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## **Evaluation of robotic surgery for transoral resection of T1-2 squamous cell carcinoma of the tonsillar fossa.**

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## **Abstract**

**Goal:** To evaluate transoral robotic surgery (TORS) for isolated previously untreated squamous cell carcinoma (SCC) of the tonsillar fossa classified as T1-2. **Method:** Retrospective analysis of two cohorts of isolated untreated T1-2 tonsillar fossa SCC consecutively operated on by a transoral approach, with (R = 21) and without (NR = 24) robotic assistance, in the period 2006-2014. Three main (survival, local control, and operative morbidity) and three secondary (pathologic data, incidence and duration of tracheotomy and nasogastric intubation, and hospital stay) endpoints were compared between groups. The significance threshold was set at  $p < .005$ . **Results:** Three- and 5-year actuarial survival estimates were 80.2% and 74.5% respectively in group R, and 91.5% and 82.5% respectively in group NR (NS:  $p = .34$ ). Three- and 5-year actuarial local control estimates were 90% and 90% respectively in group R, and 95.8% and 91% respectively in group NR (NS:  $p = .81$ ). There were no significant differences in morbidity, tracheotomy/nasogastric intubation time, or hospital stay. Positive resection margins (R1) were noted in 38.1% and 16.7% in groups R and NR, respectively (NS:  $p = .05$ ) without significant impact on 5-year actuarial local control ( $p = 0.78$ ). **Conclusion:** Robotic assistance in transoral lateral oropharyngectomy for T1-2 tonsillar fossa SCC did not significantly impact oncologic or functional outcome.

**Key-words:** oropharynx, tonsil, cancer, surgery, transoral, robotic.

## **Introduction.**

According to the indexed literature (PubMed, Embase and Cochrane databases), radiation therapy, with or without chemotherapy, is the “conservative” treatment most frequently used in T1-2 squamous cell carcinoma (SCC) originating in the tonsillar fossa [1,2]. While sparing the mandible and soft tissue, it is not without functional risk (necrosis, sclerosis) and various severe complications may occur in case of salvage surgery for local failure [2]. Moreover, radiation therapy is not easily repeated in case of metachronous head and neck cancer and incurs a long-term risk of radiation-induced cancer [2]. These limitations, in a context of increasingly frequent tonsillar SCC induced early in life by human papilloma virus, have led to renewed interest in transoral surgery, with two ongoing prospective randomized trials comparing results between the two options: ORTOR in the USA, and EORTC 1420-HNCG-ROG in Europe [2-4].

At the same time, while transoral surgery for T1-2 tonsillar SCC was classically performed using the Bowie knife or laser under microscopy [5-14], robotic assistance [15,16] was introduced without real evaluation of its potential surgical and oncological benefit. To fill this gap, the present retrospective study, based on 45 patients with previously untreated isolated T1-2 tonsillar fossa SCC, consecutively treated by a transoral approach in our department, was designed to assess the benefit of using or not using robotic assistance. Three main (survival, local control, and operative morbidity) and secondary (pathologic data, incidence and duration of tracheotomy and nasogastric feeding, and hospital stay) endpoints were analyzed, depending whether robotic assistance was used during resection or not.

## **Material and method**

Transoral robotic surgery (TORS) for SCC originating in the tonsillar fossa (tonsil or anterior or posterior pillar) classified as T1-2 according to the Union for International Cancer Control [17] was first performed in our department in 2006. To assess benefit, files of consecutive patients with T1-2

SCC originating in the tonsillar fossa consecutively treated by transoral lateral oropharyngectomy in our department between 2006 and 2014 [18] were analyzed. Patients with SCC originating from an adjacent site and extending to the tonsil, anterior or posterior pillar, with synchronous second primary cancer, who failed radiation therapy and/or had induction chemotherapy regimen were excluded. The retrospective cohort thus comprised 45 patients with an isolated and previously untreated T1-2 SCC.

