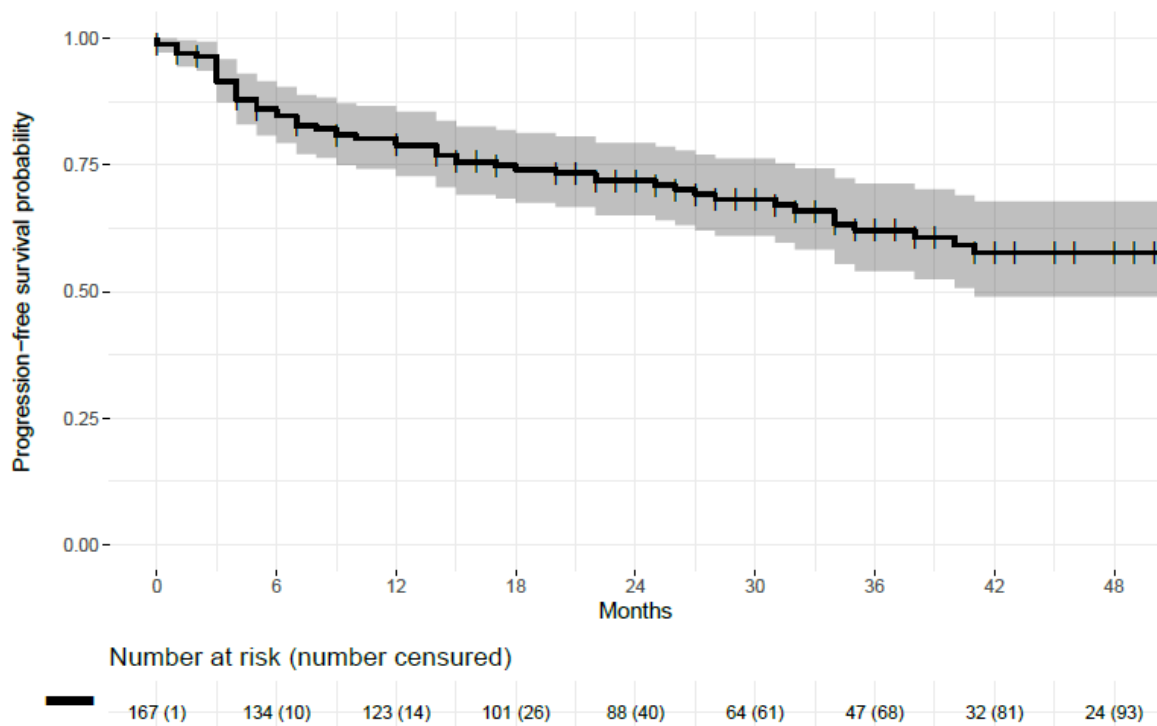


**Fig.11:** Overall survival according to T status

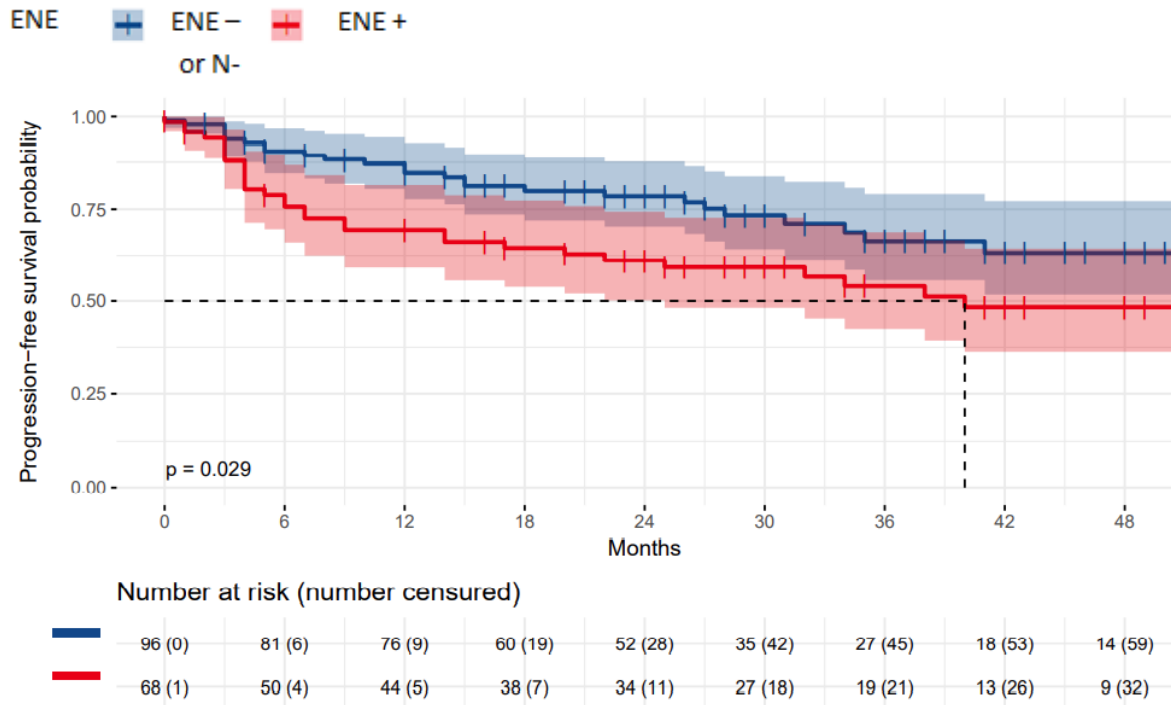


Regarding, the 1- and 2-year disease-free survival (DFS) rate are 78.9% and 71.8% respectively (Fig.12), with 75.7% among oral cavity cancer and 79.9% among oropharynx cancer (p=0.12). In univariate analysis, advanced tumor (T3-T4 stage) (p=0.001), presence of ENE (p = 0.03) were statistically associated with a poorer prognostic and in a multivariate analysis, presence of ENE and T3-T4 were independent predictors of DFS (Table 2, Fig.13, Fig.14).

**Fig.12:** Disease-free survival for the all population

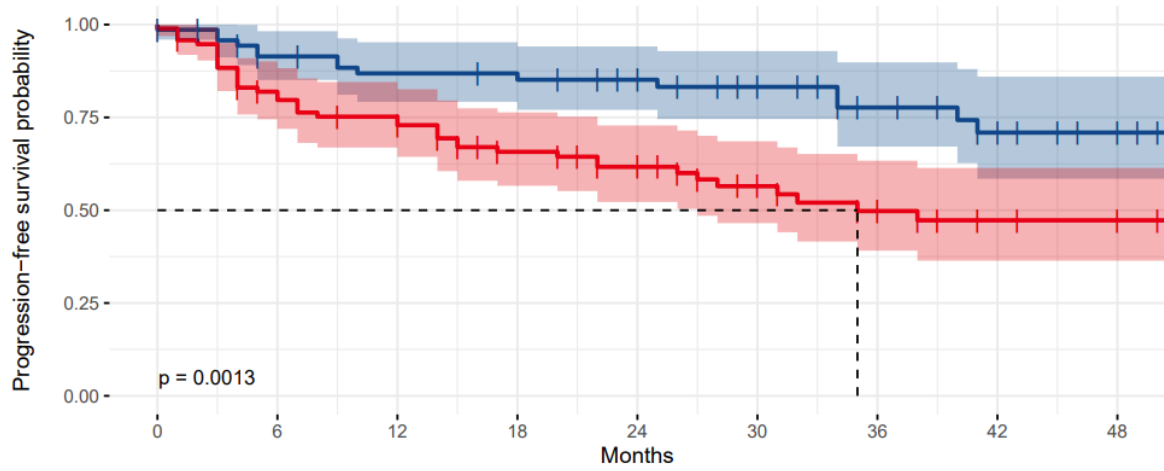


**Fig.13:** Disease-free survival according to ENE



**Fig.14:** Disease-free survival according to T status

T.012.34    ■ T0-2    ■ T3-4



Number at risk (number censored)

■	72 (1)	61 (5)	57 (6)	51 (12)	45 (18)	35 (29)	26 (33)	18 (41)	12 (47)
■	95 (0)	73 (5)	66 (8)	50 (14)	43 (22)	29 (32)	21 (35)	14 (40)	12 (46)

**Table 2: Prognostic factors***PNI +: presence of perineural invasion, RT: radiation therapy, ENE +: presence of extranodal extension*

	<b>Prognostics factors</b>	<b>Univariate Analysis HR (CI 95%)</b>	<b>Multivariate Analysis HR (CI 95%)</b>
<b>Local control</b>	T3-T4	14.135 (1.873 – 106.702) p<0.001	9.88 (1.296 – 75.315) p=0,03
	PNI +	6.633 (1.887 – 23.323) p<0.001	5.127 (1.453 – 18.089) p=0,01
<b>Locoregional control</b>	T3-T4	3.979 (1.504 – 10.524) p=0.002	3.172 (1.167 – 8.624) p=0.02
	Time from surgery to RT	1.035 (1.008 – 1.062) p=0.03	1.041 (1.003 – 1.082) p=0.04
	PNI +	2.911 (1.294 – 6.549) p=0.008	2.714 (1.17 – 6.296) p=0.02
<b>Regional control</b>	Lymph node >3	4.906 (1.581 – 15.225) p=0.009	4.906 (1.581 – 15.225) p=0.006
<b>Overall survival</b>	WHO stage 1-3	1.997 (1.067 – 3.74) p=0.03	1.651 (0.868 – 3.14) p=0.13
	T3-T4	2.606 (1.308 – 5.192) p=0.004	2.529 (1.252 – 5.111) p=0.01
	ENE +	2.167 (1.17 – 4.013) p=0.01	2.295 (1.213 – 4.345) p=0.01
<b>Metastasis-free survival</b>	T3-T4	2.551 (1.409 – 4.617) p=0.001	2.544 (1.399 – 4.625) p=0.002
	ENE +	1.785 (1.055 – 3.02) p=0.03	1.921 (1.127 – 3.273) p=0.02
<b>Disease free survival</b>	T3-T4	2.551 (1.409 – 4.617) p=0.001	2.544 (1.399 – 4.625) p=0.002
	ENE +	1.785 (1.055 – 3.02) p=0.03	1.921 (1.127 – 3.273) p=0.02

## **Radiotherapy toxicities**

- Acute toxicities:

Acute mucosal and skin toxicities grade > 2 were 14.4% and 6.6%, respectively. The rate of acute dysphagia and xerostomia  $\geq 2$  was 20.4% and 35.9% respectively.

