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HEAD AND NECK

Pyriform sinus squamous cell carcinoma: oncological outcomes in good responders of induction chemotherapy-based larynx preservation protocols

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Abstract Induction chemotherapy-based larynx preservation protocols use chemotherapy to select exclusively patients with 'chemosensitive' tumors for a nonsurgical treatment with radiation therapy. This study on pyriform sinus squamous cell carcinoma (SCC) is interested in the oncological outcome of treatment based on radiation therapy when offered to patients with tumors responding to induction chemotherapy. This was a retrospective cohort study. The cohort included good responders to induction chemotherapy, subsequently treated with definite radiation therapy (with or without concomitant chemotherapy) for pyriform sinus SCC, in a tertiary referral cancer center. The primary endpoints were overall, laryngectomy-free and disease-free survival and the secondary endpoints were analysis of treatment failures and possibilities of salvage treatment. Forty-two patients fulfilled the inclusion criteria and were retained for analysis; 7 % were stage II (3/42), 48 % stage III (20/42) and 45 % stage IV (19/42). At 1, 3 and 5 years, the overall survival was 95 % (40/42), 74 % (31/42), and 60 % (SE ≈ 0.08), respectively. For the same intervals, the laryngectomy-free survival was 90 % (38/42), 69 % (29/42) and 50 % (SE ≈ 0.08), respectively. The estimated 5-year disease-free survival was also 50 %. Disease-free survival was significantly better for N0 patients. There was a 28 % recurrence rate, mainly in the primary tumor site (9/11), with or without simultaneous nodal recurrence. Interestingly, more than one-third of all oncologic failures occurred beyond the first 3 years of follow-up. Salvage treatment was not possible or definitely inefficient in at least 2/3 of all recurrences. In candidates for larynx preservation for a pyriform sinus SCC, good response to induction chemotherapy followed by definite radiation therapy seems to be associated with a more favorable prognosis. Nevertheless, in case of locoregional recurrence the possibilities for efficient salvage treatment are limited.

Keywords Pyriform sinus · Chemosensitive · Responders · Radiation therapy · Survival

Abbreviations

SCC	Squamous cell carcinoma
ICT	Induction (neoadjuvant) chemotherapy
RT	Radiation therapy
CRT	Radiation therapy with concomitant chemotherapy
IGR	Institut Gustave Roussy
PF	Platinum salt and 5-fluorouracil
TPF	Taxane and PF
OS	Overall survival
DFS	Disease-free survival
LFS	Laryngectomy-free survival

Introduction

Decision-making regarding the treatment of squamous cell carcinomas (SCC) of the upper aerodigestive tract is generally based on the extension of the disease, while the individual tumor's behavior is rarely taken into consideration, because of the lack of established prognostic criteria. An exception might be larynx preservation protocols for laryngeal and hypopharyngeal carcinomas were tumors'

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response to induction chemotherapy (ICT) dictates the definite treatment modality. Larynx preservation may be achieved either by direct concomitant chemoradiation therapy (CRT) either by ICT-based protocols [1]. In the latter, patients usually receive 1–3 cycles of neoadjuvant chemotherapy, the definite treatment depending on clinical and radiological response of the tumor [2–5]; 'good responders' are treated with radiation therapy (RT) and retain the possibility for salvage surgery if necessary while 'non-responders' are treated with radical surgery followed by RT or CRT [6]. Hence ICT is used to select patients which are more likely to respond to nonsurgical treatment with RT.

The negative correlation between the efficacy of RT (with or without concomitant chemotherapy) and the advanced disease stage is undoubtable [7]. What is less well established for RT-based regimens is whether there is any additional oncological benefit when used in the selective treatment of 'chemosensitive' tumors. It is advocated that these tumors may also present an increased sensibility in RT which would render them more suitable candidates for a nonsurgical treatment.

