



# Resection and reconstruction of the carotid artery for head and neck squamous cell carcinoma: a GETTEC study

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## Abstract

**Objectives** *Main:* To describe 1-year overall survival (OS) after primary or salvage management of head and neck squamous cell carcinoma (HNSCC) invading the common or internal carotid artery (CCA/ICA). *Secondary:* To assess disease control rate, treatment morbidity, and radio-anatomopathologic correlation.

**Methods** Retrospective study of 67 patients, treated between 1999 and 2020 for N3bM0 HNSCC invading the CCA/ICA as identified by CT-scan. Tumors that could not have been resected with a complete en-bloc resection sacrificing and reconstructing the CCA/ICA were excluded. Patients were separated into two groups (primary or salvage treatment) and studied according to the type of treatment they received: radiotherapy/radiochemotherapy (RT/RCT), surgery, or systemic therapy (ST).

**Results** For newly treated patients, the 1-year OS was significantly better after RT/RCT (73%) than after surgery (40%,  $p < 0.0001$ ). In the salvage setting, the 1-year OS after surgery (40%) was better than after ST (14%, statistically suggestive difference with  $p = 0.0241$ ). Surgery improved cervical control, but distant metastases occurred in more than 50% of cases regardless of treatment. No neurological complication occurred after carotid reconstruction. Perioperative mortality was 7% (1/15). The carotid invasion was confirmed by pathological examination in all five patients with an arterial deformation on CT-scan, in seven among eight patients with CCA/ICA encasement greater than 270°, and in four out of seven patients with CCA/ICA encasement between 180° and 270°.

**Conclusion** Neck dissection with carotid resection and reconstruction is technically feasible with acceptable neurovascular morbidity. For newly treated patients, survival is better after RT/RCT. For salvage treatment, surgery could be proposed to selected patients.

**Keywords** Head and neck squamous cell carcinoma · N3b · Carotid bypass · Carotid resection · Overall survival

## Introduction

Locally advanced head and neck squamous cell carcinoma (HNSCC) presenting with a nodal invasion of the common or internal carotid artery (CCA/ICA), with no evidence of distant metastatic disease is classified as N3bM0 by the American Joint Committee on Cancer (8th edition, 2017). Reported radiological criteria to diagnose the carotid invasion are: arterial deformation, segmental obliteration of the fat between the lymph node and the carotid, and arterial encasement greater than 180° [1]. The prognosis is poor, and progression of the tumor may lead to carotid blowout [2]. Median survival of N3-stage HNSCC varies from 3 months with palliative care to 1.5 years with curative treatment [3].

Treatment options differ depending on patient's general conditions and medical history, as a history of HN

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radiotherapy often contraindicates definitive radiotherapy. The GETTEC (Groupe d'Étude des Tumeurs Tête Et du Cou) highlighted that a tumor encasing more than 270° of the CCA/ICA circumference is unresectable without vascular reconstruction [4].

Multimodal treatment based on surgery would require complete node dissection, sacrificing the CCA/ICA, followed by radiochemotherapy (RCT) [5]; however, some authors consider that neurovascular morbidities and functional sequelae induced by such extensive neck dissection are a contra-indication for surgery. Radiotherapy alone or with concurrent chemotherapy is the alternative, but exposes patients to acute or delayed side effects [6]. Besides, its efficiency may be reduced when the tumor volume is large. A study of 360 patients with stage III-IV HNSCC, including 31 N3, treated with RCT showed that the risk of local recurrence increases by 14% per 10 cm<sup>3</sup> of tumor volume [7].

In a salvage setting, the impossibility of curative dose re-irradiation often limits the options to palliative systemic treatments. Surgery is, however, sometimes proposed by some surgical teams.

The optimal treatment is not clearly established. The weakness of the available studies is linked with their small size and their retrospective character. In France, for example, only a few centers perform cervical neck dissection with carotid resection and reconstruction.