Two groups were distinguished: group R, with 21 patients undergoing robotic surgery (Da Vinci® Si - Intuitive, Sunnyvale, California), and group NR, with 24 patients operated on without robotic assistance. Resection in NR used the Bowie knife, without laser, under direct visual control without microscopy assistance. There were no significant inter-group differences in gender, age, Charlson comorbidity score [19], diagnostic tonsillectomy rate, basaloid and p19 SCC status, origin and extension, T and N staging, or associated treatments (neck dissection, postoperative radiation therapy) (Table 1). Type of associated neck dissection and use of postoperative radiation were decided on in multidisciplinary team meetings. The decision to use robotic assistance, the extent of transoral resection, the performance of preventive ipsilateral arterial ligation (1 lingual artery ligation in group R) and of tracheotomy, insertion of a nasogastric tube and their respective durations were at the surgeon's discretion. Ten senior surgeons (7 in group NR, 5 in group R: see Acknowledgments) performed the 45 transoral lateral oropharyngectomies. In group R, 9.5% of procedures (2/21) were finally completed without robotic assistance, due to difficulty of margin assessment in the velar palate in 1 case and the need to associate partial mandibulectomy in the other.

All patients, with the exception of 1 lost to follow-up at 8 months, were followed up for at least 3 years or until death. Three main (survival with causes of death, operative morbidity with type and rate of postoperative complications, local control with consequences of failure: salvage treatment and impact on lymph-node control, distant metastasis, and survival), and 3 secondary (pathology data, incidence and duration of tracheotomy and nasogastric intubation, and hospital stay) endpoints

were analyzed and compared between groups R and NR. Pathology data analysis comprised: resection margins (dysplasia; R0: safe margins; R1: microscopically positive margins; R2: macroscopically incomplete resection); tumoral embolism; and neural involvement. Survival and oncologic events (local, nodal and metastatic) were calculated on Kaplan-Meier estimation [20], with log-rank test for comparison. The  $\chi^2$  and Fisher parametric tests, and the non-parametric Mann-Whitney U test were used for qualitative, and quantitative variables, respectively. The significance threshold was set at  $p < .005$  [21,22].

## **Results**

### **Main endpoints**

#### **Survival**

Three- and 5-year actuarial survival estimates were 80.2% and 74.5% respectively in group R, and 91.5% and 82.5% respectively in group NR, without statistically significant difference (**figure 1**;  $p = .34$ ) Fifteen patients died: 7 (33.3%) in group R and 8 (32%) in group NR. The main cause of death was metachronous second primary (60%; 9/15) while 13.3% (2/15: 1 R, 1 NR) died of non-controlled local failure and 1 (group R) died of postoperative complications.

#### **Local control**

Three- and 5-year actuarial local control estimates were 90% and 90% respectively in group R, and 95.8% and 91% respectively in group NR (**figure 2**;  $p = .81$ ).

Salvage treatment associating radiation and chemotherapy for the 4 patients with local control failure (2 R, 2 NR) achieved local control in 2 cases, with final overall local control and mandible

sparing rates of respectively 95.2% (20/21) and 100% (21/21) in group R and of 96% (24/25) and 100% (25/25) in group NR.

Local failure did not significantly impair 5-year actuarial survival ( $p = .2$ ) or increase the 5-year distant metastasis estimate ( $p > .99$ ), but “suggestively” ( $p = .02$ ) increased the 5-year actuarial nodal failure estimate from 2.9% to 25%.

### **Morbidity.**

Morbidity data are documented in Table 2. There were no significant inter-group differences in intra- or post-operative complications (at T site or N site), general complications or postoperative radiation-induced complications. The postoperative death in group R was related to pneumopathy with septic shock.