The present study focuses on patients having responded favorably to ICT ('good responders') for pyriform sinus SCC in a larynx preservation-intent approach. The primary endpoint is the oncological outcome of definite RT in the treatment of these chemosensitive tumors while the secondary endpoints are the analysis of oncological failures and the possibilities of salvage therapy. There is no intent to evaluate individual larynx preservation protocols.

Materials and methods

The study was carried out in the 'Institut Gustave Roussy' (IGR), a tertiary referral cancer center in France. The data base of the Head and Neck tumor board was used to identify patients treated with ICT followed by definite RT (with or without concomitant chemotherapy) for pyriform sinus SCC, between 1999 and 2008.

Initial assessment of tumor's extension included at least a panendoscopy and a CT scan (head and neck, chest and upper abdomen). In the first years of the studied period, ICT consisted of three cycles of a platinum salt and 5-fluorouracil chemotherapy (PF), while docetaxel was added to PF later on (TPF). There was a 3-week interval between the cycles and evaluation of tumor's response was made with new endoscopy and a CT scan prior to the third cycle. Good responders were considered patients presenting a tumor regression $\geq$80 % and remobilization of a previous immobile arytenoid. The hypopharynx and the neck were subsequently treated with 3D conformal adjuvant RT and a total dose of 70 Gy was delivered to the primary tumor in 7 weeks. Chemotherapy was administered concomitantly to RT mainly to patients treated in the latest years of the studied period. All patients had a CT scan 3 months after the end of RT and regular clinical follow-up visits. For confirmed local recurrences which were considered operable the treatment of choice was total pharyngolaryngectomy.

The inclusion criteria were: (a) histologically proven SCC of the pyriform sinus in previously untreated patients; (b) ICT as part of a larynx preservation protocol; (c) good response to ICT; (d) definite treatment with RT or CRT; (e) treatment protocol completed as initially planned, and (f) patients followed at the IGR for at least 3 years after the end of treatment.

Exclusion criteria comprised: (a) tumors considered 'inoperable' either before or by the end of ICT, (b) chemotherapy given with a palliative intent, (c) synchronous second primary tumors, (d) metastatic disease, and (e) recent history of cancer.

The medical files of all retained patients were reviewed and the Kaplan–Meier method was used to estimate the overall, the disease-free and the laryngectomy-free survival rates as a function of time after the end of treatment. The Mantel–Cox test (log-rank test) was used for the comparison of survival curves. The comparison of the treatment subgroups in terms of T stage, N stage and disease stage was made with the Fischer exact and χ^2 tests. For all calculations, the 'MedCalc' statistical software (Ostend, Belgium) was used.

Other parameters which were analyzed included the patterns of oncological failure and the time elapsed to recurrence, the occurrence of metachronous tumors and the possibilities of salvage therapy.

Results

Between 1999 and 2008, 71 patients with previously untreated pyriform sinus SCC received neoadjuvant chemotherapy followed by RT ($\pm$ concomitant chemotherapy) with curative intent in the IGR. Among them, only 42 patients were good responders fulfilling the inclusion criteria. The remaining 29 patients could not be retained for the purposes of this study as they represented either non-responders who refused surgery, or non-responders who became inoperable during the ICT, or even patients with synchronous tumors or recent history of another cancer.

The mean age of the 42 included patients was 57.7 years (42–72 years) and the sex ratio 10:1 (38♂:4♀). Almost half of all patients (19/42) had documented comorbidities such as arterial hypertension, coronary or other vascular disease, COPD, diabetes and liver cirrhosis. Regular alcohol drinking was reported by 80 % of them and the vast majority (93 %) had a positive history of tobacco consumption, exceeding 35 pack-years in three quarters of smokers

Table 1 Summary of the T and N stage at presentation for all 42 included patients (all patients were M0)

	T1	T2	T3	T4a		
N0		3	8	1	**12**	29%
N1		2	10	1	**13**	
N2a		1	2		**3**	38%
N2b		2	3	1	**6**	
N2c			4		**4**	33%
N3		2		2	**4**	
	-	**10**	**27**	**5**	42	
			64%			

Bold values filling the cells of the table correspond to the number of patients

(76 %). All patients were followed for at least 3 years and almost 80 % of them (33/42) for at least 5 years or until they were deceased.