The primary objective of our study was to describe the overall survival 1 year after primary or salvage management of N3bM0 HNSCC with CCA/ICA replacement, in patients for whom surgical treatment was technically feasible.

The secondary objectives were to evaluate the rate of disease control, radio-anatomopathological correlation and morbidity of the following treatments: radiotherapy/radiochemotherapy (RT/RCT), surgery with carotid replacement, systemic therapy (ST).

## Materials and methods

### Population

GETTEC members who performed a neck dissection with carotid bypass for HNSCC between 1999 and 2020 were invited to include patients in the surgical group. Patients were identified by Common Classification of Medical Procedures (CCAM) coding of the surgical resection.

Suspicion of carotid invasion on the CT scan was defined as an encasement greater than 180° with segmental obliteration of the periarterial fat or arterial deformation by tumor compression. Fifteen patients were included in 5 centers.

Because CCAM or International Classification of Diseases (ICD-10) coding lacks the specific item "carotid invasion", patients in the groups treated by RT/RCT or ST over

the same period were selected one by one through the artificial intelligence software ConSoRe [8] using the keywords "carotid invasion" and "carotid infiltration," crossed with the tumor staging keyword "N3" and the diagnostic codes C01-C06 and C09-C14 (CIM-10). However, this was only possible in one center.

Exclusion criteria were:

- Other histology
- Non-resectable tumor or node with an extension to the skull base
- Exclusive supportive care treatment

A total of 26 patients were excluded from the study.

Patients were classified according to the stage of the disease: initial or salvage, and then studied according to the chosen treatment modality: RT/RCT, surgery with carotid replacement, or ST.

Retrospective chart data included demographics, tumor imaging characteristics, treatment modalities, pathologic examination, complications, disease progression, cause of death, and status at last report.

The study complied with the legislation of the General Data Protection Regulation and was registered under the number R201-004-106 at Leon Bérard Comprehensive Cancer Center.

## Treatments

### Neoadjuvant chemotherapy

Neoadjuvant chemotherapy type "PF" included cisplatin and 5-fluorouracil, and type "TPF" includes the addition of taxanes [9].

### Radio(chemo) therapy

Definitive or adjuvant external 3D conformal or intensity-modulated radiation therapy (IMRT) was delivered to the tumor site at a curative dose of more than 60 Gy, with concurrent chemotherapy when feasible, with curative intent. Concurrent chemotherapy included either cisplatin 100 mg/m<sup>2</sup> every 3 weeks, 40 mg/m<sup>2</sup> weekly, or cetuximab one week before RT followed by 250 mg/m<sup>2</sup> weekly post-RT.

### Surgery

The patency of the Circle of Willis was assessed by a pre-operative brain angioscan. Cerebral neurovascular monitoring was performed by NIRS (Near infrared spectroscopy) during the neck dissection. An arterial shunt was planned if the cerebral O<sub>2</sub> saturation differential became higher than 30% after clamping. Blood pressure was kept high and

constant with median arterial pressure > 100 mmHg. Heparin 50 U/kg and 100 mg acetylsalicylic acid were injected before clamping. After en-bloc resection, the CCA/ICA was bypassed with a saphenous vein, a superficial femoral artery, or an expanded polytetrafluoroethylene prosthesis. Pectoralis major myo-cutaneous flap covered the bypass when necessary. Post-operative neurological assessment was systematic. Antithrombotic therapy was started. In the month following surgery, an angioscan evaluated the patency of the carotid reconstruction. Adjuvant radiotherapy was performed in the absence of contra-indication. Pathological examination determined tumor resection margins and carotid invasion.

### Systemic treatment

Systemic treatments included:

- Chemotherapy (cisplatin or carboplatin, taxanes, 5-fluorouracil)
- Anti-EGFR (cetuximab)
- Anti-PD1 immunotherapy (nivolumab, pembrolizumab)

Doses were adapted to patients' general condition, comorbidities, and tolerance.