The most frequent complication (Table 2) was operative site bleeding: intraoperatively, 1 case in group R; postoperatively, 12.5% (3/21) in group R and 14.2% (3/24) in NR (NS:  $p = .86$ ). Four patients with postoperative hemorrhage underwent surgical hemostasis under general anesthesia; 1 required ipsilateral external carotid artery ligation; 1 received successful external carotid artery branch embolization; and in a 3<sup>rd</sup> case bleeding, associated with partial necrosis of a Bichat fat pad used to enhance velar competence, resolved spontaneously under surveillance and blood pressure control.

### **Secondary endpoints**

### **Pathology findings**

Table 3 document pathology data in groups R and NR. There were no significant differences in resection margins, lymphatic or vascular emboli or neural invasion. In group R, 2 patients showed moderate dysplasia and 1 showed severe dysplasia (in-situ carcinoma).

Resection margin status did not affect local control; none of the 3 cases of dysplasia had local failure, and the 5-year actuarial local control estimate was 90.9 % in microscopically positive margins (R1) and 89.6% in safe margins (R0) ( $p = .94$ ). In the subgroup of 12 patients with R1 margins, the 5-year actuarial local control estimate was 100% when postoperative radiation therapy was used and 71.4% when not; low sample sizes and the absence of any events when postoperative radiation therapy was used precluded statistical comparison.

### **Tracheotomy, nasogastric intubation, hospital stay**

Perioperative tracheotomy was performed in 2 patients in group R and 2 in group NR, for a median duration of 5 days (range, 3-120 days), without statistically significant difference between groups ( $p > .99$ ). Delayed tracheotomy was performed in the one patient suffering stroke in the NR group.

A nasogastric tube was inserted in 38.1% (8/21) of patients in group R and 16.7% (4/24) in group NR, with median enteral feeding time of 10 days (range, 2-130 days), without significant difference between groups ( $p = .2$ ). The NR group patient suffering from postoperative stroke had persistent swallowing disorder requiring 7 months' percutaneous gastrostomy.

Hospital stay was “suggestively” longer ( $p = .04$ ) in group R, at a median 7 days (range, 3-130 days), compared to 5 days (2-35 days) in group NR. This “suggestive difference” disappeared when excluding the case of stroke.



## Discussion.

In 1951, Pierre Charles Huet [5], operating on a patient with tonsillar fossa SCC with local control failure following radiation therapy, introduced transoral surgery as a conservative option for invasive SCC of the tonsillar region. Huet published no subsequent series, but several authors [6-14] adopted this mandible-sparing approach. It was referred to as “radical tonsillectomy” in the English-language literature and as “Huet’s procedure” in French and re-named “transoral lateral oropharyngectomy” in the early 2000s [8,9] while TORS was introduced [15-16]. In 2015, an American analysis of 84,449 cases of oropharyngeal SCC included in the National Cancer Data Base for 1998-2012 noted increased rates of robotic surgery following Food and Drug Administration approval in 2009, especially in T1-2 tumor (**Figure 3**) [23].

Comparing T1-2 tonsillar fossa SCC consecutively treated by transoral surgery with (group R; n=21) and without robotic assistance (group NR; n=24), the present study is the first to assess the impact of this technology in transoral lateral oropharyngectomy for such carcinomas. Although its retrospective design without randomization, multiple operators and low numbers in either arm, several are known biases that vitiate conclusions, other aspects give weight to the findings. The 2 groups were highly comparable for clinical characteristics (age, gender, comorbidity, follow-up), oncologic characteristics (presumed origin, affected sites, T and N staging, p16 status and basaloid status), and therapeutic characteristics (associated neck dissection, use of postoperative radiation therapy), with no statistically significant differences (Table 1) while a good quality of follow-up (minimum 3 years or until death, except for 1 loss to follow-up at 8 months) was achieved. Moreover, the significance threshold set at  $p < .005$  was an active contribution to the movement in favor of better application of statistics in biomedical research [21,22].