- Long term toxicities:

At 1 year, 4% of patients had grade 2 dysphagia. Grade 2 xerostomia was 20% at 1 year. Subcutaneous fibrosis at 1 year was grade 1 in 34% of patients, grade 2 in 17% of patients and grade 0 in 49% of patients.

Among the 167 patients analyzed, 7 developed osteoradionecrosis.

## **Discussion**

IMRT/VMAT has been increasingly used over the last two decades for the treatment of head and neck cancers, and is nowadays the gold standard technique of radiation therapy for these cancers. However, the data regarding the outcomes using IMRT/VMAT in the post-operative setting of oral cavity and oropharyngeal cancers are very limited [20–27]. Thus, our series, despite its relative low number of patients (n=167), represents one of the largest series reported to date. The outcomes reported in our series are in line with the ones reported in the literature [21,22,25,27–30] (Table 3). We found that postoperative VMAT reached high rates of local and loco-regional control with low toxicity. However, we found that ENE+, despite this modern radiochemotherapy era, remained a major issue.

Concerning local recurrences, during follow-up, only 17 patients (10%) developed a local recurrence with actuarial 1 and 2-year local control rates of 93% and 90%, respectively. Higher tumor stages and presence of PNI were the only predictive factors in multivariate analysis of worse LC. R1 margins were not found as predictive factors of LC. This is in line

with different recent reports in the chemoradiation era that did not find R1 margins as predictive factors of worse LC [20,23,25,31], as it was in the radiation alone era. It seems that the negative impact of R1 margins has been fully negated by using higher radiotherapy doses (usually 66Gy) and chemoradiation. However, it doesn't seem to be the case for ENE. Indeed, in our series, the presence of ENE was found as prognostic factors of worse DFS, metastasis-free survival, and OS. A recent series of 439 patients with head and neck SCC (all localizations) treated with postoperative radiotherapy has also reported the negative prognostic factor of ENE despite the use of chemoradiation [31]. This finding highlights the necessity to find new strategies for patients with ENE treated postoperative chemoradiation as in the ongoing NIVOPOSTOP trial testing the addition of Nivolumab to standard cisplatin-based chemoradiation (NCT03576417).

We also found that oral cavity cancers are globally worse outcomes than oropharyngeal cancers, with 2-year LC rates of 85.1% vs 96.7% ( $p=0.031$ ) (Figure 1); and 2-year OS rates of 77.3% vs 83.8% (non-significant, probably to a lack of statistical power). This is in-line with previously reported series [21,25,32].

Regarding chemotherapy, 72 patients (43%) were treated with radiotherapy combined with chemotherapy (16 weekly cisplatin, 55 cisplatin every 3 weeks, 7 others). The LC and OS rates of these high-risk patients were similar to the patients with lower risk of recurrence, treated without chemotherapy. It is possible that without concomitant chemotherapy the outcome in high-risk patients would have been worse [25]. The total amount of failures in this series is, however, too low to make any firm calculations between subgroups.

IMRT/VMAT has been mainly developed to spare normal tissues and thus reduce toxicity [33–36]. The most prominent late effect was xerostomia for 20% of patients having grade 2 xerostomia at 1-year. No higher than grade 2 xerostomia was observed. In comparison, in the RTOG 9501 phase 3 trial (416 patients treated with 2-D or 3-D

postoperative radiotherapy), 24.9% of patients developed at least 1 grade 3-5 late toxicity in the postoperative chemoradiotherapy group and 20.5% in the postoperative radiotherapy alone group. Another well-known issue following RT of the head and neck has been mandibular osteoradionecrosis (ORN). In a study by Studer et al. [37], factors associated with an increased risk of ORN was the dose >60Gy and previous surgery to the mandible, and mainly the type of surgery. Quinlan-Davidson et al.[20] reported 7% of ORN among 289 patients treated with post-operative IMRT for oral cavity SCC. In our study, 7 (4.2%) patients experienced ORN.

There are few limitations in our study that needs to be highlighted. Potential biases, which are inherent to any retrospective analysis, could have affected the results of this study. Due to the retrospective nature of the study, data missing in the medical files could not be assessed for all patients; for example, the depth of invasion for oral cavity cancers was often missing. This series was also monocentric, however, all patients were treated in the same institution on a rather homogeneous way by surgery and post-operative radiotherapy regarding both dose prescription and delineation.



**Table 3:** Outcomes by previous reports concerning post-operative IMRT in oral cavity and oropharynx SCC

OC: oral cavity, OP: oropharynx, LC: local control, LRC: loco-regional control, OS: overall survival, NR: not reported, DOI: depth of invasion, PY: pack-year, R1: positive margins

Authors	Study Period	Sites (No. of patients)	Median Follow-up (months)	LR recurrence (No., %)	Local recurrence (No., %)	2-year LC rate	2-year LRC rate	2-year OS rate	Risk factors (in multivariate analysis)
Quilan-Davidson et al. [20]	2000-2012	289 OC	35	63 (22%)	31 (11%)	86%	79%	69%	<ul style="list-style-type: none"> <li>- <b>LC recurrence:</b> DOI&gt;1.5mm, R1, tobacco &lt; 20PY, no free flap reconstruction,</li> <li>- <b>LR recurrence:</b> DOI, R1, no free flap reconstruction, neck dissection status, and tobacco &lt; 20PY</li> <li>- <b>OS:</b> neck dissection status, lymphovascular invasion, DOI</li> </ul>
Chan et al. [22]	2005-2010	180 OC	34	38 (21%)	22 (12%)	87%	78%	65%	<ul style="list-style-type: none"> <li>- <b>LC recurrence:</b> Oral tongue subsite,</li> <li>- <b>LR recurrence:</b> N2</li> <li>- <b>OS:</b> Oral tongue subsite, N2, R1, tumor size</li> </ul>
Collan et al. [25]	2001-2007	40 OC 62 OP	55	8 (8%): 5 OC et 3 OP	3 (3%)	OC: 85% OP :94%	NR	OC: 82% OP: 96%	<ul style="list-style-type: none"> <li>- <b>LC recurrence:</b> Oral cavity site,</li> <li>- <b>OS:</b> Oral cavity site</li> </ul>
Present study	2011-2019	100 OC 67 OP	33	26 (15%)	17 (10%)	OC: 85.1% OP: 96.7%	85.6%	OC: 77.3% OP: 83.8%	<ul style="list-style-type: none"> <li>- <b>LC recurrence:</b> T3-T4 stage, ENE +</li> <li>- <b>LR recurrence:</b> T3-T4, time from surgery to RT, PNI</li> <li>- <b>OS:</b> T3-T4 stage, ENE +</li> </ul>

## **Conclusion**

Our outcomes of postoperative radiotherapy in the modern era of intensity modulated radiotherapy and chemoradiotherapy are very encouraging with high rates of locoregional control (85.6% at 2 years), and low rates of late toxicity. However, the management of ENE seems still challenging as they were identified as strong unfavorable prognostic factors.

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### III- Impact of the method chosen for the analysis of recurrences after radiotherapy for head and neck cancers: volume-based, point-based and combined methods

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#### Impact of the method chosen for the analysis of recurrences after radiotherapy for head and neck cancers: volume-based, point-based and combined methods



*Impact des différentes méthodes d'analyse des récurrences après radiothérapie pour les cancers des voies aéro-digestives supérieures : méthodes volumétriques, poncutelles et combinées*

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#### ABSTRACT

Intensity modulated radiation therapy for head and neck is a complex technique. Inappropriate delineation and/or dose distribution can lead to recurrences. Analysis of these recurrences should lead to improve clinical practice. For several years, different methods of analysis have been described. The purpose of this review is to describe these different methods and to discuss their advantages and limitations. The first published methods used a volume-based approach studying the entire volume of recurrence according to initial target volumes, or dose distribution. The main limitation of these methods was that the volume of recurrence studied was dependent on the delay in diagnosis of that recurrence. Subsequently, other methods used point-based approaches, conceptualizing recurrence either as a spherical expansion from a core of radioresistant cells (center of mass of recurrence volume) or using a more clinical approach, taking into account tumor expansion pathways. More recently, more precise combined methods have been described, combining the different approaches. The choice of method is decisive for conclusions on the origin of recurrence.

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#### RÉSUMÉ

La radiothérapie conformationnelle avec modulation d'intensité des cancers des voies aéro-digestives supérieures est une technique complexe. Une délimitation et/ou une dosimétrie inappropriée peut être à l'origine de récurrences (dans le volume tumoral ou volume cible, marginales ou hors volume traité). L'analyse de ces récurrences devrait permettre l'amélioration des pratiques. Depuis plusieurs années, différentes méthodes d'analyse ont été décrites. L'objectif de cette revue de littérature est de décrire ces différentes méthodes et de discuter de leurs avantages et inconvénients. Les premières méthodes publiées utilisaient une analyse « volumétrique » étudiant le volume entier de la récurrence en fonction des volumes cibles, ou de la dosimétrie initiale. Ces méthodes avaient pour principal inconvénient que le volume de récurrence étudié était dépendant du délai diagnostique de cette récurrence. Par la suite, d'autres méthodes ont utilisé des analyses « ponctuelles », conceptualisant la récurrence soit comme une expansion sphérique à partir d'un noyau de cellule radio-résistantes (barycentre du volume de la récurrence), soit en

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utilisant une analyse plus clinique, prenant en compte les voies d'expansions des tumeurs. Plus récemment, d'autres méthodes « mixtes » plus précises ont été décrites regroupant les différentes approches. Le choix de la méthode est déterminant sur les conclusions sur l'origine des récurrences.

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## 1. Introduction

Intensity modulated radiation therapy (IMRT) is nowadays the recommended radiation technique for the treatment of head and neck cancers (Fig. 1) [1]. IMRT for head and neck cancers is a complex technique both from target volume delineation and dosimetry. In recent years, several publications have demonstrated that inappropriate delineation and/or dosimetry could lead to recurrence and thus worsen the prognosis of patients [2,3].

The criteria and methods used to analyze recurrences are complex and must take into account the specificities of the techniques in order to improve clinical practice. The classical definition of recurrence as “local” and/or “regional” was appropriate in conventional 3D-radiotherapy with large and homogeneous volumes and doses, but is inadequate with IMRT. Over the past years, different methods have been described for the analysis of recurrences after IMRT for head and neck cancers: “volume-based” methods that study the entire volume of recurrence according to initial target volumes or dosimetry [3–7]; “point-based” methods that study a point as the origin of recurrence [8,9]; and “combined” methods that combine different approaches [10–12].

The purpose of this paper is to describe the different methods to analyze head and neck cancers recurrence after IMRT and discuss their advantages and limitations.

## 2. Volume-based methods

### 2.1. Overlap between recurrence volume and initial target volumes

This method quantifies the rate of overlap between the entire volume of recurrence and the initial target volumes [5,6].