### Follow-up

For patients treated with ST, overall survival was defined as the time interval from the diagnosis of carotid invasion to the time of death or last follow-up. For patients treated with RT/RCT or surgery overall survival was defined as the time interval from the end of treatment to the time of death or last follow-up.

### Statistical analysis

Overall survival was calculated according to the Kaplan–Meier method, compared by a log-rank test, using Prism® software. A  $p$  value < 0.005 was considered statistically significant, and  $p$  < 0.05 was considered suggestive [10].

## Results

### Primary treatment for newly treated patients

#### Patients

Among the forty-three patients that were newly treated: 26 received RT/RCT, 5 had surgery and RT and 12 received ST. The median age was 61 years [49–89 years] with a predominance of men (37/43, 86%). Severe comorbidities were

observed in all groups with a Charlson score > 4 in 80% of patients (34/43). The most frequent comorbidities were hypertension (21/43, 49%), chronic obstructive pulmonary disease (COPD) (15/43, 35%) and peripheral arterial disease (10/43, 23%). The initial tumor sites included the hypopharynx, oropharynx, and larynx (Table 1).

### Treatments

In the initial RT/RCT group, 21 patients (80%) received neoadjuvant chemotherapy. Radiotherapy was delivered at a median dose of 70 Gy [60–80 Gy] with concurrent chemotherapy completed in 20 patients (77%) and discontinued early in 4 patients for toxicity.

In the initial surgery group, all patients except one received neoadjuvant chemotherapy followed by radio-chemotherapy for progressing disease.

In the initial ST group, patients received chemotherapy combining carboplatin and taxol ( $n = 8$ ) or reduced dose of TPF ( $n = 4$ ).

### Follow-up

For newly treated patients, the 1-year overall survival was significantly better for patients treated with RTCT (73%) than for patients treated with surgery (40%) and patients treated with ST (8%) ( $p < 0.0001$ ) (Fig. 1.).

Local control was better in patients treated with surgery (4/5) than patients treated with RTCT (7/26, statistically suggestive difference with  $p = 0.041$ ).

The rate of metastasis was similar in all groups: 21/26 after RTCT, 3/5 after surgery and 8/12 with ST. The most frequent metastatic site was lungs (18/43 = 42%), followed by bone (7/43 = 16%), mediastinum (3/43 = 7%), liver (3/43 = 7%), base of the skull (2/43 = 5%) and brain (1/43 = 2%).

For patients treated with RTCT, median follow-up was 15 months [5 months–15 years]. Twenty-one (21/26, 81%) patients died of distant metastases. Metastases were diagnosed on average 4 months after the end of the treatment [31 days–17 months]; 3/26 patients died of intercurrent events with no evidence of disease (aspiration pneumonia; stroke; pulmonary embolism); two patients were alive with no evidence of disease, after 5 years of follow-up.

For patients treated with surgery, median follow-up was 8 months [7 months–3.4 years], 3/5 patients died of pulmonary metastasis occurring 3.8 months, 5.5 months and 6.7 months after surgery. One patient was alive with no evidence of disease after 3 years of follow-up. One patient died of an intercurrent event.

For patients treated with ST, median follow-up was 4.8 months [30 days–14 months], all patients died of their disease, with distant metastasis in 8/12 patients (67%).

