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T but not N stage predicts survival for patients with tonsillar carcinoma treated with external radiotherapy and brachytherapy

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Abstract

Background. Our aim was to determine the efficacy of a therapeutic schedule including external radiation and brachytherapy in a consecutive and retrospective series of tonsillar carcinoma patients. *Patients and methods*. Ninety-six patients with tonsillar carcinoma were treated between 1988 and 2000 and were followed up for at least for three years. All patients were treated with accelerated hyperfractionated external radiotherapy, 68 patients had additional brachytherapy and 69 patients with advanced stages also received chemotherapy. There was no planned surgery even though 73% had N+ disease. Eleven patients with persistent neck nodes underwent ultimate salvage surgery. *Results*. The overall three-year survival (OS) was 70%. OS for the T stage was T1 90%, T2 89%, T3 54% and T4 60%. The corresponding numbers for the N stage were N0 61.5%, N1 73%, N2 78% and N3 66%. Accordingly OS was influenced by the T stage ($p>0.001$) rather than by N stage. Only four patients with salvage surgery had viable tumour cells in the specimen, their survival was not inferior. *Discussion*. The primary tumour stage is an essential determinant for survival in patients with irradiated tonsillar carcinoma. Neck dissection should be confined only as a salvage procedure.

Most tonsillar carcinomas are associated with cervical lymph node metastasis at first presentation. This aggressive behavior has lead to many institutions suggesting combined treatment with surgery and radiotherapy. In the most recent decade, however, there has been a trend towards full dose radiation in combination with chemotherapy in advanced cases. Surgery has become more an adjuvant salvage for cases with persistent tumors after radiotherapy.

The reason for this development is primarily that there has been a refinement of both pre-therapeutic imaging with more accurate staging procedures as well as a technical development of irradiation techniques.

We have used an unmodified therapeutic program for patients with tonsillar carcinomas since 1988. This includes accelerated hyperfractionated irradiation of locoregional sites followed by interstitial brachytherapy to increase loco-regional control without enhanced late side effects. Patients with advanced disease stage III-IV and good performance status have also received induction chemotherapy. Surgery has been confined to salvage patients.

The aim of the present study was to analyze the effectiveness of our therapeutic program on survival in a series of consecutive patients with tonsillar carcinomas and to determine the extent to which surgery is worthwhile.

Materials and methods

Ninety-six patients with carcinoma of the tonsillar region confirmed by biopsy from the tumour were included in this retrospective and consecutive study. They were treated from 1988 to 2000 and followed up for at least three years at Sahlgrenska University Hospital. The patients were staged according to the AJCC system, including a CT scan or MRI of the head and neck region and a plain chest x-ray. All patients were assessed by a multidisciplinary team where treatment options were suggested.

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All patients were treated with radiotherapy. An external radiotherapy dose of 40.8 Gy was used for T1-2 tumours, followed by a brachytherapy boost of 25–30 Gy given as an interstitial implant with a low-dose rate (LDR) plastic tube technique and iridium 192. T3-4 tumours were treated with an external radiotherapy dose of 64.6 Gy, and this was followed by a brachytherapy boost of 10–12 Gy. Clinical N0 disease received an external radiotherapy dose of 40.8 Gy to the area 2–4 bilaterally, while N1-3 disease received a dose of 64.6 Gy to the lymph node area affected and 40.8 Gy to other areas of the neck. Patients were treated with 3D-CRT using linear accelerators with 6 MV photons. The planning target volume (PTV) was defined as a tumour visible on CT/MRI or clinical examination with a 1.5–2 cm margin. An accelerated fractionation was used with 1.7 Gy BID and at least six hours between fractions. All patients were treated with external radiotherapy at a minimum dose of 40.8 Gy. Twenty-eight of the patients were assessed not to receive brachytherapy because of age and/or poor performance status. Accordingly, 68 patients were treated with an interstitial brachytherapy dose ranging between 10 and 30 Gy.

Sixty-nine patients with advanced stage, good performance status and no severe co-morbidity also received chemotherapy prior to radiotherapy. Induction chemotherapy consisted of cisplatin (100 mg/m^2 day 1) and 5-flurouracil (1000 mg/m^2 day 1–5) for two cycles (range 1–3). All 96 patients received radiotherapy +/– chemotherapy. Eleven patients underwent ultimate salvage surgery.

All patients completed the radiotherapy without any unplanned interruptions. Evidence of mucositis and nutritial status was assessed weekly during the therapy. Patients were followed up at six weeks and every third month for the first two years and every six months thereafter for at least three years.

The survival rates were compared by using the log-rank test and Kaplan-Meier's graphs. We chose overall survival as the end point. The patients who died of another disease after three years of follow-up or who were still alive after the follow-up were coded as censored.

