Locally advanced nasal pyramid squamous cell carcinoma: our 15 years' experience in a series of 35 total rhinectomies*

Jebrane Bouaoud[1,2], Nadia Benmoussa[1], Quentin Hennocq[1], Jean-François Honart[2], Ingrid Breuskin[1], Philippe Gorphe[1], Odile Casiraghi[3], Marion Classe[3], Pierre Blanchard[4], François Janot[1], Frederic Kolb[2], Nicolas Leymarie[2], Stephane Temam[1], Antoine Moya-Plana[1]

[1] Department of Head and Neck Surgical Oncology, Gustave Roussy Institute, University Paris-Saclay, Villejuif, France

[2] Department of Plastic and Reconstructive Surgery, Gustave Roussy Institute, University Paris-Saclay, Villejuif, France

[3] Department of Pathology, Gustave Roussy Institute, University Paris-Saclay, Villejuif, France

[4] Department of Radiation Oncology, Gustave Roussy Institute, University Paris-Saclay, Villejuif, France

Rhinology 58: 6, 638 - 640, 2020

https://doi.org/10.4193/Rhin20.381

***Received for publication:**

July 28, 2020

Accepted: September 3, 2020

To the Editor:

Locally advanced nasal pyramid squamous cell carcinoma (LA-NPSCC) are rare malignancies. Their specific outcomes are unclear. Their management remains challenging with several controversies, in particular regarding the realization of total rhinectomy and the role of elective neck node treatment [(1)].

Between 2005 and 2019 in our department (Gustave Roussy Cancer Campus), n=35 patients with LA-NPSCC were treated with at least total rhinectomy (Supplementary data 1). The typical presentations were males (63%), with a median age of 61 years, smokers (78%), presenting stage IVa LA-NPSCC (AJCC 8th), originated from the nasal mucosa, especially the anterior nasal septum (Supplementary data 2). Thirteen patients (37%) presented with clinical and/or radiological cervical lymph node involvement at diagnosis (cN+).

One third (n=11) were previously treated then referred to our department for management of local relapses/progressions (Supplementary data 3).

Regarding management, twelve (34%) patients received a Platine based neoadjuvant chemotherapy (neoCT) due to fast-growing tumours (rapid evolution within the last two months based on the patient's and surgeon's appreciation and photographs). Good (< 10% of viable tumoral cells) and partial (tumoral necrosis but >10% of viable tumoral cells) pathologic responses were reported in 5 (42%) and 3 (25%) cases, respectively (Supplementary data 4).

A primary total rhinectomy (no previous treatment) was realized for 15 (45%) patients. Salvage surgery (previous surgical treatment and local progression/relapse context) was performed for 11 (31%), including 3 patients receiving neoCT before salvage surgery. Post neoCT rhinectomy (without previous surgery) was performed in 9 (24%) patients. In all, 12 patients in the study received neoCT. Resection margins were clear R0 in 25 (72%), marginal (i.e. microscopically invaded) R1 in six (17%) and invaded R2 in four (11%) cases.

Cervical lymph nodes were managed by neck dissection (ND) for 24 (69%) patients, usually a bilateral selective ND. Lymph node involvement (pN+) was confirmed in ten (42%) cases, especially the IB submandibular group, with two third of extracapsular spread (ECS+). Among cN0 patients (n=22), twelve underwent a ND while two (17%) were pN+.

Post-operative radiotherapy (PORT) was realized for n=27 patients (77%) and usually included the cervical lymph nodes (81%).

With a median follow-up of 52 months (range 6-165), four patients (11%) experienced a local recurrence (R1 resections, median time of 3 months [range 1-7]) and four (11%) had a nodal relapse (median time of 15 months [range 3-25]).

Three-year local and regional control rates were 88% (95% CI, [73; 100]) and 86% (95% CI, [74; 100]), respectively. Four patients (11%) died during the follow-up, including two following malignant progression.

The 5-year Overall (OS), disease specific (DSS) and disease-free (DFS) survivals were 89% (95% CI, [77; 100]), 93% (95% CI, [85; 100]), and 75% (95% CI, [61; 92]), respectively.

Clear R0 margins were significantly associated with better DSS ($p = 0.03$) and local control ($p = 0.002$) (Figure 1). PORT was significantly related to better OS ($p = 0.01$, data not shown) and DFS ($p = 0.04$).