**Table 1** Patient characteristics

	Primary						Salvage						p value
	RT/RTC	Surgery	ST	Total	Surgery	ST	Total	Surgery	ST	Total	p value		
	26	5	12	43	10	14	24	10	14	24			
Age													
Years (median)	58	[49–76]	61	[54–89]	61	[49–89]	66	[49–74]	61	[54–73]	64	[49–74]	
Sex													
Female	2	8%	1	20%	3	25%	6	14%	1	10%	2	8%	1
Male	24	92%	4	80%	9	75%	37	86%	13	90%	22	92%	
General state													
BMI (kg/m <sup>2</sup> )	[14–38]		[15–35]	[13–34]	[13–38]		[19–34]		[16–33]		[16–34]		
< 18.5	4	15%	1	20%	5	42%	10	23%	0	0%	3	13%	0.163
18.5–25	16	62%	1	20%	4	33%	21	49%	5	50%	13	54%	
> 25	6	23%	3	60%	3	25%	12	28%	5	50%	8	33%	
Performance status													
0–1	15	58%	4	80%	4	33%	23	53%	5	50%	12	50%	1
≥ 2	11	42%	1	20%	8	67%	20	47%	5	50%	12	50%	
Charlson score	[2–8]		[3–7]	[3–9]	[2–9]		[2–8]		[3–8]		[2–8]		
≤ 3	7	27%	1	20%	1	8%	9	21%	2	20%	4	17%	1
≥ 4	19	73%	4	80%	11	92%	34	79%	8	80%	20	83%	
Habitus													
Smoking status													
Current	17	65%	3	60%	10	83%	30	70%	2	20%	7	29%	0.653
Former	7	27%	2	40%	1	8%	10	23%	8	80%	17	71%	
Never	2	8%	0	0%	1	8%	3	7%	0	0%	0	0%	
Alcohol history													
Current	10	38%	1	20%	4	33%	15	35%	2	20%	5	21%	0.938
Former	5	19%	1	20%	4	33%	10	23%	3	30%	8	33%	
Never	11	42%	3	60%	4	33%	18	42%	5	50%	11	46%	
Primary tumor site													
Oral cavity	1	4%	0	0%	3	25%	4	9%	0	0%	0	0%	0.1664
Oropharynx	9	35%	1	20%	4	33%	14	33%	2	20%	10	42%	
Larynx	6	23%	1	20%	0	0%	7	16%	3	30%	6	25%	
Hypopharynx	9	35%	3	60%	5	42%	17	40%	3	30%	6	25%	
Unknown primary	1	4%	0	0%	0	0%	1	2%	2	20%	2	8%	
T													
T1–T2	6	23%	2	40%	1	8%	9	21%	6	60%	11	46%	
T3–T4	19	73%	3	60%	11	92%	33	77%	2	20%	11	46%	

Table 1 (continued)

	Primary				Salvage				p value
	RT/RTC	Surgery	ST	Total	Surgery	ST	Total	Total	
Patients (N=):	26	5	12	43	10	14	24		
Tx	1	0	0	1	2	0	2	8%	
	4%	0%	0%	2%	20%	0%	0%		

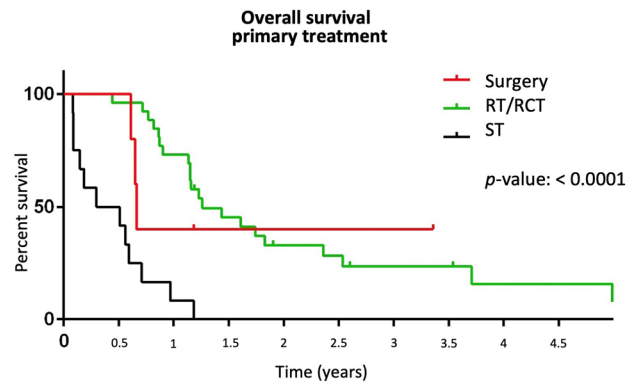


Fig. 1 Kaplan–Meier overall survival curves in the primary treatment group

Metastasis were diagnosed on average 3 months after diagnosis [31 days–11 months].

**Salvage treatment**

**Patients**

Twenty-four patients presented with a recurrent HNSCC in a previously irradiated neck. The median time from diagnosis of N3b to the end of initial radiotherapy was 3 years [6 months–5 years]. Median age was 64 years [49–74 years] with a predominance of men (92%). Fourteen patients received systemic therapy and 10 patients underwent salvage surgery with carotid reconstruction. General status was similar in both groups (Table 1).

**Treatments**

Salvage surgery was performed on a previously operated neck in 6 patients (25%). No cervical re-irradiation was possible.