Concerning TNM staging (Table 1), 76 % of the patients (32/42) had locally 'advanced' T3 or T4a tumors, while T3 tumors alone represented almost 2/3 (64 %) of cases. Regarding nodal stage, 29 % of the patients were N0 (12/42), 38 % N1/N2a (16/42) and 33 % N2bc/N3 (14/42). Almost half of all patients (20/42 or 48 %) were stage III, 45 % were stage IV (19/42) and only 7 % were stage II (3/42).

In terms of histology, detailed data on the differentiation were available for 37 patients: 65 % of them (24/37) had well-differentiated, 24 % had moderately (9/37) and 11 % poorly differentiated (5/37) SCC.

Treatment modalities used for larynx preservation included mainly PF and TPF for ICT (20 patients treated with each) and exclusive RT and concomitant CRT for adjuvant treatment (21 patients for each protocol).

Survival

Eleven patients (26 %) died within the first 3 years after the end of RT; among them five died with a recurrence and six from an intercurrent disease. The overall survival (OS) rate observed at 1 and 3 years was 95 % (40/42) and 74 % (31/42), respectively, and the estimated 5-year OS was 60 % (SE $\approx$ 0.08). The disease-free survival (DFS) rate at 1, 3 and 5 years was 86 % (36/42), 65 % (27/42) and slightly more than 50 % (SE $\approx$ 0.08), respectively (Fig. 1). During the follow-up period, seven patients had a total laryngectomy, six due to a local recurrence (at 6, 11, 34, 45, 46 and 47 months) and one due to a metachronous contralateral laryngeal carcinoma (at 18 months), without evidence of pharyngeal recurrence. The 1-, 3- and 5-year laryngectomy-free survival (LFS) was 90 % (38/42), 69 % (29/42) and 50 % (SE $\approx$ 0.08), respectively.

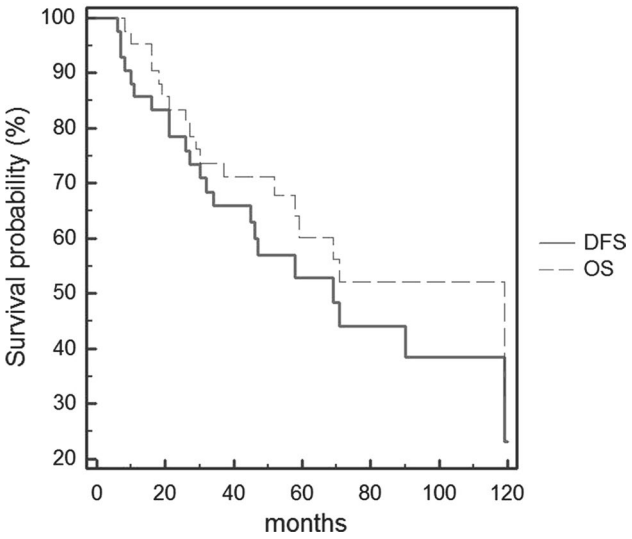

Fig. 1 OS and DFS probability for all 42 patients included in the study

Examining the DFS separately for N0 and N+ tumors, we observe that for the 12 N0 tumors the 5yDFS is 80 vs 40 % for the 30 N+ ($p < 0.05$), while the two groups have no significant difference in OS ($p = 0.12$). Interestingly, there is no significant difference in the DFS and OS between N1/N2a and N2bc/N3 subgroups (Fig. 2).

Calculating separately for 'smaller' and 'bigger' tumors, the 5yDFS is better for T2 (80 %) than for T3/T4a tumors (40 %), although this difference does not reach levels of statistical significance.