The results highlight the lack of any significant differences on any of the study criteria. Three- and 5-year actuarial survival estimates were respectively 80.2% and 74.5% in group R and

91.5% and 82.5% in group NR (Figure 1;  $p = .34$ ). Metachronous second primary cancer accounted for 60% of causes of death, far greater than the 13.3% related to local failure, in agreement with our team's previous reports [5,9,11]. Likewise, the actuarial local control estimate was 90.2% at both 3 and 5 years in group R, and respectively 95.8% and 91% in group NR (Figure 2;  $p = .81$ ), again in agreement with our previous report at 10 years' interval documenting cohorts of more than 100 patients with "early stage" tonsillar SCC operated on without robotic assistance [9,14]. Also, morbidity did not significantly differ between groups R and NR, whether in terms of hospital stay, incidence and duration of tracheotomy or enteral feeding or onset of postoperative complications (Table 3). Surgery site bleeding was the most frequent complication (Table 3), with incidence of 12.5% in group R and 14.5% in NR ( $p = .86$ ). To prevent this complication, at the time of transoral robotic oropharyngeal cancer surgery, it has been recommended to ligate the branches of the external carotid artery [24-27]. In the present series, a single ipsilateral lingual artery ligation was performed, and we would not recommend this as a systematic attitude, as the tonsillar fossa is not exclusively vascularized by the lingual artery, ligation of which does not abolish hemorrhagic risk [25]. The real question concerns preventive ligation of the ipsilateral external carotid artery[24-27] and it should be borne in mind that Huet [5], in his princeps report, performed preventive ipsilateral external carotid artery ligation (in a patient in whom the procedure was performed as salvage surgery after local failure of radiation therapy) for fear of postoperative hemorrhage. Two retrospective studies, published in 2017, reported that this maneuver did not affect incidence of postoperative bleeding, which, on the other hand, was never life-threatening [26, 27]. This benefit needs, in our opinion, to be weighed against two inherent drawbacks: postoperative embolization of external carotid branches is rendered impossible in case of onset of postoperative bleeding, and postoperative radiation therapy may be rendered less effective due to reduced oxygenation of remaining lateral oropharyngeal wall tissue. We therefore consider that preventive ipsilateral external carotid artery ligation should not be systematically performed but rather reserved to particular cases in which bleeding is feared or would

be difficult to manage: difficult intraoperative exposure or hemostasis, weak patient with bleeding risk factors, and/or difficulties of postoperative access to a qualified health-care structure.

In our study, no significant inter-group differences (Table 3) were noted for pathological data. However, the p-value threshold was set at .005, in line with recent progress in the concept of “significance” [21,22] and with a threshold of  $p = .05$ , the resection margin analysis “suggested” more frequent microscopically positive margins (R1) in group R (38.1 %) than group NR (16.6 %). Although this difference did not impact the 5-year local control estimates (89.6% in R0 healthy margins and 90.9% in R1 microscopically positive margins), it “suggested” that the issue would be worth analyzing in a cohort of several hundred patients, preferably in a multicenter study. At all events, the risk should be minimized, as R1 margins are an indication for postoperative radiation therapy. Unfortunately, this “complementary treatment” is not free of risk functionally as documented in Table 3 with 8 major complications noted in the subgroup of 26 patients irradiated postoperatively while, oncologically, it “sacrificed” a treatment option for head and neck metachonous primary cancer, of which the 10-year actuarial estimate has been reported to be 73.7% in this population [12]. Theoretically, surgeons at the peak of their learning-curve might achieve lower rates of microscopically positive margins; this could not be analyzed in the present study, with its numerous operators and small numbers per arm. The literature, however, suggests that experience in TORS for oropharyngeal SCC is not a factor affecting resection margin status. White et al. [28], in a single-center prospective study of 168 patients with oropharyngeal SCC treated by TORS between 2007 and 2011, noted that the learning curve reduced operative time and hospital stay, but not the rate of microscopically positive margins. In a retrospective study of the impact of the learning curve on margin status for 3 surgeons operating on 160 patients with oropharyngeal SCC treated by TORS between 2010 and 2016, Albergotti et al. [29] found that 2 of the surgeons showed a learning curve peaking at respectively 25 and 30 procedures, while the third did not. The question thus remains open, especially as published series include all oropharyngeal sites and T stages [28,29]. More than