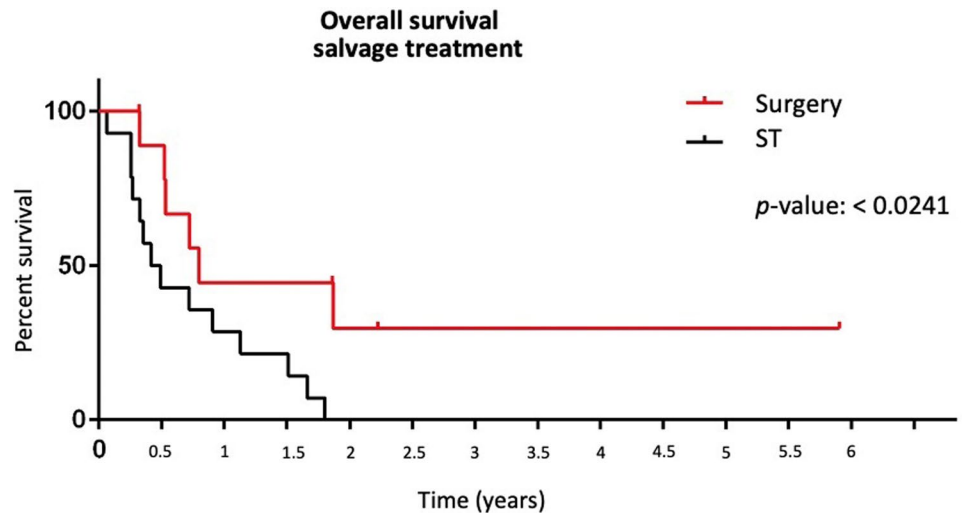
ST included platinum (n=4), anti-EGFR (n=9), taxol (n=3), and anti-PD1 (n=2).

**Follow-up**

The 1-year overall survival in the salvage surgery and salvage ST group was 40 and 14%, respectively (Fig. 2.). Median survival was 9.1 months and 5.5 months, respectively (p=0.024).

In the salvage surgery group, median follow-up was 9 months [4 months–6 years]. Four (4/10) patients died of HNSCC, 3 with distant metastases, occurring 3–8 months after surgery and one with concomitant metastatic and local relapse; 3/10 patients died of intercurrent events with no evidence of disease (aspiration pneumonia = 2; carotid blowout = 1); 3/10 patients were alive without

**Fig. 2** Kaplan–Meier overall survival curves in the salvage treatment group



disease progression, after 1.8 years, 2.2 years and 5 years of follow-up, respectively.

In the salvage ST group, median follow-up was 5 months [23 days–2 months]. All patients died of their disease, with distant metastasis in 11 (79%) patients.

### Surgical techniques and morbidities

No vascular shunt was necessary because of the patency of the circle of Willis and the stability of the NIRS after carotid clamping. Sacrifice of the internal jugular vein was systematic (100%); other elements that were sacrificed were the sternocleidomastoid muscle (13/15 = 87%), the X, XI or XII cranial nerves (11/15 = 73%) and the sympathetic chain (7/15 = 47%). Median clamping time was 31 min [17–44 min]. The proximal anastomosis was performed on the CCA or the ICA, and on the homolateral subclavian artery in one case.

Type of reconstructions used were:

- Saphenous vein ( $n = 10$ )
- Superficial femoral artery ( $n = 1$ ) in a patient with a history of vein stripping
- Prosthesis ( $n = 3$ )
- Direct anastomosis between the distal and proximal carotid portion ( $n = 1$ )

No early neurological deficits or acute donor site complications were observed. A pedicle flap was performed in 73% (11/15). The median hospital stay was 19 days [5–69 days]. Angioscan showed asymptomatic graft thrombosis in one patient (7%, 1/15). Perioperative mortality (< 30 days) was 7% (1/15) due to carotid blowout on day 10 of the procedure.