The different steps of this method are as follows:

- delineation of the volume of recurrence ( $V_{\text{recur}}$ ) on diagnostic radiological imaging;
- the radiologic imaging of recurrence was co-registered with the pretreatment CT data set used for treatment planning with a rigid [5] or a deformable [6] image registration;
- the recurrences were categorized as “infield”, if > 95% of the  $V_{\text{recur}}$  was within the initial target volume; “marginal”, if 20–95% of the  $V_{\text{recur}}$  was within the initial target volume; or “outfield”, if < 20% of the  $V_{\text{recur}}$  was within the initial target volume.

### 2.2. Overlap between recurrence volume and the 95% isodose

This method was first described by Dawson et al. [3] and then widely used [3,7,13–16]. This method quantifies the rate of overlap between the volume of recurrence and the 95% treatment isodose.

The different steps of this method are as follows:

- delineation of the  $V_{\text{recur}}$  on diagnostic radiological imaging;
- rigid (or deformable) registration of this recurrence imaging on the initial planning CT-scan;
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within the 95% isodose; or “outfield”, if < 20% of the  $V_{\text{recur}}$  was within the 95% isodose.

### 2.3. Advantages and limitations of volume-based methods

These methods are quite simple and reproducible. However, they have several limitations. The first limitation is common to all volume-based methods, i.e. the volume of recurrence is definitely dependent on the delay in diagnosis of the recurrence. For example, a recurrence detected early, of small volume, may be considered “in-field” if the volume is within the 95% isodose or the initial target volume; whereas it will be considered “marginal” if it is diagnosed later, at a bigger size and only occurs between 20 and 95%. Moreover, the choice of 20 and 95% cut-offs to define the different types of recurrence is not based on any precise physical or biological rationale. Another more specific limitation of the volume-based method comparing initial target volumes only is that it does not take dosimetry into consideration, as there may be a target volume that can be correctly contoured without being correctly covered by the 95% isodose (the dose may not be homogeneous in the target volume).

The choice of co-registration, rigid or deformable, and its validation are also important in the analysis of the recurrence volume on the initial planning CT-scan. In the study of Shakam et al. [6], the concordance rate of recurrence volumes on the planning CT-scan between a rigid and deformable registration was only 0.54 (0.28–0.69). In any case, there may be a risk of error linked to the risk of co-registration between two examinations carried out with significant time intervals, in different positions, with possible significant gains or losses of substance. Deformable co-registration is increasing but is still under evaluation [17–19]. Validation of the volume of recurrence, or even manual adaptation [6], is necessary to limit inter-observer variations [19]. In total, these volume-based methods seem reliable for identifying “out-field” recurrences, but the interpretation of “in-field” or “marginal” recurrences seems unclear.

## 3. Point-based methods

In order to avoid the main bias of volume-based methods, i.e. the delay in the diagnosis of recurrence, different point-based methods have been developed. The main hypothesis of these methods is the concentric development of a recurrence from a core of radioresistant cells.

### 3.1. Point of origin of the recurrence as the center of mass of the recurrence volume

Raktov et al. [8] have developed an alternative method for the analysis of recurrence based on the definition of a point, which is the center of mass of the volume of recurrence. This point would constitute the origin of the recurrence. Indeed, in this method, tumor recurrence is considered as a centrifugal expansion from a core of radioresistant cells surviving after radiotherapy.

The different steps of this method are as follows:



utilisant une analyse plus clinique, prenant en compte les voies d'expansions des tumeurs. Plus récemment, d'autres méthodes « mixtes » plus précises ont été décrites regroupant les différentes approches. Le choix de la méthode est déterminant sur les conclusions sur l'origine des récurrences.

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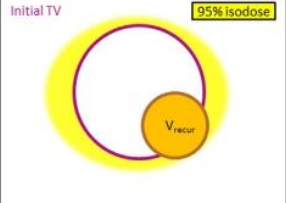
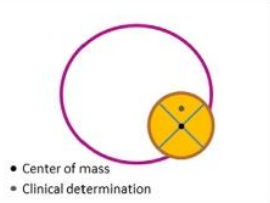
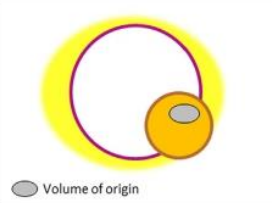
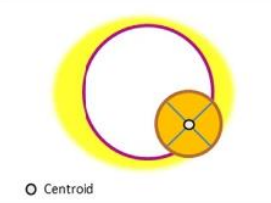
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The different steps of this method are as follows:

Volume-based methods [3-7]	Point-based methods [8,9]	Combined methods	
Overlap between the $V_{\text{recur}}$ and the initial TV or the 95% isodose	Point of origin of the recurrence: center of mass or clinical determination	Volume of origin ( $V_{\text{origin}}$ ) of the recurrence: multidisciplinary clinical determination [12]	Centroid method (centroid = center of mass + 2-mm margin) [10,11]
«Infield» if > 95% of $V_{\text{recur}}$ is in the initial TV or the 95% isodose, «marginal» if between 20 and 95%, and «outfield» if < 20%.	« Infield » if the point of origin is inside the initial TV, « marginal » if at the boundary, and « outfield » if outside.	Double evaluation: 1/ of the position of the $V_{\text{origin}}$ according to initial TV; and 2/ of the dose received by the $V_{\text{origin}}$	Double evaluation: 1/ of the position of the centroid according to initial TV; and 2/ of the dose received by the $V_{\text{recur}}$
	 <ul style="list-style-type: none"> <li>• Center of mass</li> <li>• Clinical determination</li> </ul>	 <ul style="list-style-type: none"> <li>• Volume of origin</li> </ul>	 <ul style="list-style-type: none"> <li>• Centroid</li> </ul>
$V_{\text{recur}}$ is highly dependent on the delay of its diagnosis. No consideration of treatment doses if comparison with initial TV only.	Simple and reproducible for <i>center of mass</i> method but no consideration of natural expansion pathways. Inter-observer variability for <i>clinical determination</i> method. No consideration of treatment doses if comparison with initial TV only.	Inter-observer variability (limited by multidisciplinary analysis). More precise method, but more time consuming.	More complete but also more complex method. Suggestions for improvement according to the type of recurrence.

**Fig. 1.** The different methods for the analysis of recurrences after radiotherapy for head and neck cancers. Abbreviations:  $V_{\text{recur}}$ : volume of recurrence; TV: target volume.

- delineation of the volume of recurrence on diagnostic radiological imaging;
- rigid (or deformable) registration of the recurrence imaging on the initial planning CT-scan;
- automatic determination of the center of mass of recurrence volume;
- calculation of the position of the center of mass (center of mass and uncertainty margins) relative to the edges of the initial target volumes;
- if this center of mass is outside the initial target volume, recurrence is considered “outfield”; if this center of mass is inside the initial target volume, recurrence is considered “infield”; and if this center of mass is on the boundary of the initial target volume, recurrence is considered “marginal”.

### 3.1.1. Advantages and limitations of this method

This method is relatively simple and reproducible, the determination of the point of origin of recurrence is automatically determined as the center of mass of the volume of the recurrence. Recurrence is considered as a concentric and homogeneous expansion from one or more original cells surviving after radiotherapy. However, due to anatomical barriers and natural expansion pathways (bone, fat spaces...), this expansion is not homogeneous in all directions. Moreover, this method is relatively dependent on the quality of the co-registration. In the study of Raktoe et al. [8] which evaluated the accuracy of co-registration by measuring differences in distance between four anatomical markers around the tumor on the planning and recurrence CT-scans, the inaccuracy was measured up to 14.8 mm.

### 3.2. Point of origin of the recurrence: clinical determination

Due et al. [9,20] introduced the notion of a point of origin of the recurrence, determined clinically by the radiation oncologist, based on his knowledge of the anatomy and cancer spread pathways.

The different stages of this method are as follows:

- delineation of the volume of recurrence on diagnostic radiological imaging;
- clinical determination by the oncologist of the expected point of origin of recurrence called “PO-R” on the recurrence CT-scan;
- rigid (or deformable) registration of the recurrence imaging on the initial planning CT scan;
- clinical adjustment by the radiation oncologist of the clinical point of origin of recurrence on the planning CT-scan, called PO-T, after co-registration.

### 3.3. Advantages and limitations of this method

This method introduces a more clinical concept to the determination of the point of origin of recurrence by considering the anatomical barriers and natural expansion pathways of cancers. This makes this method less reproducible but more clinical. Thus, in the study by Due et al. [9], which initially described this method on 29 volumes of recurrence, significant differences in the location of the point of origin were found depending on the operators, the type of CT-scan (recurrence or planning CT-scan), and the co-registration used (rigid or deformable), with differences of up to 25 mm.

## 4. Combined centroid method

Mohamed et al. [10,11] developed a combined method classifying recurrences according to both the initial target volumes and dose distribution.

The different steps of this method are as follows:

- delineation of recurrence volumes by a radiation oncologist and validation by a radiologist specialized in head and neck anatomy on diagnostic radiological imaging;
- deformable registration of the imaging of the recurrence on the initial planning CT-scan;



- determination of a centroid, corresponding to the central voxel (center of mass) of the recurrence volume on the initial planning CT-scan with a 3D-margin of 2 mm;
- double evaluation: position of the centroid in regarding the initial target volumes; and estimation of dose received by the recurrence volume, and the dose level;
- classification of recurrences according to the following nomenclature:
  - type A: central high dose failure, where the mapped failure centroid originates in high dose CTV and the dose to 95% recurrence volume is  $\geq 95\%$  dose prescribed to corresponding high risk CTV,
  - type B: peripheral high dose failure, where the mapped failure centroid originates from high risk CTV but the dose to 95% recurrence volume receives  $< 95\%$  dose prescribed to this CTV,
  - type C: central elective dose failure, where the failure centroid originates from elective dose CTV and the dose to 95% recurrence volume receives  $\geq 95\%$  dose prescribed to the respective CTV,
  - type D: peripheral elective dose failure, where the failure centroid originates from elective dose CTV and the dose to 95% recurrence volume receives  $< 95\%$  dose prescribed to the respective CTV,
  - type E: extraneous dose failure, where the failure centroid originates outside all target volumes,
  - type F: junctional failures at the site of IMRT/supraclavicular match line for patients treated with low-neck supraclavicular field matched to the IMRT fields (no longer relevant in current IMRT),
  - type G: low neck failures at the site of low-neck supraclavicular field, for patients treated with low-neck supraclavicular field matched to the IMRT fields (no longer relevant in current IMRT).