Results

In the 96 patients included in the study, the mean age was 61 years ranging between 33 and 88 years. Seventy-six percent of the patients were males and 24% were females. At the time of diagnosis, 26 patients had no palpable lymph node in the neck, while 11 had N1, 41 N2 and 18 N3 (Table I). N+ stages (N1-3) were evenly distributed when comparing T1-T2 (71%) with T3-T4 (74%) (Table II). The overall three-year survival was 70%. The overall three-year survival according to T stage was 90% for T1, 89% for T2, 54% for T3 and 60% for T4. For N stage we found a corresponding overall three-year survival for N0, N1, N2 and N3 of 61.5%, 73%, 78% and 66% respectively. There was only one patient in stage I. The overall three-years survival rates for stage II (n=10), III (n=14) and IV (n=71) were 80%, 64% and 73% respectively (Table I).

Table I. TNM: Classification and three-year overall survival in the study patients

TNM classification	total	Overall survival	
		survivors	%
T1	10	9	90
T2	28	25	89
T3	33	18	54
T4	25	15	60
N0	26	16	61.5
N1	11	8	73
N2	41	32	78
N3	18	12	66
I	1	1	100
II	10	8	80
III	14	9	64
IV	71	52	73

Eleven of these patients subsequently received salvage surgery of the neck when there was a persistent tumour palpable in the neck more than six weeks after completion of the radio-chemotherapy (Table III). The physical neck status was mostly confirmed by CT-scan examination. We found that seven of these 11 patients who underwent salvage surgery of the neck demonstrated no viable malignant cells in the neck specimen.

Among the 85 patients treated with radiotherapy +/– chemotherapy the survival rates were influenced only by T stage and not by any other variable. The p-value was <0.001 when we compared T1+T2 against T3+T4 (Figure 1). The p-value was still significant after adjustment for the age and sex in overall survival. The N0 tested against N1, N2 and N3 demonstrated no significant difference (Figure 2), and neither did stage I+II tested against stage III+IV (Figure 3).

No statistical difference was found in survival rates between the patients who were treated with chemo-radiotherapy and patients treated with

Table II. T and N stages in all patients group.

	N0	N1-N3	%N+
T1	1	9	90%
T2	10	18	64%
T3	8	25	68%
T4	7	18	72%

Table III. TNM: Classification of 11 patients treated with surgery of the neck owing to insufficient response to radio-chemotherapy. n=number of patients

	N0	N1	N2	N3	n
T1	0	0	2	0	2
T2	0	0	0	0	0
T3	0	0	4	3	7
T4	0	1	1	0	2
n	0	1	7	3	11

additional surgery. Two of 11 patients in the salvage surgery group died before three years. The number of patients in this group was too small to make a statistical analysis.

Discussion

In this retrospective series of patients with irradiated tonsillar carcinoma, the three-year overall survival rate was 70%. All patients were treated with accelerated hyperfractionated radiotherapy and an additional brachytherapy boost in most cases in order to increase the local dose and possibly local control. Advanced stages also received induction platinum based chemotherapy. Induction chemotherapy was chosen instead of concomitant regimens due to the use of accelerated fractionation and the risk of severe acute mucositis, even though meta-analyses have shown an even better effect with concomitant chemotherapy [1]. In cases of persistent or recurrent disease, salvage surgery was considered.

The outcome of the patients was primarily dependent on the primary tumour status. Thus, overall three-year survival was 90%, 89%, 50% and 60% for patients with T1, T2, T3 and T4 disease respectively. These figures are consistent with those of Wong [2]. On the other hand, we found no significant difference in the survivals between negative (N0) and positive (N1-N3) status. Our results however are partly in contrast to Perez [3], Shirazi [4] and Charbonneau [5], who demonstrated that both the primary tumour size and the nodal status were correlated to survival irrespective of the treatment received. N-stage has been considered the strongest prognostic factor for survival. Perez [3] concluded that a combination of surgery and postoperative irradiation in patients with T3-T4 tumours offers the best tumour control.

Conversely, Mendelhall [6] demonstrated that radiotherapy provides cure rates that are as good as those after surgery and is associated with a lower rate of severe complications. This observation was similar to that of Chen et al. [7], although most of their patients treated with the combination of external and interstitial radiotherapy were presented with tongue base carcinomas.