### Radio-anatomopathological and clinical correlation

Carotid adventitial invasion was histologically confirmed in 7/8 operated patients with an encasement greater than 270°; in 4/7 patients with an encasement between 180° and 270°; and in 5/5 patients in case of carotid deformation. The CCA/ICA was not invaded in 4/15 patients, two of whom were alive without disease progression at 2 and 5 years after the operation.

The resection margins were in healthy area (R0) in 13/15 patients, and microscopically invaded (R1) in 2 patients who evolved locally.

### Complications

A carotid blowout was observed in 7/12 (58%) under initial ST, 6/26 (23%) after initial RCT and in 2 patients (20%) after salvage surgery. Regarding these 2 salvage surgery patients, carotid blowout occurred early on day 10 postoperatively, and was attributed to a pharyngostoma and the absence of a covering flap. In the second patient, it was related to a tumor recurrence at 6 months postoperatively. An ischemic stroke occurred in a patient at a distance from the salvage surgery and was attributed to his cardiovascular risk factors; the patient was alive without evolution after 2 years of follow-up with a sequential hemiparesis. The risk of stroke was not increased after surgery (Table 2).

The proportion of patients requiring tracheostomy or prolonged enteral feeding was similar in the three groups. The main etiology of swallowing disorders was xerostomia after RT/RCT, nerve sacrifices after surgery, and disease progression on ST. Among the 11 patients who had resection of the X and XII nerves, 7 patients recovered independent oral feeding after speech therapy.



**Table 2** Complications observed according to the stage of the disease and the type of treatment

	Primary			Salvage							
	RT/RCT		Surgery	ST	Surgery	ST					
Patients (N=):	n = 26		n = 5		n = 12		n = 10		n = 14		
Neurovascular											
Stroke	2/26	8%	0/5	0%	0/12	0%	1/10	10%	1/14	7%	
Carotid blowout	6/26	23%	0/5	0%	7/12	58%	2/10	20%	5/14	36%	
Functional											
Tracheostomy	7/26	27%	1/5	20%	7/12	58%	2/10	20%	2/14	14%	
Oesogastric tube/ gastrostomy	10/26	38%	2/5	24%	5/12	42%	2/10	20%	8/14	57%	

Cutaneous-mucosal side effects of radiotherapy with grade II epithelitis in 9 patients (35%) and grade II mucositis in 13 patients (50%) had a favorable evolution.

Recurrent syncope due to carotid sinus compression and cerebral low flow was observed in 3 patients in the ST group.

## Discussion

Head and neck squamous cell carcinoma with nodal carotid invasion is an advanced disease with a poor prognosis: in our series, the one year overall survival was less than 15%, with a median survival of less than 6 months with primary or salvage systemic treatment. Our study showed a better prognosis after RT/RCT compared to surgery with CCA/ICA bypass as first-line treatment.

Surgical feasibility of neck dissection resecting and reconstructing the CCA/ICA has already been reported with a neurovascular morbidity ranging from 0 to 5% [11]. This is the only oncologic technique that allows to perform en-bloc resection when the CCA/ICA is invaded. On the one hand, a subadventitial dissection weakens the arterial wall and poses the risk of tumor residue [12]. Indeed, an invasion of the intima of the CCA/ICA was observed in more than 70% of pathological specimens in our series. On the other hand, carotid ligation without reconstruction carries a risk of stroke up to 55% [13]. Strokes are caused by two different mechanisms: immediate due to contralateral vascular insufficiency; or delayed (but still < 5 days) caused by thromboembolic phenomenon due to the arterial stump. The latter risk cannot be predicted by the preoperative carotid occlusion test [14].