#### 4.1. Advantages and limitations of this method

This method combines a point-based method (center of mass of recurrence volume) and a volume-based method to analyze and classify recurrences. Like the previously described methods, it has the advantage of being reproducible. However, this method is more complex than each method taken separately, with not three types of recurrences (“infield”, “marginal” and “outfield”) but five different types of recurrences (in current IMRT). This method is based on a deformable co-registration of the recurrence imaging on the initial planning CT-scan, which, according to the authors, would lead to a more rigorous classification. Thus, they compared the classification of 26 recurrences and reported that the use of a rigid rather than deformable registration would lead to a misclassification in 4/26 cases (16%), all being classified as type B “peripheral high dose failure” rather than type A “central high dose failure”.

### 5. Multidisciplinary “volume of origin” combined method

Martin et al. [12] proposed a method for analyzing pattern of recurrence based on the determination of a volume (instead of a point) of origin of recurrence, determined clinically and multidisciplinary by a radiation oncologist, an ENT surgeon and a radiologist specialized in head and neck anatomy.

The different steps of this method are as follows:

- delineation of recurrence volumes by a radiation oncologist and validation by a radiologist specialized in head and neck anatomy on diagnostic radiological imaging;
- rigid (or deformable) registration of this imaging of the recurrence on the initial planning CT-scan;
- analysis of the initial imaging, clinical features, post-operative and pathological reports and the volume of recurrence to deter-

mine a volume of probable origin of the recurrence. This volume of origin is located within the recurrence volume and is at least 1 cm in diameter to be clinically relevant. The volume of origin is determined jointly and multidisciplinary by a radiation oncologist, an ENT surgeon and a radiologist specialized in head and neck anatomy;

- the recurrences were classified as “infield” if  $> 95\%$  of the volume of recurrence was within the initial 95% isodose; “marginal”, if 20% to 95% of the volume of recurrence was within the initial 95% isodose; or “outfield” if  $< 20\%$  of the volume of recurrence was inside the 95% isodose;
- each recurrence was also classified in their respective volumes with the corresponding dose level (high or low risk).

#### 5.1. Advantages and limitations of this method

This method is based on the volume-based method with comparison to the 95% isodose treatment described by Dawson et al. [3] but tries to improve its main disadvantage, namely the delay in the diagnosis of recurrence. This is achieved by determining a volume of clinical origin, rather than a simple point of clinical origin as described by Due et al. [9], in a multidisciplinary approach. Even if this volume of origin is determined in a multidisciplinary approach, its reproducibility is not established. Moreover, this method is more time-consuming than other methods mentioned above.

### 6. Comparison of different methods and discussion

The criteria and methods used to analyze the recurrence of head and neck cancers after IMRT are diverse, with various degrees of complexity, and different advantages and limitations. Interpretation of data is complex and may yield different results depending on the methods used. Due et al. [9,20] compared their clinical point-based method with the center of mass and volume-based methods in a study of 29 recurrences. The volume-based method was significantly more likely to assign recurrences as “marginal” rather than “infield” compared to the clinical point-based method. The authors noted that the later the recurrence was diagnosed, the greater the volume of the recurrence and the more likely it was to be classified as “marginal”, whereas the point-based methods were less dependent on the delay in diagnosis. With respect to the point-based methods, the clinical point of origin method resulted in more central “infield” recurrences than the center of mass method. The center of mass method is described as reproducible because it is automatically defined [8]. However, this method is based on the assumption of symmetrical and proportional increase around a point. Due to anatomical barriers and natural expansion paths, this expansion cannot be homogeneous in all directions. The approach with the clinical determination of point of origin is more subjective [9,20]. Indeed, it is a single point, chosen by an expert.

Point-based methods assume a single point as the origin of recurrence and do not take into account the doses received by the whole area of recurrence. For this reason, Mohamed et al. [10,11] proposed a combined method (point-based and with an evaluation of the doses received) and a new nomenclature. The purpose of this nomenclature is to propose ways of improvement according to the type of recurrence. Type A central high dose failure leads to maximum resistance to treatment and is not dependent on the technique or the operator. These recurrences should motivate future therapeutic strategies (dose escalation, therapeutic combinations, etc.). Type B peripheral high dose failure and Type D peripheral low dose failure suggest the need to improve contouring and/or volume coverage. Type C central low dose failure raises the question of allocating certain areas to higher dose levels, and underlines the need for precise analysis of the data available at the time of treatment



planning (imaging, surgical and pathological reports, etc.). Type E extraneous dose failure recurrences raise the problem of the choice of target volumes to be treated.

With regard to the co-registration of the diagnostic images of recurrence on the images used for treatment planning, rigid registration is used in most studies [4,5,13,21,22]. Indeed, this method is simple, quick and commonly used, but it allows only six degrees of freedom and does not take into account changes in shape in the different regions of interest [23]. Shakam et al. [6] were the first to use deformable registration in the analysis of recurrences. Due et al. [9] evaluated that deformable registration seemed to have better reproducibility in identifying the site of origin of recurrence compared to rigid registration. Mohamed et al. [24] also concluded that rigid registration appears to be less accurate than deformable registration.

## 7. Conclusion

Methods to analyze recurrence after IMRT for head and neck cancers are based on comparing volumes or points of origin of recurrence to the initial target volumes and/or doses received. They range from the simplest volume comparison, possibly error prone, to more complex multidisciplinary approaches associating volumes, points and dose distribution, which are more precise but more complex to apply. The choice of the method is decisive for conclusions on the origin of the recurrence.

## Author statement

C. Mione: writing – original draft preparation.  
 F. Martin: writing – original draft preparation.  
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 N. Pham Dang: writing – review & editing.  
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## Disclosure of interest

The authors declare that they have no competing interest.

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## **IV- Patterns of local failure following post-operative intensity-modulated radiotherapy in oral cavity and oropharynx cancers: impact of the different methods of classification**

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## **Introduction**

Surgery is one of the cornerstone treatment of oropharyngeal and oral cavity cancers [1]. Adjuvant postoperative radiation therapy is recommended for patients with adverse features including advanced staged disease and inadequate margins. The addition of concurrent chemotherapy is recommended, particularly for patients who have 'high risk' pathologic features which include extranodal extension (ENE) and/or a positive surgical margin [1,2].

IMRT (Intensity Modulated Radiation Therapy) is nowadays the recommended radiation technique for treatment of head and neck cancers, given the excellent local control outcomes [3–7] and normal tissue-sparing capabilities, especially for the preservation of the salivary function [8–11]. However, by providing a significant dose gradient between structures, there is a risk of recurrence in case of too small irradiation volumes [12,13]. The delineation of the target volumes is therefore an essential step, which determines the results of the treatment, particularly in terms of locoregional control [14,15], and requires a solid knowledge of the medico-physical team [16,17].

Recurrences of head and neck cancers are mostly locoregional, and most often lead to death [18]. It is therefore necessary to determine the etiology of these recurrences in order to improve clinical practice. Several criteria and methodologies have been used to analyze recurrences, but they remain complex.

Over the past years, different methods have been described for the analysis of recurrences after IMRT for head and neck cancers : "volume-based" methods that study the entire volume of recurrence according to initial target volumes or isodose [12,19–22]; "point-based" methods that study a point as the origin of recurrence [23,24]; and "combined" methods that combine different approaches [25,26]. Using these several methods, recurrences are classified as in the field or in the treatment volume, known as "infield", which indicate the need for an

escalation of the therapeutic intensity (doses or therapeutic associations), "marginal" recurrences, which point to a contouring defect at the edge of the field, and finally, "outfield" recurrences, which mainly suggest a contouring error of the target volumes to be treated. We have done a previous literature review, summarizing this [27].

Using the patterns of failure of patients with oral cavity and oropharynx carcinoma, treated with post-operative radiotherapy in our institution, the purpose of this work was to analyze the sites of local recurrence and to evaluate the disparity in the classification of recurrences when different methods are used.

## **Material and Methods**

### **Patients**

Between May 2011 and December 2019, 167 who underwent post-operative radiation therapy, for oral cavity or oropharyngeal squamous cell carcinoma were retrospectively reviewed. Among these 167 patients, local recurrence occurred in 17 (10,2%).

Exclusion criteria were the patients with distant metastases at the time of diagnostic, a previous radiation to the head or neck, and tumors with non-squamous cell carcinoma histology.

Patient characteristics are described in Table 1.

**Table 1:** Patient and disease characteristics

ENE +: Extranodal extension

Characteristics	N (%)
<b>Gender</b>	
Male	122 (73)
Female	45 (27)
<b>Median Age (range)</b>	60 (20-94)
<b>Site</b>	
Oral Cavity	100 (60)
Oropharynx	67 (40)
<b>T-stage</b>	
1-2	72 (43)
3-4	95 (57)
<b>N-stage</b>	
0-1	72 (43)
2-3	95 (57)
<b>UICC Stage 2009</b>	
I	-
II	23 (13,7)
III	37 (22,1)
IVa	94 (56,4)
IVb	13 (7,8)
<b>P16</b>	
Positive	24 (14)
Negative	38 (23)
Unspecified	105 (63)
<b>Smokers</b>	125 (75)
<b>WHO status</b>	
0-1	151 (90)
2-3	16 (10)
<b>Treatment</b>	
<b>Chemotherapy</b>	
Concomitant	72 (43)
Neoadjuvant	5 (3)
No	90 (54)
<b>Nodal surgery</b>	
Bilateral	90 (53.9)
Homolateral	77 (46.1)
<b>Tumor characteristics</b>	
<b>ENE+</b>	68 (42)
<b>Tumor differentiation</b>	
Well	74 (44)
Moderate	56 (34)
Poor	19 (11)
Unspecified	18 (11)
<b>Lymphovascular invasion</b>	
Yes	48 (29)
No	117 (70)
Unspecified	2 (1)
<b>Perineural invasion</b>	
Yes	70 (42)
No	91 (54)
Unspecified	6 (4)
<b>Margin status</b>	
R2	-
R1	56 (34)
R0 close < 5mm	63 (37)
R0	41 (25)
Unspecified	7 (4)



## Treatment

The overall treatment strategies were individualized for each patient and recommended at our multidisciplinary tumor board.

### - Surgery:

All included patients underwent surgery of the primary tumor associated or not with lymph node dissection. The operative technique depended on the location and initial extension of the disease.

### - Radiotherapy:

Patients underwent radiotherapy in case of advanced tumors (stage T3-T4), close or positive margins, lymph nodes involvement with extranodal extension (ENE), the presence of lymph-vascular space invasion, or perineural invasion (PNI) [28,29].

All patients were irradiated with VMAT with simultaneous integrated boost (Rapidarc®, Varian Medical Systems, Palo Alto, CA, USA).