In a previous study Mendenhall et al. [8] concluded that radiotherapy alone or in combination with planned neck dissection remains the treatment of choice for patients with tonsillar carcinoma and

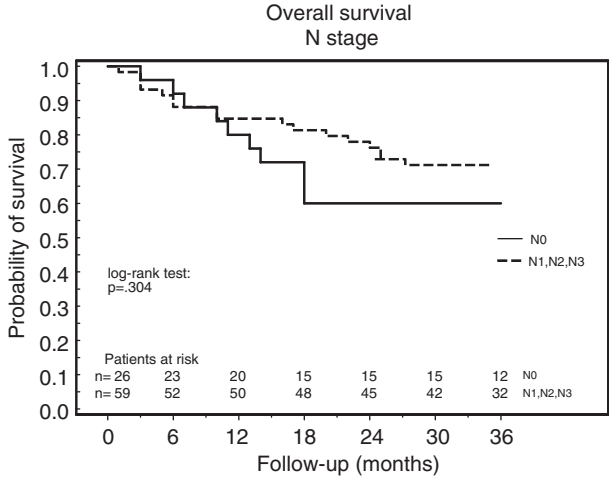

Figure 2. Overall survival by N-status, n=85.

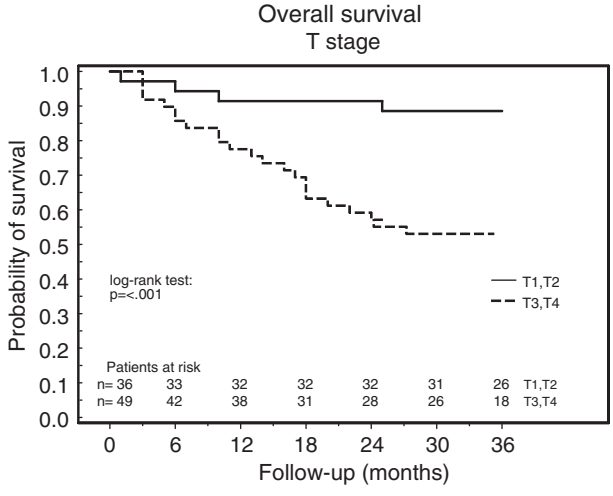

Figure 1. Overall survival by T stage n=85.

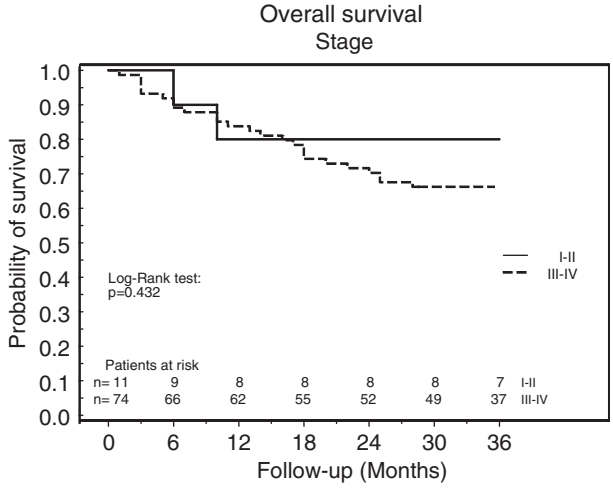

Figure 3. Overall survival by stage, patient population 85.

that concomitant cisplatin-based chemotherapy is considered in advanced disease.

However, we are not convinced that neck dissection should be planned in advance. Gourin [9] demonstrated that only 29% of patients with predominantly oropharyngeal cancers were histopathologically positive in the planned postradiologic neck dissection specimens.

Accordingly 71% of the patients would then be over-treated on the condition that the histopathological analyses of the neck specimens were reliable. There is also support for the view that salvage surgery based on positive fine needle aspiration cytology may be optimal and sufficiently beneficial for the patient. In this context, PET-CT does not seem sufficiently specific or sensitive to reliably predict the need for post treatment neck dissection [9]. Galati [10] demonstrated that 62% had died of the disease after the attempt of salvage surgery after failing irradiation therapy. Peters [11] observed that in patients with clinical evidence of persisting or recurrence of neck nodes four to six weeks after radiotherapy an employed neck dissection will recognize that only 50% of the specimens contain viable tumour cells. Furthermore, even partial responders to radiotherapy need not have remaining viable tumour cells despite initial histopathological evidence of malignancy [12,13]. In our study we found that nine of 11(80%) patients with persisting post radiation neck nodes were disease-free for at least three years after salvage neck dissection. Seven of these patients were without viable cancer cells in the histopathologic neck specimens.

At our institution we have seen a remarkable improvement of irradiated tonsillar carcinoma patients survival during the last 30 years [14]. This most certainly depend on the development and refinement of external radiotherapy and brachytherapy and the addition of chemotherapy, but also has to do with improved diagnostics in neck nodes with unknown primaries. Consequently, after an undefined primary assed by MRT of the oropharynx and neck tissues, patients over 40 years of age presenting with cervical cyst in the neck routinely undergo ipsilateral tonsillectomy for serial sectioning for histopathological analysis at our institution irrespective of cytological findings in the cyst [15].