The regional control was significantly higher for patients with bilateral neck treatment compare to others (5-years regional

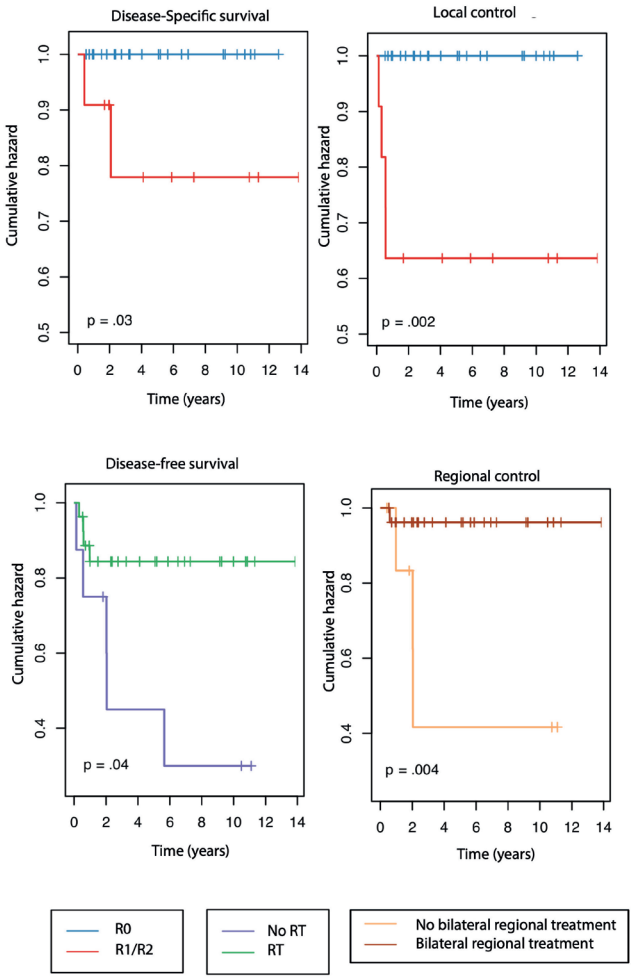

Figure 1. Disease-specific survival, disease-free survival, local control and regional control after total rhinectomy for patients with locally advanced nasal pyramid squamous cell carcinoma and regarding margin status (clear R0 margins blue curve, invaded R1/R2 margins red curve), complement by post-operative radiotherapy (yes for green curve, no for purple curve) and bilateral regional treatment, i.e. cervical lymph node dissection and/or PORT (yes for brown curve, no for orange curve). Survival distributions of both groups were estimated using the Kaplan-Meier method and compared with the log-rank test (p-value in the bottom left corner) as well as using a Fine-Gray model for local relapse/progression and regional relapse to take into account the presence of competing risks.