A dosimetric CT scan, supine, in the treatment position, was performed, with 2.5-mm-thick slices, and a personalized thermoformed mask with 5 points of attachment.

Tumor target volumes and organs at risk were delineated according to the different expert recommendations and contouring consensus [30–35]. Three clinical target volumes (CTV) were typically defined. CTV1 (59.4 to 60 Gy) was defined as the preoperative tumor bed with margin (1 to 2 cm), and manually adjusted according to anatomical barriers.

CTV2 (54 Gy) was defined as subclinical sites at risk not operated, according to the risk of tumor involvement following guidelines [32–34]. Prophylactic node was irradiated with this same dose, following guidelines [30,31,33]. CTV 3 (66 Gy) was occasionally identified, in cases of ENE and/or positive margin. Planned target volumes (PTV) related to positioning errors and movements were obtained by adding a 4 mm margin around the CTVs.

Treatment was delivered in 30-33 fractions.

The planning system was Eclipse® (Varian Medical Systems), according to the recommendations of the International Commission of Radiation Units report n°83 [36] . The treatment was delivered using a Clinac IX® or Novalis TX® (Varian Medical Systems) linear accelerators delivering 6-MV photons, with daily position control by KV/KV beams or CBCT.

### **Follow-up**

Weekly evaluations were done by the treating radiation oncologist for all patients during radiation treatment. The first post treatment follow-up was at 3 months after radiation completion and then, every 3 months for the first and the second-year alternating surgeon and radiation oncologist, and at least twice a year for up to 5 years, afterward yearly. A CT- scan was performed annually.

### **Clinical data collection, image registration and dosimetric analysis**

Local recurrences were confirmed via radiologic imaging (i.e. progression in subsequent imaging or high SUV on PET imaging) or pathology specimens (i.e. from surgical biopsy). Diagnostic contrast-enhanced CT and/or PET/CT or MRI documenting the initial evidence of local recurrence (rCT) was identified.

Radiologically evident recurrent tumor volume ( $V_{\text{recur}}$ ) was manually segmented on rCT and reviewed by two experienced radiation oncologists (CM and JB). Corresponding original planning CTs (pCT) were identified and original plans were restored.

rCT was co-registered with pCT using a deformable image registration (Aria with MIRS application, version 2.1, Varian Medical Systems) [25,37].

$V_{\text{recur}}$  was transferred to the pCT and was subsequently deformed according to the deformable co-registration between rCT and pCT. A clinical validation was made by the radiation oncologist.

A mathematical center of mass (corresponding to the geometrical center of the  $V_{\text{recur}}$ ) was defined [24]. A margin of 2 mm was added to this center of mass to define the centroid [25]. The doses of radiation received by  $V_{\text{recur}}$  and by the centroid were calculated and analyzed using dose–volume histograms.

### **Pattern of local recurrence**

We already published a review of literature, summarizing the different methods to analyze the recurrences [27]: volume-based methods [19–21], point-based methods [23,24], and combined methods [25,26]. In our study, we assessed the patterns of local recurrences according to 4 methods: 1/ volume-based method using the volume overlap between  $V_{\text{recur}}$  and initial target volumes, 2/ volume-based method of overlap between  $V_{\text{recur}}$  and the 95% treatment isodose, 3/ point-based method using the position of the barycenter of  $V_{\text{recur}}$  and 4/ combined centroid method classifying recurrences according to both, the initial target volumes and dose distribution. For the 2 volume-based methods, recurrences were classified as “in-field” if 95% or more of  $V_{\text{recur}}$  was within the initial CTV or the 95% isodose; “marginal” if 20% to 95% of  $V_{\text{recur}}$  was within the initial CTV or the 95% isodose; or “outfield,” if less than 20% of the  $V_{\text{recur}}$  was within the initial CTV or the 95% isodose. For the point-based method, recurrences were defined as “marginal” when the minimum distance between the barycenter and the closest CTV border was within  $\pm 3$  mm; “infield” when the barycenter was within the CTV use more than 3mm from the closest CTV border; and “outfield” when the center of mass was outside the CTV use more than 3mm from the closest CTV border. For the combined centroid method [25], recurrences were classified in five types: Type A for central high dose recurrence, where the centroid is in high dose CTV and receives  $\geq 95\%$  of the prescribed dose (considered as “infield”); Type B for peripheral high dose recurrence, where the centroid is in high dose CTV but receives  $< 95\%$  of the prescribed

dose (considered as “marginal”); Type C for central elective dose recurrence where the centroid is in low dose CTV and receives  $\geq 95\%$  of the prescribed dose; Type D for peripheral elective dose recurrence where the centroid is in low dose CTV but receives  $< 95\%$  of the prescribed dose; and Type E for extraneous dose recurrence where the centroid is outside all CTV. Finally, two experienced radiation oncologists (CM and JB) extensively reviewed each case to make a clinical judgment on these classifications and assessed them as “appropriate”, “possible”, or “inappropriate”.

## **Results**

### **Treatment outcomes**

The median follow-up was 33 months. Seventeen patients (10.2%) developed local recurrences. The actuarial 1 and 2-year local control rates were 93% and 90%, respectively. Patients who developed local recurrence characteristics are described in Table 2. For the 17 patients with a local recurrence, 11 had local recurrence alone, 3 had both local and regional recurrence, 2 had local and metastasis recurrence and 1 patient had local, regional and metastatic recurrence. Mean  $V_{\text{recur}}$  volume was 31.5 cc ranging from 0.4 to 121.3 cc. Forty-two patients (25%) died during follow-up. The overall survival rate was 88.6% at 1 year and 80% at 2 years.

**Table 2:** Initial characteristics of the 17 patients, who developed a local recurrence

*R1= positive margin, R<5mm=close margin <5mm, R0=negative margin, ENE +: extranodal extension, ENE -: positive node without extranodal extension, N - : none positive node, Surgery – RT interval: interval between surgery and the first day of radiotherapy*

<b>Patients</b>	<b>TNM</b>	<b>Age at diagnosis</b>	<b>P16</b>	<b>Sub-Location</b>	<b>Nodal Extension</b>	<b>Margin</b>	<b>Chemotherapy</b>	<b>Surgery-RT interval (days)</b>	<b>Prescribed Dose (Gy)</b>	<b>Treatment Time (days)</b>
1	T4aN2aM0	52	ND	Mobile tongue	ENE +	R1	Yes	39	66	46
2	T3N2cM0	78	ND	Base of tongue	ENE +	R1	No	41	66	50
3	T4aN0M0	50	ND	Mandibular vestibule	N -	R1	No	53	66	50
4	T4aN2cM0	54	ND	Mobile tongue	ENE +	R1	Yes	49	66	49
5	T3N1M0	77	ND	Mobile tongue	ENE -	R0	No	47	66	45
6	T3N1M0	59	ND	Floor of mouth	ENE -	R1	Yes	48	66	46
7	T4aN2cM0	42	ND	Floor of mouth	ENE +	R<5 mm	Yes	48	60	38
8	T4aN0M0	62	ND	Floor of mouth	N -	R<5 mm	No	48	60	38
9	T3N1M0	60	ND	Upper lip	ENE +	R0	Yes	83	60	48
10	T3N0M0	77	P16-	Cheek	N -	R1	No	35	66	45
11	T3N0M0	56	ND	Base of tongue	N -	R1	Yes	38	66	47
12	T4aN2bM0	65	ND	Retromolar area	ENE -	R1	Yes	41	66	43
13	T4aN2cM0	26	P16-	Mobile tongue	ENE +	R1	Yes	35	66	45
14	T3N0M0	79	P16-	Hard Palate	N -	R1	No	41	66	44
15	T1N0M0	65	P16-	Tonsil	N -	R<5 mm	No	39	66	45
16	T4N1M0	72	P16-	Retromolar area	ENE +	R<5 mm	No	51	66	48
17	T4N2cM0	20	P16+	Floor of mouth	ENE +	R<5 mm	Yes	41	60	45

## **Local recurrences classification and comparison**

### **- Volume-based methods**

For the volume-based method using overlap between  $V_{\text{recur}}$  and initial CTV, 1/17 local recurrence was considered as “infield”, 11/17 as “marginal”, and 5/17 as “outfield”; whereas using overlap between  $V_{\text{recur}}$  and the 95% prescribed isodose, 9/17 local recurrences were considered as “infield”, 6/17 as “marginal” and 2/17 as “outfield”. Only 7/17 local recurrences had the same classification between those 2 volume-based methods. Using the overlap between  $V_{\text{recur}}$  and the 95% prescribed isodose affected the recurrences more central than using the overlap between  $V_{\text{recur}}$  and the CTV with 9/17 local recurrences classified as “infield” vs 1/17; the remaining 7/17 being classified as “marginal” and 1/17 being classified as “outfield”.

### **- Point-based method**

Local recurrences using the point-based method were classified as follow: 8/17 “infield”, 5/17 as “marginal”, and 4/17 as “outfield”. 13/17 local recurrences had the same classification between this point-based method and the volume-based method of overlap between  $V_{\text{recur}}$  and the 95% prescribed isodose, and 9/17 with the volume-based method of overlap between  $V_{\text{recur}}$  and the initial CTV.

### **- Combined centroid method**

8/17 local recurrences were classified as Type A, 3/17 as Type B, 2/17 as Type C, 3/17 as Type D and 1/17 as Type E.

### **- Methods comparison**

The four different methods of local recurrence classification were in accuracy only in 5/17 (29%) of cases: 1 case of “infield” recurrence, 2 cases of “marginal” recurrences and 2 cases of “outfield” recurrences (Fig. 1).

For the 8/17 local recurrences classified as Type A (i.e. central high dose recurrence considered as “infield”), only 1 of them (Patient 6) was classified as “infield” with the 3 other methods; and 6 were classified as “infield” with the point-based method and the volume-based method comparing  $V_{\text{recur}}$  with the 95% prescribed isodose, but “marginal” with the volume-based method comparing  $V_{\text{recur}}$  with the initial CTV (Patients 1, 2, 3, 5, 7 and 13). For these 6 patients, the volume-based method comparing  $V_{\text{recur}}$  with the initial CTV was judged as clinically “inappropriate” due to high  $V_{\text{recur}}$  volumes (see example in Fig.2 and Discussion). Taking this into consideration, 11/17 (65%) of local recurrences were considered in accuracy, according to the 3 remaining methods.

For the 3/17 local recurrences classified as Type B (i.e. peripheral high dose recurrence, considered as “marginal”; Patients number 8, 9 and 14), 2 of them (Patients 8 and 14) were also classified as “marginal” with the 3 others methods and were clinically judged as “appropriate” (Fig. 3). However, for 1 local recurrence (Patient 9), the point-based method classified it as “infield” (Fig.4). For this local recurrence, it was the point-based method that was clinically judged as “appropriate” due to the size of  $V_{\text{recur}}$ .