experience as such, knowledge of the characteristics of mucosal and muscular extension of T1-2 tonsillar fossa SCC seems to us to be essential to achieving healthy R0 margins. Lee et al. [30], in a cohort of 43 patients with T1-2 tonsillar cancer treated on a transoral approach, reported that pathologic examination of specimens found superior pharyngeal constrictor muscle involvement in 33.3% of T1 and 71.4% of T2 tumors. The tumor infiltrated a mean 3 mm into the muscle and microscopic infiltration in the horizontal (mucosal) plane exceeded the macroscopic margins by a mean 0.8 mm [30]. Likewise, Park et al. [31], studying pathology analysis of specimens of tonsillar SCC resected by a transmandibular approach or by lateral pharyngotomy, found constrictor involvement in 17.2% of T1 and 76.9% of T2 tumors. The deep side of the muscle was involved in 12.8% of T2 tumors, and never in T1. These findings highlight the importance of wide margins in both muscle and mucosa. We think this may be difficult in robotic surgery, partly due to the absence of force feedback indicating real infiltration and partly because 3D magnification can lead the surgeon to unconsciously close in on the tumor during resection. To get around this, the surgeon can use frozen section examination, but the muscle retraction induced by sectioning renders the analysis hazardous when findings are negative. The surgeon can also leave the monitor to palpate the surgical field or, in case of doubt, complete resection without robotic assistance, as in 9.5% of the present group R cases. Moving away from the monitor like this seems unsatisfactory to us; it raises the question of why we use robotic assistance in the first place, since magnification can just as well be achieved using a microscope or magnifying lens. Of much more interest, to us, is tattooing the resection field adjusted by palpation on preoperative endoscopy since this resulted in a 99% incidence of healthy margins in the report by Hinni et al. [32], in a series of 99 cases of tonsillar fossa SCC managed with transoral lateral oropharyngectomy. Finally, the new generation of flexible robotic instruments [33] promises better visualization and maneuverability, with better perception of force feedback, and is well worth assessing – even if it is clear that promises commit only those who believe in them.

## **Conclusion.**

Two points emerge from this study dedicated to the analysis of robotic assistance during transoral lateral oropharyngectomy in T1-2 tonsillar fossa SCC. Firstly, this technology increased the rate of microscopically positive resection margins. Prior tattooing of the resection field is easy to perform and, in our opinion, could reduce this rate. The second point, which raises the question of the cost/benefit ratio of robotic surgery, is that robotization failed to improve functional or oncologic results. Two medico-economic situations are to be distinguished here. In countries in which the level of development does not presently allow robots to be introduced, it seems unadvisable to wait for their arrival before adopting transoral lateral oropharyngectomy as a “conservative” alternative to radiation therapy. In developed countries, robotic assistance incurs non-negligible costs and should not be considered indispensable for transoral resection of T1-2 tonsillar fossa SCC. Neither should it be rejected by head and neck surgeons, but rather considered as a key step in training in this technology, so as to optimize its use and contribution in other surgical indications.

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## **Table and figure legends**

**Table 1:** Characteristics of the 2 groups: R (n=21) with and NR (n=24) without robotic assistance in transoral oropharyngectomy (ant: anterior; post: posterior; SD: standard deviation).

**Table 2: Pathology data** (R0: healthy margins; R1: microscopically positive margins).

**Table 3: Surgical morbidity** (\* fatal complication; ° intraoperative hemorrhage and difficult exposure necessitating lateral pharyngotomy associated to the transoral lateral oropharyngectomy; <sup>α</sup> distributions respectively for the 41 patients with associated neck dissection and 24 patients with postoperative radiation therapy).