Oncologic failures

'Oncologic failures' were considered all local, regional, locoregional and metastatic failures in the follow-up. The oncological outcome could be evaluated with certitude as 'successful or failure' in 39/42 cases. Three cases were considered as 'doubtful'; specifically, one patient presented a metachronous laryngeal carcinoma without hypopharyngeal recurrence necessitating total laryngectomy at 18 months, a second one deceased with a clinically suspect lesion but biopsies were negative and a third patient deceased with multiple metastases attributed to a probable hepatocellular carcinoma but histological evidence was missing. Most of the following statistics regarding analysis of the oncological failures refer to 39 patients, and do not take into consideration these 3 doubtful cases.

In total, there were 11 oncologic failures corresponding to a 28 % failure rate (Table 2); two-thirds (7/11) were diagnosed within 3 years after the end of treatment and almost all of them (10/11) within 4 years. Five patients presented an isolated recurrence in the pyriform sinus (45 % of

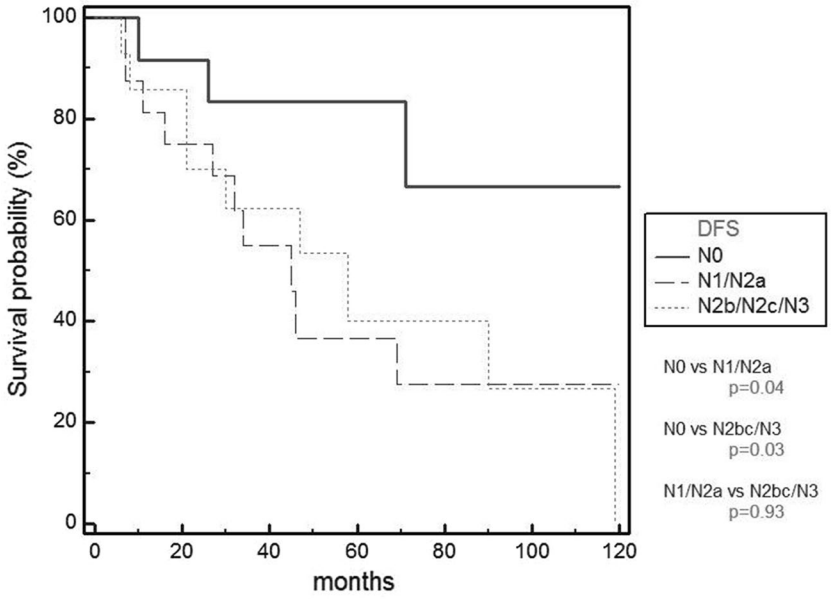

Fig. 2 Disease-free survival probability for the 12 N0, 16 N1/N2a and 14 N2bc/N3 patients. N0 patients have a better DFS probability ($p < 0.05$), while there is no significant difference among patients with a single homolateral nodal metastasis (N1/N2a) and those with more advanced (N2bc/N3) neck disease. ($p = 0.93$, 95 % CI 0.40–2.32)

Table 2 Details on treatment failures, the salvage treatment offered and its results

	Failure level	Initial stage	(C)RT to recurrence interval	ICT regimen	Definite tx	Salvage tx offered	Outcome of salvage tx	Disease-free since salvage tx
1	T	T3N1	11 months	PF	RT	TPL + ND	Failure	
2		T3N1	34 months	PF	RT	TPL		49 months
3		T3N1	45 months	TPF	RT	TPL + ND	Failure	
4		T2N2a	46 months	TPF	RT	TPL + reRT		67 months
5		T3N2c	47 months	PF	RT	TPL		44 months
6	N	T3N1	7 months	TPF	CRT	ND + reRT	Failure	
7		T3N1	32 months	TPF	RT	ND + reRT		14 months
8	T + N	T3N1	7 months	TPF	RT	Chemo	Failure	
9		T3N2c	6 months	PF	CRT	TPL + ND	Failure	
10		T4aN3	21 months	PF	CRT	Chemo	Failure	
11		T4aN3	90 months	PF	RT	Chemo	Failure	