Concerning the 2/17 local recurrences classified as Type C, the barycenter of  $V_{\text{recur}}$  was located outside the high dose CTV but in the prophylactic CTV. For Patient 17, it was situated at the edge of the high dose CTV, classifying it as “marginal” with the point-based method. For Patient 10, the barycenter was more than 3 mm from the closest CTV border, classifying it as “outfield”. For this patient, due to the very small volume of  $V_{\text{recur}}$  (0.4cc), the local recurrence was even classified as “infield” with the volume-based method comparing  $V_{\text{recur}}$  and the 95% isodose and “outfield” when comparing with initial CTV (Fig. 5).

Concerning the 3/17 local recurrences classified as Type D; for Patient 11, the initial location of the tumor was the right base of tongue with extensive perineural invasion. The local recurrence was due to a macroscopic perineural invasion (PNI) of the lingual nerve up to the

skull base (Fig.6). All methods classified it as “outfield” or “marginal”. Since PNI spread in a retrograde way, and since the 2 first cm of this recurrence was included in the 66-60Gy CTV, this classification was judged as clinically “inappropriate” for all methods. For Patient 15, the initial tumor was located in the left tonsil, invading the anterior pillar. The recurrence was in the mobile tongue, anteriorly to the homolateral tongue scar. It was classified as “marginal” with the 3 other methods which was clinically judged as “appropriate”. The Type D classification was judged as “inappropriate”, due to the  $V_{\text{recur}}$ , expanding anteriorly and thus receiving <95% of the prescribed dose. For Patient 16, the initial tumor was located in the right retromandibular trigone and the local recurrence in the digastric muscle. All methods classified it as “outfield” which was clinically judged as “appropriate” (Fig.7).

For the 1/17 local recurrence classified as Type E, all other methods also classified it as “outfield”, and this was considered as “appropriate. This patient had an initial tumor in the retromolar trigone and a recurrence in the masticator muscles around the mandibular ascending branch with perinervous extension to the cavum of Meckel.



**Table 3:** Characteristics and pattern of failure*fD95%: dose to 95% of the failure volume.**N.B.: The numbering of the patients follows the numbering in Table 2*

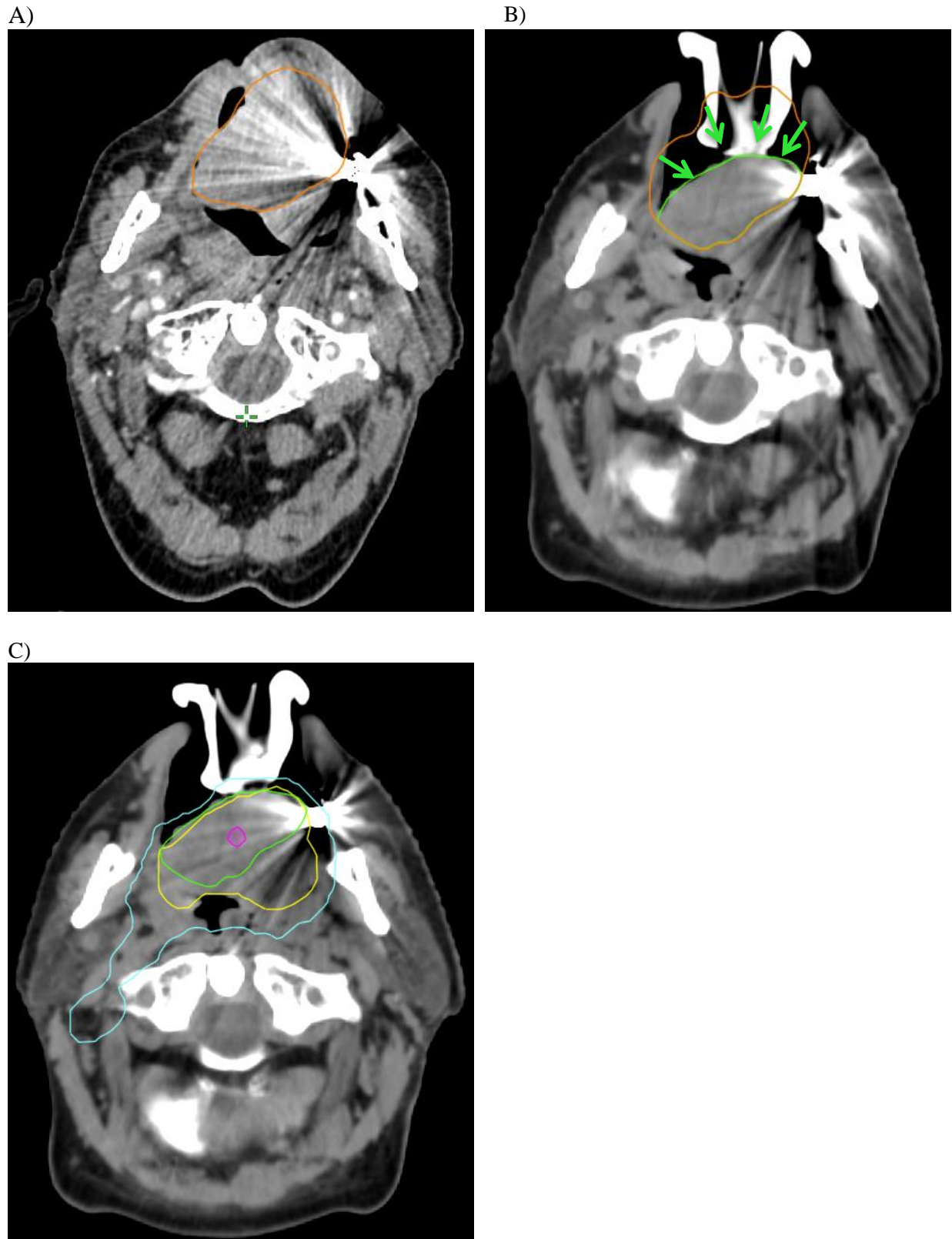
Patient	Sub-Location	Time to recurrence (months)	Recurrence anatomical description	Recurrence level dose	%overlap $V_{recur}/CTV$	%overlap $V_{recur}/95\%$ isodose	Barycenter location	D95% CENTROID	fD95% (Gy)	Mixed Method	Point-Based Methods	Overlap-Based-Methods	
												CTV	Isodose
1	Mobile Tongue	9,2	Tongue/tongue flap junction	66	71	96	in CTV66 in isodose 62,7	66	63,3	A	Infield	Marginal	Infield
				59,4	1,3	99							
2	Base of Tongue	7,1	Base of Tongue	66	13	98	in CTV66 in isodose 62,7	66,7	65,1	A	Infield	Marginal	Infield
3	Mandibular Vestibule	20,7	Homolateral mandible	66	67	95	outside CTV66 in isodose 56,4	66,3	63,2	A	Infield	Marginal	Infield
				59,4	80	99							
4	Mobile Tongue	15,7	Mobile tongue/ base of tongue junction	66	50	95	in CTV66 in isodose 62,7	66,1	65,2	A	Marginal	Marginal	Infield
5	Mobile Tongue	16,4	Mobile tongue	66	73	95	in CTV66 in isodose 62,7	67,7	63,9	A	Infield	Marginal	Infield
				59,4	86	98							
6	Floor of mouth	4,2	Mobile tongue/ floor of mouth junction	66	99	96	in CTV66 in isodose 62,7	65,6	63,8	A	Infield	Infield	Infield
				59,4	91	100							
7	Floor of mouth	4,7	Tongue/tongue flap junction	60	41	95	in CTV60 in isodose 57	67,4	54	A	Infield	Marginal	Infield
8	Floor of mouth	2,7	Inferior gingiva	60	21	50	in CTV60 in isodose 57	60,2	52,3	B	Marginal	Marginal	Marginal
9	Upper lip extended to nasal cavity	3,1	Upper jaw	60	85	70	in CTV60 in isodose 57	60,5	42,4	B	Infield	Marginal	Marginal
10	Cheek	27,8	Mandible	66	0	100	in CTV54 in isodose 62,7	64,2	64,3	C	Outfield	Outfield	Infield

11	Base of Tongue	29,1	Right facial nerve	66	7	20	in CTV54 in isodose 56,4	59	42,8	D	Outfield	Outfield	Marginal
				59,4	14	30							
12	Retromolar area	11	Infratemporal fossa	66	13	6	outside CTV66 in isodose 62,7	49	15,6	E	Outfield	Outfield	Outfield
13	Mobile tongue	1,4	Base of tongue	66	86	99	in CTV66 in isodose 62,7	66,5	64,8	A	Infield	Marginal	Infield
				59,4	90	100							
14	Hard Palate	6,6	Hard Palate	66	54	82	in CTV66 in isodose 62,7	65,2	56,4	B	Marginal	Marginal	Marginal
15	Tonsil	4,8	Mobile Tongue	66	38	57	outside CTV66 in isodose 62,7	63,4	54,5	D	Marginal	Marginal	Marginal
				59,4	57	86							
16	Retromolar area	12,3	Digastric muscle	66	0	4	outside CTV66 in isodose 51,3	53,8	49,7	D	Outfield	Outfield	Outfield
				54	62	85							
17	Floor of mouth	3	Oropharynx Hypopharynx	59,4	13	58	outside CTV59.4 in isodose 51,3	56.5 55.4	51	C	Marginal	Outfield	Marginal

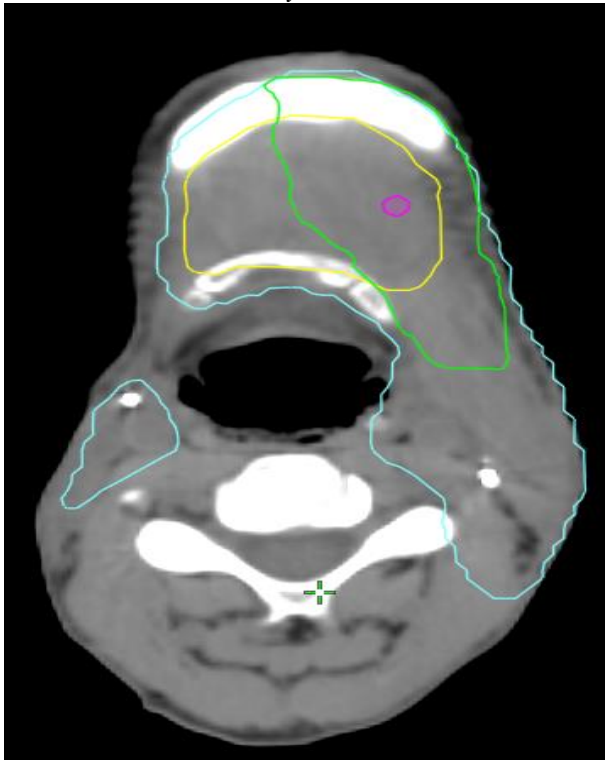
**Fig. 1:** Patient 6. Initial SCC of the floor of the mouth T3N1, ENE -, R1. Recurrence at the junction mobile tongue and floor of mouth.