**Figure 1:** Actuarial survival curves (red dots: group R; blue dots: group NR); no significant difference.

**Figure 2:** Actuarial local control curves (red dots: group R; blue dots: group NR); no significant difference.

**Figure 3:** Progression of rate of cT1-T2 or cT3-T4 oropharyngeal squamous cell carcinomas treated by transoral robotic surgery (TORS) in the USA between 1998 and 2012 [22].

**Table 1.**

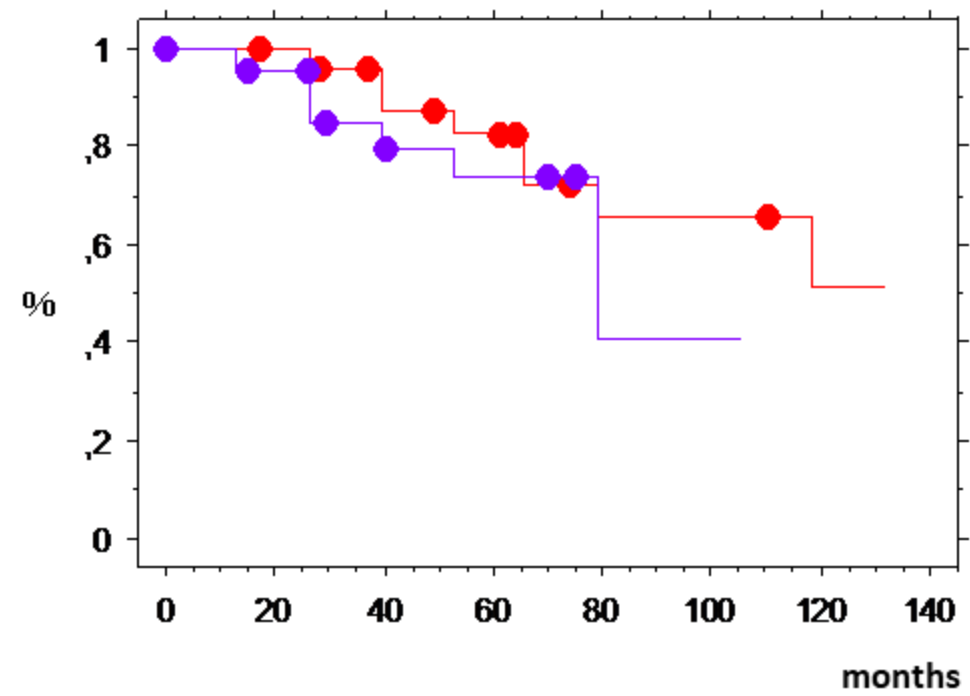
<b>Variables</b>	<b>R (n=21)</b>	<b>NR (n=24)</b>	<b>P</b>
- Age (years): Median / range	61/ 44-80	62 / 44-82	.5
- Gender: Male/Female	14/7	14/10	.8
- Comorbidity score <sup>19</sup> : Median + SD	2 ± 2	1 ± 2	.8
- Basaloid squamous: Yes/no	2/19	4/20	.7
- Papilloma virus screening: Yes/no	12/9	9/15	.2
P16+/P16-	7/5	7/2	> .99
- Origin: tonsil/ ant pillar/ post pillar	15/3/3	19/5/0	.2
- Diagnostic tonsillectomy: Yes/no	0/21	2/22	.5
- Sites involved			
Anterior tonsillar pillar	7	5	.5
Junction zone	1	0	.5
Soft palate	2	2	> .99
Posterior tonsillar pillar	6	1	.038
Subtonsillar	4	2	.2
Glossotonsillar groove	1	3	> .99
- T staging: T1/T2	8/13	9/15	> .99
- N staging: N0/N1/N2/N3	8/7/5/1	10/6/8/0	.7
- Associated neck dissection			
ipsilateral II-IV: Yes/no	19/2	22/2	> .99
ipsilateral I: Yes/no	1/20	1/23	.7
contralateral II –IV: Yes/no	4/17	1/23	.2
- Postoperative radiation therapy: Yes/no	10/11	16/9	.2
Dose T (Gray): Median + SD	63 ± 6	60 ± 5	.2
Dose N (Gray): Median + SD	61 ± 7	63 ± 5	.2
Associated chemotherapy: Yes/no	5/16	3/21	.6