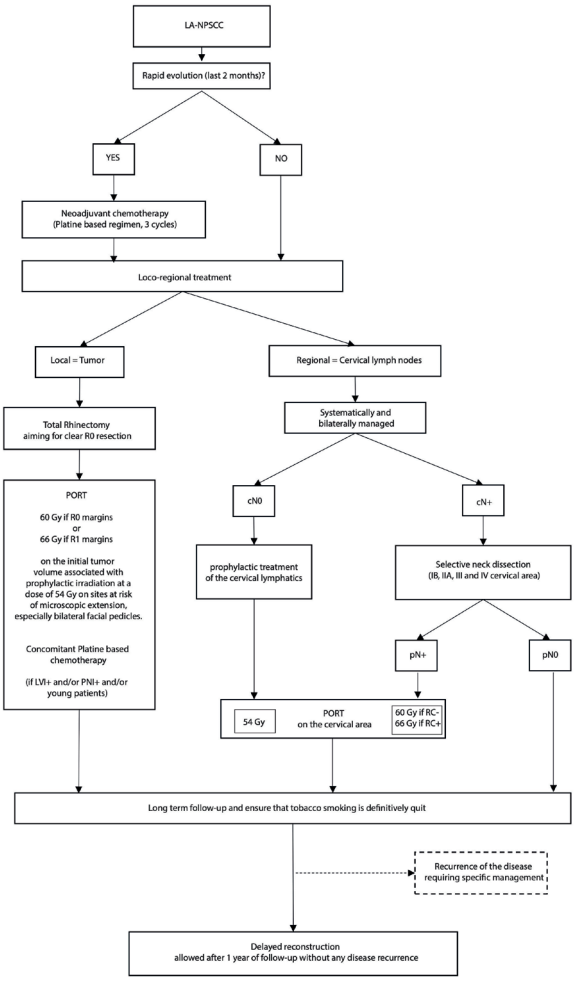

Figure 2. Gustave Roussy Cancer Campus management algorithm for LA-NPSCC. Rapid evolution within the last two months was based on the patient's and surgeon's appreciation and supported by photographs. (LA-NPSCC: locally advanced nasal pyramid squamous cell carcinoma; PORT: post-operative radiotherapy; LVI: Lymphovascular invasion; PNI= peri neural invasion, cN0: no clinical/radiological involvement of cervical lymph nodes; cN+: clinical/radiological involvement of cervical lymph nodes).

controls: 96% (95%CI [89; 100]) vs. 42% (95%CI, [15; 100]), p = 0.004). Invaded R1/R2 margins were strongly associated with poorer DFS (HR 8.5, CI 95% [0.82; 88.0], p = 0.07, multivariate analysis) and bilateral regional treatment (lymph node ND and/or radiotherapy) was significantly associated with a better regional control (HR 0.033, CI 95% [0.002; 0.498], p = .0014) (Supplementary data 5).

While comparisons remain limited (small and heterogeneous reported series), several points require attention.

Firstly, total rhinectomy is the cornerstone of management [1–3]. In our series, total rhinectomy with clear R0 margins was an independent prognostic factor for better DFS. This surgery should be considered as a primary treatment for all resectable LA-NPSCC. Oncologic results are favourable and allow planning secondary nasal reconstructions.

Second, PORT should be systematically realized. PORT has already proved its benefits and safety in large series of nasal cavity SCC [4].

Thirdly, cervical lymph nodes should be systematically and bilaterally treated.

In our series, the proportion of cN+ patients at diagnosis was non negligible (37%) and tumoral invasion (cN+/pN+) was con-

firmed for 67% of them. Several meta-analyses (>1000 patients) (5–7) report up to 20% of nodal involvement at diagnosis for LA-NPSCC. Thus, for LA-NPSCC with cN+, we recommend bilateral cervical lymph node dissection, followed by PORT if pN+ (level of evidence IV). The elective neck management for cN0 patients remains controversial. In our series, two patients (17%) presented infra-clinic lymph node involvement (cN0/pN+). Furthermore, among the four regional relapses, three occurred in patients for whom cervical lymph node areas have not been treated while bilateral regional treatment was a strong prognostic factor of regional control. Subsequent nodal recurrences in large cohorts of cN0 nasal initially SCC have been reported ranging from 13% to 41% of cases [6,8]. According to SEER database analysis, elective nodal treatment may lead to a six-fold decrease of nodal recurrence in these patient [7]. Moreover, elective neck management was proved to be a prognostic factor of DFS in LA-NPSCC cohorts [6,9]. Therefore, we recommend prophylactic cervical lymph node treatment for cN0 patients with LA-NPSCC, preferentially using neck irradiation (non-negligible rate of pN0 after bilateral ND).

Fourthly, salvage management allow satisfactory outcomes. In our series, salvage total rhinectomy was realized for 11 (31%) patients. While half of the recurrences occurred in this subgroup, underlining the importance of the initial local control, two thirds of these patients are still in complete remission (median follow-up of 128 months). Tumours of the infrastructure are considered to be more readily amenable to a satisfactory resection, improving chance for local control.

Fifthly, local events are early (first year of follow-up) and of poor prognosis (50% of death in our series)[1]. Current smoking at the time of treatment is a predictive factor for inferior locoregional control[2]. Thus, tobacco cessation appears crucial. Overall, we recommend a one-year wait after the end of PORT before beginning the reconstruction program (level of evidence IV).

Sixthly, neoCT may be beneficial for a fast-growing LA-NPSCC, but larger cohort is required for validation. To finish, we provide our algorithm of management (Figure 2).

Despite the inherent limitations due to the retrospective data collection and the non-negligible number of patients that are censored (many of them early in the study) making the Kaplan-Meier less reliable, our study includes a large number of patients with LA-NPSCC homogeneously treated.