tx Treatment, *ND* neck dissection, *reRT* re-irradiation, *TPL* total pharyngolaryngectomy, *chemo* palliative chemotherapy)

all failures), four had a simultaneous pharyngeal and nodal recurrence (36 % of all failures) and two had an isolated recurrence in the cervical lymph nodes (18 % of all failures). Hence, the vast majority of the oncologic failures (9/11) presented a recurrence in the pyriform sinus, with or without a simultaneous neck recurrence. When all 39 patients of the study are taken into consideration there is a 23 % recurrence rate in the pyriform sinus (9/39). In total, there were no cases of isolated metastatic failure without prior local or nodal failure except for a single doubtful case where a cirrhotic patient deceased with a hepatic tumor compatible either with a hepatocellular carcinoma or with a liver metastasis of the SCC, along with multiple other metastases.

As illustrated in Table 2, most cases of simultaneous locoregional failure (3/4) concerned patients with advanced disease (T3/T4a, N2c/N3), while the two T4a patients who recurred (out of five T4a patients included in the study) presented a simultaneous recurrence in the pyriform sinus and the cervical lymph nodes. Bigger primary tumors presented an increased risk for recurrence compared to smaller ones (10 % T2, 22 % T3, 40 % T4a).

None of the N0 patients presented later with a nodal failure, while there were in total 6 cases of nodal recurrence out of 30 patients initially staged N+ (20 % N+). Half of all nodal failures (3/6) concerned patients initially staged N1. The overall rate of nodal failure for the 42 good responders was 14 % (6/42). If we regroup patients with

different nodal stages into three groups (N0 vs N1/N2a vs N2bc/N3), we observe that the only group with lower risk for nodal recurrence was the N0 group (0/12), while nodal failure rates for the N1/N2a and the N2bc/N3 groups were 19 % (3/16) and 21 % (3/14), respectively.

Metachronous aerodigestive tract tumors were identified in the follow-up of 6 patients, corresponding to 14 % of the 42 good responders; only 3 of them (7 %) concerned ENT localizations (oral cavity, oropharynx, larynx), while the remaining 3 concerned pulmonary tumors. All second primaries were identified between 1½ and 8½ years after the end of RT.

Salvage treatment was attempted in 8 of 11 recurrences, while palliative chemotherapy was offered to the remaining 3 patients (Table 2). Only 1 out of 4 simultaneous locoregional failures was considered 'operable'. In total, six total pharyngo-laryngectomies were performed, associated to neck dissection in three cases (in 2 of these 3 cases nodal recurrence was not confirmed by definite histology) and to re-irradiation in one case. The two cases of isolated nodal recurrence were treated with salvage neck dissection followed by re-irradiation.

Salvage treatment was definitely inefficient (attempted but failed or totally impossible) in 7 out of 11 oncologic failures (64 %), including all cases of simultaneous locoregional failure, 50 % of the isolated nodal failures (1/2), 40 % of failures limited in the pyriform sinus (2/5) and 50 % of salvage pharyngo-laryngectomies (3/6).

Discussion

So far, the majority of randomized, prospective preservation trials had studied purely laryngeal localizations of SCC [2, 3, 8] or mixed populations of laryngeal and hypopharyngeal tumors [9]. Few prospective trials demonstrating the efficacy of larynx preservation were exclusively interested in hypopharyngeal localizations [4, 5]. The oncological efficacy of nonsurgical preservation strategies in the treatment of hypopharyngeal SCC, either as ICT followed by RT [10–12] or as concomitant CRT [12, 13], is also supported by several retrospective series. In contrast to other studies concerning larynx preservation, the aim of the present one is to evaluate the efficacy of RT specifically in the treatment of patients with chemosensitive hypopharyngeal tumors selected by ICT. At the same time, the study design allows to 'recalculate' prognosis for patients included in larynx preservation protocols once it is known that a tumor responds favorably to ICT.