Autologous material, such as the saphenous vein [15], the superficial femoral vein [16] or even the superficial femoral artery [17] can be used. Those are easy to harvest and resistant to infection and irradiation [11], while infection of prosthetic materials are rarely observed [18, 19]. A myocutaneous flap covering the bypass and protecting it from the pharynx is recommended [11]. In our study, the peri-operative mortality (1/15) was consistent with the meta-analysis

data of Back et al., ranging from 0 to 15% [11]. In addition, the rate of tracheostomy and long-term enteral feeding was similar regardless of treatment modality, as found by Carsuzaa et al. [20].

Oncologic outcomes of HNSCC with CCA/ICA invasion are poorly studied. Available studies focusing on carotid resection and reconstruction are retrospective, noncomparative, with a small number of patients [15, 18, 21]. Besides, these series often analyze first line and salvage treatments together [21, 22], with thyroid carcinomas sometimes included [23, 24]. The largest series of surgically treated N3 patients by Mourad et al. studied 41/51 patients who benefited from primary surgery with adjuvant RCT. Locoregional progression occurred in only one patient (1.9%), and distant metastases in 4 patients (7.8%), without cervical relapse. Overall survival at 2 years was 82% [21]. These excellent results must be used with caution as patients' characteristics and pathological results were not specified. Our findings are consistent with the results of a recent meta-analysis including 357 patients, with 63% having undergone salvage surgery, showing an overall survival at 1 year of 52.4% [11].

Only one retrospective Korean study [25] of 23 patients compared the different treatment modalities. In this study, median survival after surgery (16.5 months;  $n = 11$ ) was better than after RT (11.5 months;  $n = 6$ ) or palliative treatment, including TS and supportive care, alone (3 months;  $n = 6$ ). Overall survival 2 years after surgery was 24.5%, and was similar to overall survival after RT.

A study by Carsuzaa et al. [20] of 301 N3 patients, without distinction of N3b, compared RCT alone and surgery followed by RCT, and did not find any difference in overall survival and metastases rate at 5 years. Locoregional control was better after surgery with an increased morbidity due to nerves sacrifice. Similarly, Ko et al. [26] did not find any survival difference in a study of 1464 patients treated with surgery and 3403 patients treated with RCT. Only patients with HPV-negative oropharyngeal tumors had a slightly better survival rate when treated with surgery.

En-bloc resection improves local control, but the risk of metastatic progression remains. In a study of 31 patients

treated with extensive neck dissection with vascular replacement by Illuminati et al. [18], 48% experienced metastatic progression 22 months [9–87 months] after the end of treatment. Undetected micrometastases at time of diagnosis or spread of tumor emboli during surgery [27], could explain this despite R0 resection. Nevertheless, complete remission is sometimes reported [16, 18]: it was observed in our study in two patients in the RT/RCT group and one patient in the surgery group, whose CCA was not invaded on histological examination.

Extensive surgical treatment for advanced disease is often discussed on a case-by-case basis: our study encourages to reserve this discussion to salvage situations. Nevertheless, patients should probably be selected, since reported 1-year mortality rate after salvage surgery for recurrent HNSCC being 27.7%, with 17.3% patients staying in hospital until their death [28].

Our study presents several limitations. Groups are small and heterogeneous, which strongly reduces the power of our study. The inclusion of patients who underwent operations from several centers was a bias that was made unavoidable by the uncommon and non-consensual practice of this surgery in France. The selection of patients treated by surgery was based on unsystematized criteria. Patients treated with radiotherapy were based only in one center. This may have increased selection bias. In addition, the retrospective nature of the study may have underestimated the number of neurovascular complications. However, this study is only the second to compare therapeutic modalities for patients treated for N3 HNSCC with CCA/ICA resection and reconstruction, and the first to compare patients for whom surgical treatment was technically feasible.

## Conclusion

Locally advanced HNSCC with CCA/ICA invasion has a poor prognosis. Surgery with carotid resection and reconstruction is technically feasible with acceptable neurovascular morbidity. For newly treated patients, treatment with RT/RCT allows a better overall survival in our study. In case of salvage situation, surgery could be proposed to selected patients.

## Declarations

**Conflict of interest** The authors declares that there is no conflict of interest.

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