Acknowledgement

None

Authorship contribution

All authors have participated to the conception and design, acquisition of data, or analysis and interpretation of data; have participated to the drafting the article or revising it critically for important intellectual content; have approved the final version to be published; have participated to the agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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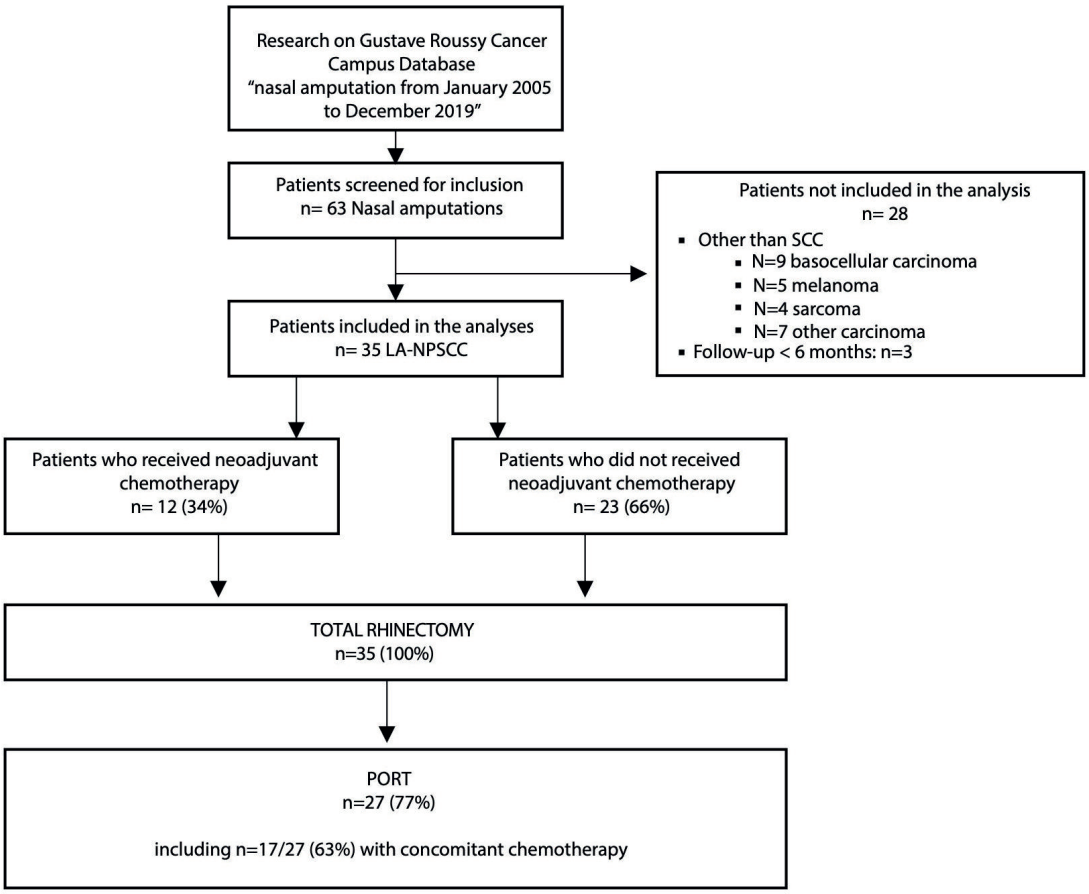
Jebrane Bouaoud, M.D, PhD student
Head and Neck Surgical Oncology Department
Gustave Roussy Cancer Campus
114, Rue Edouard Vaillant
Villejuif 94805
France

Tel: +33-142114603
E-mail: jebrane.bouaoud@gmail.com

SUPPLEMENTARY DATA



Supplementary data 1. Flow chart: patients' selection and treatment (LA-NPSCC: locally advanced nasal pyramid squamous cell carcinoma; SCC: squamous cell carcinoma; PORT: post-operative radiotherapy).

Supplementary data 2. Patients' baseline and tumors characteristics (n = 35).