In the present study, 60 % of good responders are expected to be alive at 5 years and slightly more than 50 % of good responders are expected to be alive and free-of-laryngectomy. Among the 29 patients who were not retained for the study, 7 represented 'non-responders' who were nevertheless treated with RT or CRT and follow-up data were available for 6 of them; interestingly, only a third of them (2/6) was still alive after 2½ years and at 5 years only 1 patient was alive and free-of-disease (17 %), compared to 50 % for good responders. Similar survival rates are difficult to extract retrospectively from publications of randomized trials on larynx preservation as in most series survival data published concern collectively all patients randomized in the arm of ICT, including good responders treated with RT, non-responders treated with surgery and also some non-responders treated with RT (after refusing surgery or becoming inoperable during ICT).

Analysis of the therapeutic strategies used on patients retained in this study revealed changes in the treatment modalities for larynx preservation during the 10-year period studied. More specifically, in the earlier years, PF-ICT followed by exclusive RT represented the standard treatment while in the latest years TPF-ICT and adjuvant treatment with CRT became the dominant protocol. In total, 50 % of the 'good responders' (21 patients) had definite treatment with exclusive RT and 50 % with concomitant CRT. Similarly, ICT was administered as PF in 20 patients, TPF in 20 patients, one patient received TP (taxane + platinum salt), and in one case the regimen was not clearly documented. This switch in molecules' association used in ICT can be justified from the results of trials demonstrating the superiority of TPF compared to PF [14, 15].

As illustrated in Table 2, 8 out of 11 observed oncologic failures (73 %) concerned patients treated with adjuvant RT without concomitant chemotherapy. Nevertheless, the study design does not allow us to conclude any superiority of adjuvant CRT compared to RT. As already mentioned, patients treated with exclusive RT were principally those having had PF-ICT, principally treated in the earlier years of the study period. Hence, these patients were followed longer compared to those treated with CRT, allowing more failures to be detected, and had ICT with a regimen which is probably inferior to the more recent TPF [14, 15].

In regard to the lymph node status, DFS in our study was significantly better only for patients with N0 disease (Fig. 2) and even the presence of a single and small metastatic lymph node (N1) seemed sufficient to influence survival negatively as the presence of multiple ones.

Analysis of the oncologic failures shows that only 2/3 of recurrences were diagnosed within the first 3 years. Hence, studies following patients for short periods may fail to identify 'late' recurrences. For the majority of the recurrences, there was no efficient salvage treatment available. Interestingly, a considerable number of metastases are described in the follow-up of most series of hypopharyngeal SCC [4, 7, 16]; nevertheless, in this series of good responders no patients presented an isolated metastatic failure without

Table 3 Patients included in the present study had more advanced or at least equivalent disease stages compared to patients included in the EORTC 24891 trial

Disease stage	Present cohort of 42 good responders (%)	EORTC 24891	
		ICT arm (100 pts) (%)	Upfront surgery (94 pts) (%)
Stage II	7	7	6
Stage III	48	59	54
Stage IV	**45**	**34**	**39**

Table 4 Survival rates of good responders (present study) compared to patients treated either with upfront surgery or with a PF-based larynx preservation protocol (EORTC 24891 trial)

Survival rates	Present cohort of 42 good responders (%)	EORTC 24891	
		ICT arm (100 pts) (%)	Upfront Surgery (94 pts) (%)
5yOS	60	38	33
5yDFS	50	32	26

5yOS, 5yDFS overall and disease-free survival 5 years after the end of treatment

prior locoregional recurrence (with the exception of a single, already mentioned doubtful case).

Survival statistics for patients with hypopharyngeal SCC are provided from data bases of cancer patients and the literature series. It is still considered that no nonsurgical approach has provided so far superior survival chances compared to upfront radical surgery followed by adjuvant CRT [6] or RT [17]. The present study did not intend to investigate whether there is a survival benefit for chemosensitive tumors in general as in that purpose survival of responders should be compared to the survival of non-responders and, moreover, the outcome would probably depend on the post-induction treatment modality; to our knowledge, no randomized trial has addressed this question so far.