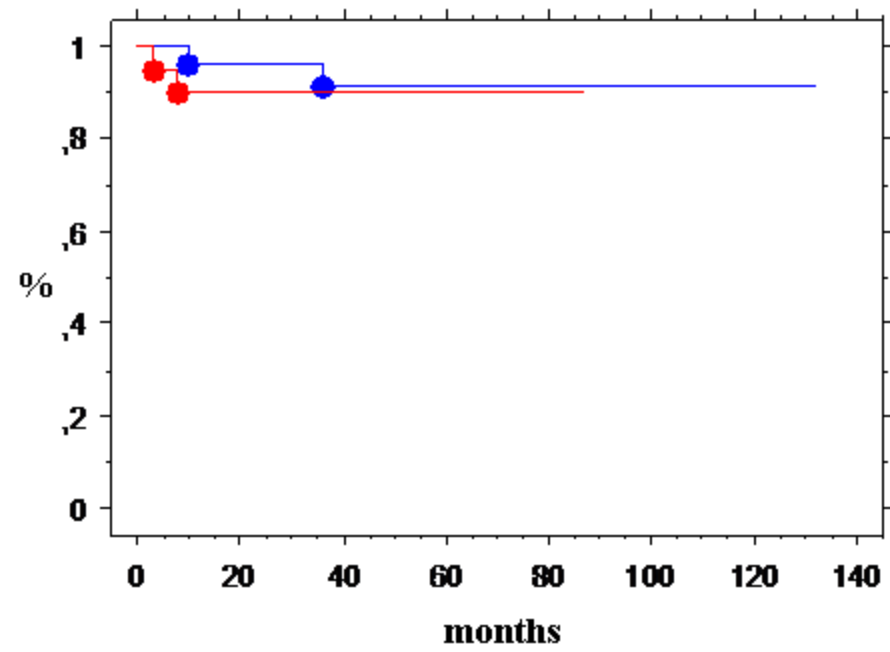
**Table 2.**

<b>Pathology data</b>	<b>R (n=21)</b>	<b>NR (n=24)</b>	<b>P</b>
Resection margins: (R0/R1/Dysplasia)	10/8/3	20/4/0	.05
Vascular embolism at T site: Yes/no	8/13	5/19	.2
Lymphatic embolism at T site: Yes/no	1/20	1/23	> .99
Perineural invasion: Yes/no	3/18	0/24	.09

**Table 3.**

<b>Complications</b>	<b>R (n=21)</b>	<b>NR (n=24)</b>	<b>P</b>
- Intraoperative at T site: Yes/no	2/19	0/24	> .99
Hemorrhage	1	0	
Cervical communication °	1	0	
- Postoperative at T site: Yes/no	3/18	4/19	.7
Hemorrhage	2	3	
Flap necrosis	1	0	
Prolonged swallowing disorder (n)	1	1	
- Cervical postoperative <sup>¤</sup> : Yes/no	2/19	1/22	.4
Cervical hematoma	0	1	
Salivary leak °	1	0	
Cranial nerve palsy	2	0	
- General postoperative: Yes/no	2/19	2/22	.6
Pneumopathy*	1	0	
Severe depression	1	1	
Stroke	0	1	
- Post-radiotherapy <sup>¤</sup> : Yes/no	5/9	3/15	.07
Isolated severe trismus	1	1	
Osteonecrosis (mandible, styloid)	2	2	
Pharyngeal ulceration	2	0	
Carotid rupture	1	0	
Lhermite syndrome	1	0	
Severe hypothyroidism	1	0	





Percentage of Patients Receiving Surgery