Variables	Overall population	
Age (median, range)	61	35-90
Gender (N, %)		
Male/Female	22 / 13	63% / 37 %
ECOG-PS at diagnostic (N, %)		
0	18	51%
1	17	49%
Chronic exposition to tobacco (N, %)		
Current smokers	22	63%
Formers smokers	5	15%
No	4	11%
Missing data	4	
Chronic exposition to alcohol (N, %)		
Active	7	20%
Occasionally	1	3%
No	20	57%
Missing data	7	

Variables	Overall population	
Chronic exposition to professional toxic (N, %)		
Yes	2	6%
No	15	43%
Missing data	18	
Suspected tumor origin (N, %)		
Nasal Mucosa	27	78%
Nasal skin	4	11%
Missing data	4	
Clinical and/or radiological Lymph node involvement		
N0	22	63%
N+	13	37%
AJCC stages at first presentation 8th edition (N, %)		
III	3	12%
IVa	21	88%
Non available (N)	11	

Supplementary data 3. Treatment characteristics and therapeutic management.

Variables	Overall population	
Carcinologic context		
Primary diagnosis (no previous treatment)	24	69%
Local relapse / progression	8 / 3	23% / 8%
Neoadjuvant chemotherapy (N, %)	12	34%
Platinum-based combination	10	83%
Total Rhinectomy (N, %)	35	100%
Context of the surgical resection (N, %)		
Salvage surgery (previous surgical treatment)	11	31%
Primary surgery (no previous local/systemic treatment)	15	45%
Post neoCT surgery	9	24%
Missing data	4	
Neck dissection (N, %)	24	69%
Bilateral dissection	21	88%
Selective Neck Dissection	17	71%
Post-operative Radiotherapy (N, %)	27	77%
Radiation field (N, %)		
Tumoral site + Cervical lymph node area	17	63%
Tumoral site only	4	15%
Missing data	6	
Concomitant chemotherapy site (N, %)	17	63%
Regimen (N, %)		
Platinum based	12	71%

Supplementary data 4. Histological outcomes.

Variables	Overall population	
Tumor grading (N, %)		
Well differentiated	18	51%

Variables	Overall population	
Moderate differentiated	8	23%
Few differentiated	2	6%
Missing data	7	
Neoadjuvant chemotherapy histological response (N, %)		
Good response (< 10% of viable tumoral cells)	5	42%
Partial response (tumoral necrosis but > 10% of viable tumoral cells)	3	25%
No response	4	33%
Total rhinectomy resection margins (N, %)		
R0 (clear margins)	25	72%
R1 (marginal)	6	17%
R2 (invaded)	4	11%
Perineural invasion (N, %)		
Yes / No	12 / 10	34% / 29%
Missing data	13	
Lymphovascular invasion (N, %)		
Yes / No	5 / 14	14% / 40%
Missing data	16	
Lymph node invasion (N, %)		
pN+ ECS+ / pN+ ECS-	7 / 3	29% / 13%
pN0	14	58%

Supplementary data 5. Univariate and multivariate cox proportional hazard models.

	Univariate analysis		Multivariate analysis	
	HR [%95 CI]	p-value	HR [%95 CI]	p-value
DFS				
Previous local treatment	1.726 [0.461; 6.460]	0.418		
cN+	1.347 [0.361; 5.018]	0.658		
neoCT Pathological response	0.238 [0.030; 1.904]	0.176		
R1 / R2 margins	3.220 [0.861; 12.04]	0.082	8.467 [0.815; 87.96]	0.074
Lymphovascular invasion	2.925 [0.404; 21.18]	0.288		
Perineural invasion	5.054 [0.606; 42.18]	0.135		
pN+	1.536 [0.310; 7.618]	0.599		
Adjuvant radiotherapy	**0.211 [0.057; 0.787]**	**0.021**	0.415 [0.017; 10.00]	0.577
Adjuvant chemotherapy	1.150 [0.309; 4.289]	0.835		
Regional control				
Previous local treatment	2.336 [0.329; 16.59]	0.396		
cN+	5.343 [0.555; 51.47]	0.147		
R1 / R2 margins	0.748 [0.078; 7.202]	0.802		
LND: unilateral	2.045 [0.179; 23.34]	0.565		
LND: bilateral	0.207 [0.019; 2.283]	0.198		
pN+	1.422 [0.089; 22.74]	0.803		
Adjuvant radiotherapy	0.260 [0.036; 1.851]	0.178		
Bilateral regional treatment	**0.070 [0.007; 0.677]**	**0.022**	**0.033 [0.002; 0.498]**	**0.014**