The EORTC 24891 phase III trial [4, 18] enrolled 194 patients with pyriform sinus carcinoma randomized in 2 arms; 92 (out of 94 eligible patients) were treated with upfront surgery followed by RT and 97 (out of 100 eligible patients) were treated with a PF-based ICT preservation protocol. As illustrated in Table 3, the 42 patients of the present study have slightly more (or at least not less) advanced disease stages compared to those included in the EORTC 24891 trial. The survival rates are shown in Table 4. The 5yOS and 5yDFS seem to be clearly better in the 'pure' population of good responders of the present cohort compared to any of the 2 arms of the EORTC study, i.e., those treated with upfront surgery (92 patients) and those randomized in the induction chemotherapy arm, including 50 good responders treated with RT (out of 97 patients having received induction chemotherapy). Similarly, in a big series of almost 3,000 patients with hypopharyngeal SCC, Hoffman et al. [7] reported a 5-year disease-specific survival of 42 % for stage III and 22 % for stage IV disease, while Hall et al. [19] reported in another series of 595 patients with T1–T4 hypopharyngeal SCC a 5yOS of around 25 % for patients treated for cure.

The above-mentioned differences are interesting but they should be interpreted with caution. A first hypothesis is that the satisfactory survival of good responders in this cohort is due to a positive correlation between 'chemosensitivity' and 'radiosensitivity', or in other words a selection effect of ICT allowing treatment with RT of tumors which are more prone to respond [20]. Another hypothesis is that chemosensitive tumors may have a better prognosis anyway; Chitose et al. [21] reported that the prognosis of patients treated with ICT followed by surgery for locally advanced hypopharyngeal SCC was positively correlated to reduced tumor cellularity after ICT. Improved prognosis could also be attributed to a direct therapeutic effect of chemotherapy on local and metastatic control of chemosensitive tumors [20].

There is no evidence whether any survival benefit would be observed in our patients if post-induction treatment consisted of surgery instead of RT. Moreover, it is known that a lack of response to ICT cannot invariably predict a lack of response to RT; in the RTOG 91-11 trail for instance, 10 of the non-responders to ICT who were subsequently treated with adjuvant RT presented a complete response at the end of treatment although the long-term outcome for these patients was not provided [3]. Similarly, in a big series of hypopharyngeal carcinomas Chang et al. [12] report the case of 11 patients who refused surgery despite poor response to ICT; they were consequently treated with CRT and all of them seemed to present a complete remission.

No matter whether chemosensitive tumors behave differently and what the exact effect of ICT is, it is undoubtable that if there was a way to predict radiosensitivity of a tumor, substantial improvements in survival could be achieved by choosing to irradiate the 'appropriate' candidates and offering a more 'aggressive' treatment to the others.

One of the main limitations of the present study is the small number of patients. This is not surprising as ICT-based protocols concern only a minority of all patients with hypopharyngeal carcinomas. Moreover, we were strictly interested in a subgroup of this minority, i.e., patients with tumors of proven chemosensitivity. Hence, retaining a bigger number of patients would probably necessitate a multicenter collaboration. Other limitations of our study are related to its retrospective character and the different treatment modalities used during the 10-year period.

Conclusions

The present study on chemosensitive SCC of the pyriform sinus, treated with ICT followed by RT or CRT showed an interesting 5yOS of 60 % and a 5yLFS and DFS of 50 %. Disease-free survival was significantly influenced by the presence of any metastatic lymph nodes (≥N1). The oncologic failure rate was 28 % and salvage treatment was definitively inefficient (or not possible at all) in 64 % of oncologic failures.

It seems that responding to ICT may predict a favorable oncological outcome for most patients treated with adjuvant RT or CRT while recurrences leave relatively low chances of success to any attempt of salvage treatment.

Conflict of interest None.

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