A)  $V_{\text{recur}}$  on the rCT. B)  $V_{\text{recur}}$  co-registered with the pCT using a deformable image registration, and deformed with a clinical validation (removal of the air and the immobilization device). C) All methods classified the recurrence as infield

Orange:  $V_{\text{recur}}$  before deformation, Green:  $V_{\text{recur}}$ , Pink: Barycenter, Yellow: CTV 66, Blue: Isodose 62.7Gy

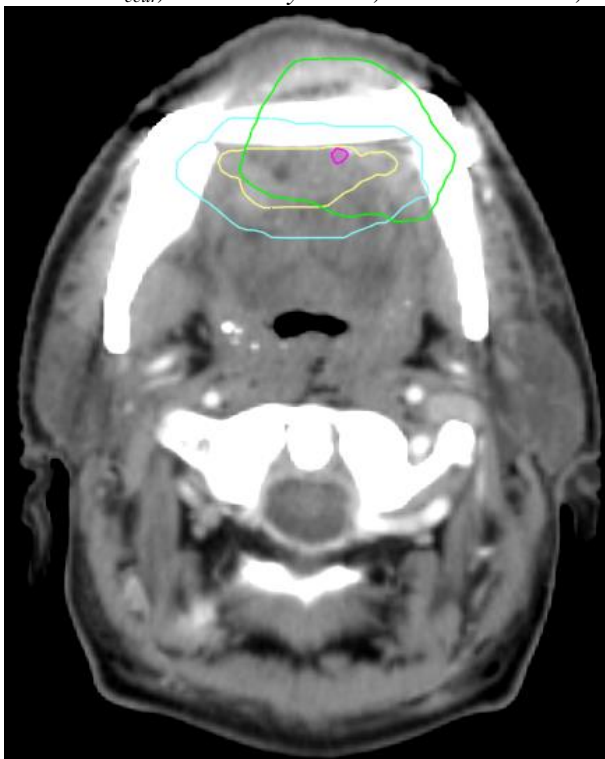


**Fig. 2:** Patient 7. Initial SCC of the floor of the mouth T4aN2cM0, ENE +, R<5mm. Recurrence occurred at the junction between the tongue and the flap of the tongue. The volume-based method comparing  $V_{\text{recur}}$  with the CTV is not appropriate due to high  $V_{\text{recur}}$ .  
*Green:  $V_{\text{recur}}$ , Pink: Barycenter, Yellow: CTV 60, Blue: Isodose 56.4 Gy*

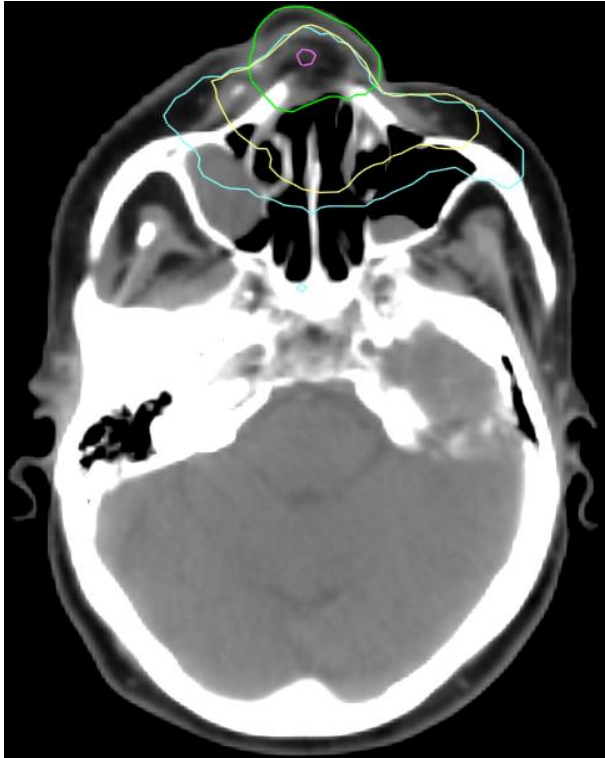


**Fig. 3:** Patient 8. Initial SCC of the floor of the mouth T4aN0M0, R<5mm. Recurrence occurred in the homolateral inferior gingiva. All methods are in accuracy to classify the recurrence as marginal.

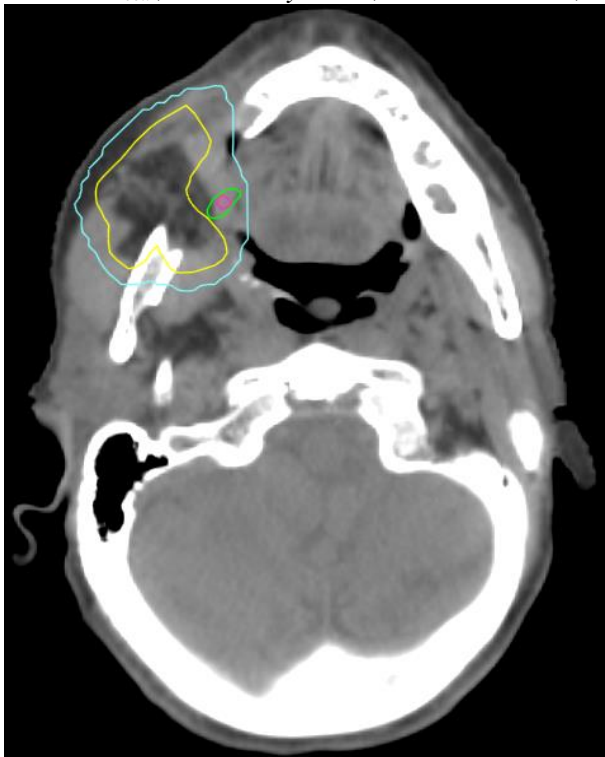
*Green:  $V_{\text{recur}}$ , Pink: Barycenter, Yellow: CTV 60, Blue: Isodose 56.4Gy*



**Fig. 4:** Patient 9. Initial SCC of the upper lip, extended to nasal cavities T3N1M0, ENE +. Recurrence occurred in the upper jaw. All but the point based method classifies the recurrence as marginal. The point-based method seems the most appropriate.  
*Green:  $V_{recur}$ , Pink: Barycenter, Yellow: CTV 60, Blue: Isodose 56.4Gy*



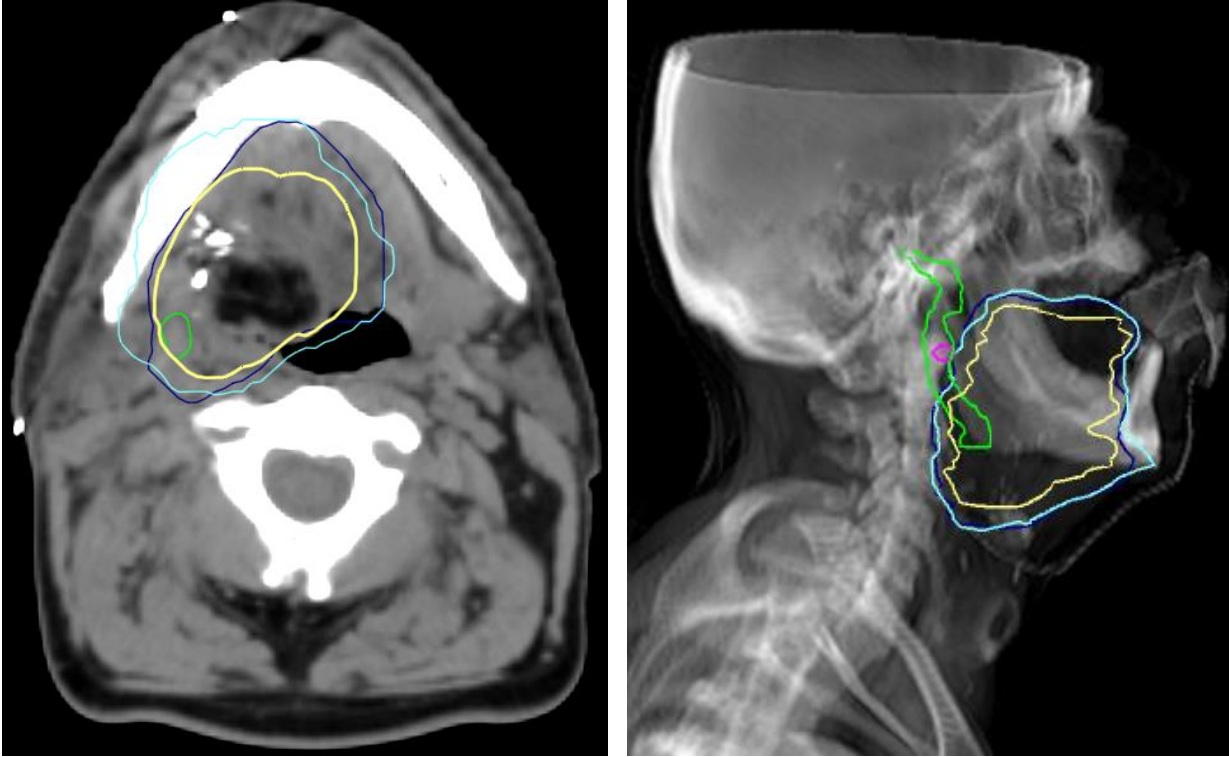
**Fig. 5:** Patient 10. Initial SCC of the right cheek T3N0M0, R1. Recurrence occurred in the homolateral mandible. Due to the very small  $V_{recur}$ , the volume based method comparing  $V_{recur}$  and the initial CTV, classifies the recurrence as outfield.  
*Green:  $V_{recur}$ , Pink: Barycenter, Yellow: CTV 66, Blue: Isodose 62.7Gy*