Another aspect is that the average age of the patients with tonsillar carcinoma has decreased and the total incidence has significantly increased [16]. The association with human papilloma virus DNA has been identified in several cases [17–19] with a more favourable prognosis than other tonsillar carcinoma. These observations suggest that several tonsillar carcinomas may be induced by environmental factors and that a "new" subset of cancers is appearing on the clinical stage in association with the discovery of new molecular biologic markers. This in turn may explain different sensitivities to various treatment strategies.

In conclusion, the primary T-stage seems to be an essential factor for survival in patients with irradiated tonsillar carcinoma. The N-stage seems to a lesser extent influence prognosis. Radiotherapy provides a good cure rate compared to primary surgery. Neck dissection should be confined to patients with persistent or recurrent neck disease.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet. 2000;355(9208):949–55.

[2] Wong CS, Ang KK, Fletcher GH, Thames HD, Peters LJ, Byers RM, et al. Definitive radiotherapy for squamous cell carcinoma of the tonsillar fossa. Int J Radiat Oncol Biol Phys 1989;16:657–62.

[3] Perez CA, Patel MM, Chao KS, Simpson JR, Sessions D, Spector GJ, et al. Carcinoma of the tonsillar fossa: Prognostic factors and long-term therapy outcome. Int J Radiat Oncol Biol Phys 1998;42:1077–84.

[4] Shirazi HA, Sivanandan R, Goode R, Fee WE, Kaplan MJ, Pinto HA, et al. Advanced-staged tonsillar squamous carcinoma: Organ preservation versus surgical management of the primary site. Head Neck 2006;28:587–94.

[5] Charbonneau N, Gelinas M, del Vecchio P, Guertin L, Larochelle D, Tabet JC, et al. Primary radiotherapy for tonsillar carcinoma: A good alternative to a surgical approach. J Otolaryngol 2006;35:227–34.

[6] Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Malyapa RS, Werning JW, et al. Definitive radiotherapy for tonsillar squamous cell carcinoma. Am J Clin Oncol 2006;29:290–7.

[7] Chen J, Pappas L, Moeller JH, Rankin J, Sharma PK, Bentz BG, et al. Treatment of oropharyngeal squamous cell carcinoma with external beam radiation combined with interstitial brachytherapy. Head Neck 2007;29:362–9.

[8] Mendenhall WM, Amdur RJ, Stringer SP, Villaret DB, Cassisi NJ. Radiation therapy for squamous cell carcinoma of the tonsillar region: A preferred alternative to surgery? J Clin Oncol 2000;18:2219–25.

[9] Gourin CG, Williams HT, Seabolt WN, Herdman AV, Howington JW, Terris DJ. Utility of positron emission tomography-computed tomography in identification of residual nodal disease after chemoradiation for advanced head and neck cancer. Laryngoscope 2006;116:705–10.

[10] Galati LT, Myers EN, Johnson JT. Primary surgery as treatment for early squamous cell carcinoma of the tonsil. Head Neck 2000;22:294–6.

[11] Peters LJ, Weber RS, Morrison WH, Byers RM, Garden AS, Goepfert H. Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. Head Neck 1996; 18:552–9.

[12] Mau T, Oh Y, Bucci MK, Eisele DW. Management of cervical metastases in advanced squamous cell carcinoma of the tonsillar fossa following radiotherapy. Arch Otolaryngol Head Neck Surg 2005;131:600–4.
[13] Strasser MD, Gleich LL, Miller MA, Saavedra HI, Gluckman JL. Management implications of evaluating the N2 and N3 neck after organ preservation therapy. Laryngoscope 1999;109:1776–80.
[14] Edstrom S, Jeppsson PH, Lindstrom J. Carcinoma of the tonsillar region. Aspects on treatment modalities with reference to a study on patients treated by irradiation. Laryngoscope 1978;88:1019–23.
[15] Granstrom G, Edstrom S. The relationship between cervical cysts and tonsillar carcinoma in adults. J Oral Maxillofac Surg 1989;47:16–20.
[16] Hammarstedt L, Dahlstrand H, Lindquist D, Onelov L, Ryott M, Luo J, et al. The incidence of tonsillar cancer in Sweden is increasing. Acta Otolaryngol 2007;127: 988–92.
[17] Dahlstrand H, Dahlgren L, Lindquist D, Munck-Wikland E, Dalianis T. Presence of human papillomavirus in tonsillar cancer is a favourable prognostic factor for clinical outcome. Anticancer Res 2004;24:1829–35.
[18] Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet 2004; 363(9420):1488–9.
[19] Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. Int J Cancer 2006;119:2620–3.