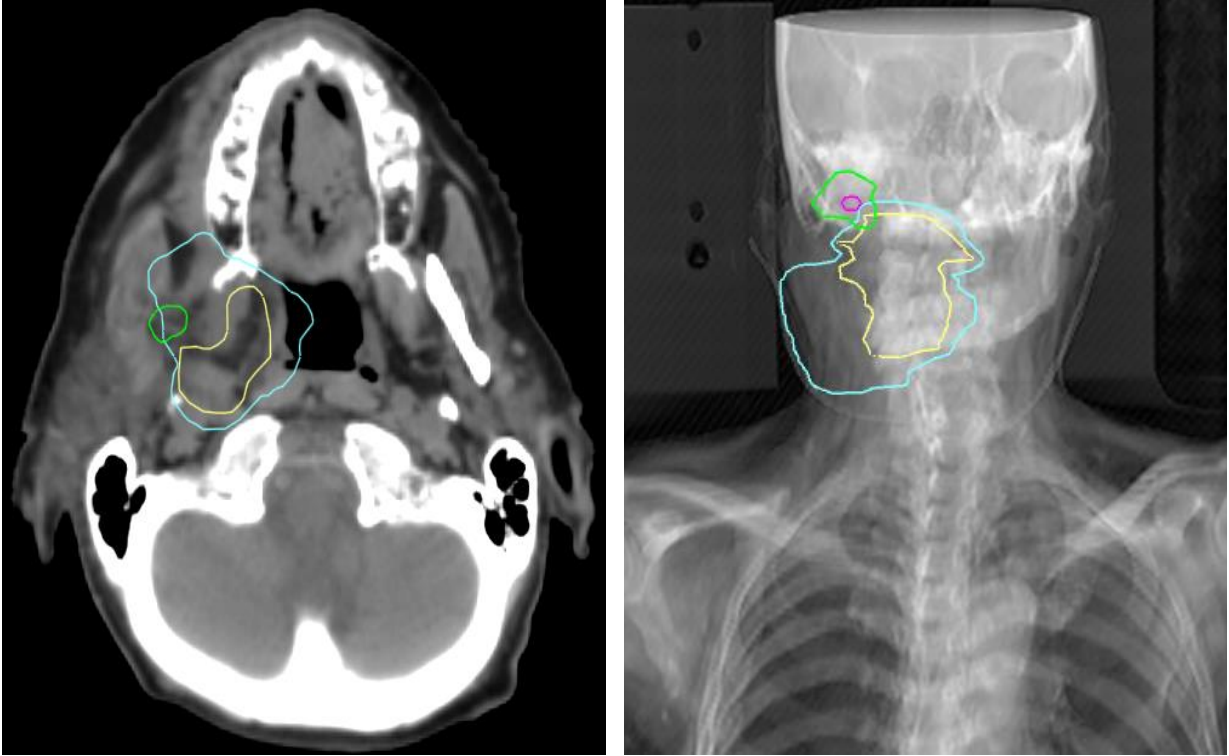
**Fig. 6:** Patient 11. Initial SCC of the base of the tongue T3N0M0, R1. Recurrence was due to a macroscopic perineural invasion of the lingual nerve.

Green:  $V_{recur}$ , Yellow: CTV 66, Blue: Isodose 62.7Gy, Dark Blue: CTV 59.4



**Fig. 7:** Patient 16. Initial SCC of the right retromolar area T4N1M0, ENE +. Recurrence occurred in the homolateral digastric muscle. All methods are in accuracy to classify the recurrence as outfield.

Green:  $V_{recur}$ , Yellow: CTV 66, Blue: Isodose 62.7Gy



## Discussion

The aim of our study was to classify the local recurrences (n=17/167) following post-operative IMRT for oral cavity or oropharyngeal SCC according to 4 different published methods, and to compare these different methods [27]. We found that only 5/17 (29%) of the local recurrences were classified the same way according to the 4 different methods. Methods to analyze recurrences are still controversial. Other authors as Ferreira et al. [38] tried to compare the different methods. As our study, they found that the classification of each recurrence was highly dependent on the method of evaluation used. In our study, the volume-based method comparing  $V_{\text{recur}}$  with initial CTV judged as the most “inappropriate” since this method is highly dependent on the volume of  $V_{\text{recur}}$  and thus the timing of the  $V_{\text{recur}}$  diagnosis: the longer the recurrence is allowed to grow, the larger the volume at the time of detection, and more peripheral it is classified. All volume-based methods (comparing  $V_{\text{recur}}$  and the 95% isodose, and partially the combined centroid method) have this major limitation, but it is particularly true when comparing with initial CTV since initial CTV is by definition smaller than the 95% isodose (which takes into account the expansion for the PTV determination). Thus, in our study, volume-based methods assigned recurrences more peripheral than the point-based method, as found in the study by Dawson et al. [19]. When excluding the volume-based method comparing  $V_{\text{recur}}$  and initial CTV (which seemed the most inappropriate), we still found that only 12/17 (71%) had the same classification using the 3 remaining methods. Regarding the point-based methods, centroid are easily reproducible since they represent the mathematical center of mass of  $V_{\text{recur}}$ ; but it based on the fact that the recurrence is considered as a concentric and homogeneous expansion from one original cell surviving after radiotherapy. Due to anatomical barriers and natural expansion pathways, this expansion is obviously not homogeneous in all directions. This is especially true in a post-operative setting, where recurrences in operated tissues, where large volumes of tissue are removed and

potentially replaced with free flaps are less likely to occur in a concentric way, as are recurrences that occur after definitive irradiation.

The combined centroid method, described by Mohamed et al. [25,26], is more complete, but also more complex and therefore more difficult to use in daily practice. In addition, it does not classify recurrences into three categories, like all the other methods, but into five, which makes it even more difficult to compare with other methods. This method combines point-based method and volume-based method, which adds up the advantages of each method, but their limitations still remain.

To try to avoid the above cited limitations, some authors proposed more clinical methods to classify the recurrences [24,39]. These methods propose to determine the point of origin of the recurrence, determined clinically by the radiation oncologist or a multidisciplinary team, based on their knowledge of the anatomy and cancer spread pathways. In the study by Due et al. [24], who first introduced this method, 29 volumes of recurrence were analyzed and significant differences in the location of the point of origin were found depending on the operators, the type of CT-scan (recurrence or planning CT-scan), and the coregistration used (rigid or deformable), with differences of up to 25 mm. However, this type of method introducing a clinical reflection seems necessary for some type of local recurrences such as PNI recurrences (as Patient 10).

Recurrences which are “infield” are considered resistant to maximal therapy and could not be prevented by technical/operator dependent processes. However, recurrences which are “marginal” or “outfield” represent a major goal for IMRT quality assurance and improvement. Up-to-date, there are no published methods that would give complete satisfaction, especially in the setting of post-operative head and neck IMRT. Further research in the field is needed.



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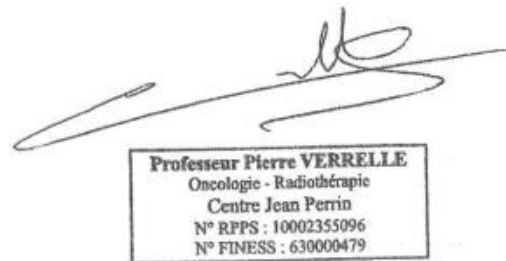
## V- CONCLUSION

Les résultats carcinologiques du VMAT post-opératoire des carcinomes épidermoïdes de la cavité buccale ou de l'oropharynx dans cette étude sont conformes aux données de la littérature. Il existe à ce jour plusieurs méthodes d'analyse des récidives publiées sans qu'aucune n'ait montré de supériorité par rapport aux autres. La méthode d'analyse des récidives employée peut affecter significativement les conclusions sur l'origine de celles-ci.

Le Doyen de l'UFR de Médecine  
Pierre CLAVELOU



Le Président du Jury  
Pierre VERRELLE



## **(Conseil national de l'ordre des médecins)**

### **SERMENT D'HIPPOCRATE**

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

## **SERMENT D'HIPPOCRATE**

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

## **Radiothérapie conformationnelle par modulation d'intensité des cancers de la cavité buccale et de l'oropharynx : analyse des résultats carcinologiques et des récurrences locales**

### **Résumé:**

**Objectif:** Evaluer les résultats carcinologiques de la radiothérapie conformationnelle par modulation d'intensité (RCMI) post-opératoire des carcinomes épidermoïdes de la cavité buccale et de l'oropharynx; avec un focus particulier sur les récurrences locales et les différents modèles d'analyse de ces récurrences.

**Matériels et méthodes:** De 2011 à 2019, 167 patients ayant eu une RCMI post-opératoire pour un carcinome épidermoïde de la cavité buccale ou de l'oropharynx ont été analysés. Trente-quatre pourcents des patients avaient une marge R1 et 42% des engainements périnerveux. La RCMI était réalisée selon une technique d'arthérapie volumétrique (VMAT) avec 2 ou 3 niveaux de dose (54, 60 et 66Gy en 30-33 fractions). Les volumes de récurrence ont été délimités sur le scanner diagnostique de la récurrence puis recalés par une méthode déformable sur le scanner dosimétrique initial. Différentes méthodes d'analyse des récurrences ont été comparées: 1/ quantification du pourcentage de recoupe entre le V récurrence et le CTV; 2/ quantification du pourcentage de recoupe entre le V récurrence et l'isodose 95% de la dose prescrite; 3/ positionnement du barycentre du V récurrence par rapport au CTV; 4/ analyse mixte, géométrique et dosimétrique.

**Résultats:** Le suivi médian était de 33 mois. A 2 ans, la survie globale et le contrôle local étaient respectivement de 80% et 90%. Les facteurs influençant significativement la survie globale en analyse multivariée étaient la présence d'effraction extra-capsulaire et la taille tumorale (T1-T2 vs T3-T4). Il y a eu 17 récurrences locales. Le volume moyen des récurrences était de 31,5cm<sup>3</sup>. Les facteurs influençant significativement le contrôle local en analyse multivariée étaient le stade T (T1-T2 vs T3-T4) et la présence d'engainements périnerveux. Le nombre de récurrences «infield» était de 1, 9, 8 et 8, par les méthodes utilisant le CTV, l'isodose, le barycentre et mixte respectivement. Le nombre de récurrence «marginal» était de 11, 4, 5 et 3, par les méthodes utilisant le CTV, l'isodose, le barycentre et mixte respectivement. Il n'existait aucune corrélation stricte entre les différentes méthodes d'analyse.

**Conclusion:** Les résultats carcinologiques du VMAT post-opératoire des carcinomes épidermoïdes de la cavité buccale ou de l'oropharynx dans cette étude sont conformes aux données de la littérature. Il existe à ce jour plusieurs méthodes d'analyse des récurrences publiées sans qu'aucune n'ait montré de supériorité par rapport aux autres. La méthode d'analyse des récurrences employée peut affecter significativement les conclusions sur l'origine de celles-ci

**Mots-clés :** radiothérapie, modulation d'intensité, post-opératoire ; carcinomes épidermoïdes ; cavité buccale et oropharynx ; récurrences locales