Failure patterns and factors affecting prognosis of salivary gland carcinoma: retrospective study

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Objectives. To investigate the failure patterns and the prognostic factors following postoperative radiotherapy for salivary gland carcinoma.
Design. Retrospective study.
Setting. University teaching hospital, Hong Kong.
Patients. Fifty patients who had non-disseminated salivary gland carcinoma and who received primary treatment from 1984 through 1993.
Main outcome measures. Demographic data, cancer T- and N-stages, histological type, site of origin, completeness of surgery, whether postoperative radiotherapy was given, and the clinical outcome.
Results. Two (4%) patients had been treated with radiotherapy alone, six (12%) had undergone radical resection alone, and 42 (84%) had been radically treated by using both modalities. The 5-year overall survival and relapse-free survival rates were 78.4% and 63.1%, respectively. The free from local failure and free from distant metastasis rates at 5 years were 77.2% and 72.8%, respectively. The N-stage was a significant prognostic factor. The site of the primary tumour, T-stage, completeness of surgery, and use of postoperative radiotherapy were not significant independent prognosticators; however, among the T-stage tumours, the b-substage carcinomas had significantly fewer local failures (P=0.040) and better survival rates (P=0.038) than the a-substage carcinomas. There were seven (14%) locoregional failures without distant metastasis, seven (14%) cases of distant metastasis without locoregional failures, and four (8%) locoregional failures preceding distant metastasis; isolated regional relapse was rare (1/50; 2%). All regional failures (5/50; 10%) occurred ipsilateral to the primary lesion. There were no deaths due to lymphoepithelioma-like carcinoma or acinic cell carcinoma.
Conclusions. The N-stage is the main prognostic factor of overall survival, relapse- and metastasis-free recovery, and success of treatment for salivary gland carcinoma. Optimal locoregional treatment can help reduce distant metastasis, and the maximal use of postoperative radiotherapy may contribute to improved locoregional control. Elective ipsilateral neck radiotherapy is indicated for lymphoepithelioma-like carcinoma.

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Key words: Combined modality therapy; Prognosis; Radiotherapy, high-energy; Salivary gland neoplasms/therapy; Survival analysis; Treatment outcome

Introduction

Salivary gland carcinomas, most cases of which arise from the parotid glands, constitute approximately 3% of all head and neck malignancies.[1,2] The mainstay of treatment is surgical resection. Postoperative radiotherapy is indicated when the resection margin is positive or close,[3,4] the tumour is high grade,[3,4] there is tumour infiltration of adjacent organs, or regional metastasis is extensive.[5,6] The prognosis depends on the stage[5-8] and grade[3,4,9] of the cancer, the completeness of surgical resection, and, when the resection is incomplete, whether or not postoperative radiotherapy is administered.[1-3,6,10] Unlike other high-grade salivary gland carcinomas, lymphoepithelioma-like carcinomas (LELCs) are very radiosensitive,[11-13] and radiotherapy has been used instead of surgery as the primary treatment of LELC.[11] In addition, the prognosis of LELC

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in Hong Kong is good: the 5-year control rate exceeds 90% and the 4-year disease-free survival rate is higher than 80%.[12]

This study aimed to evaluate the significance of (a)various factors such as the cancer stage, the administration of postoperative radiotherapy, the presence of positive or close resection margins, and the histological types in the prognosis of salivary gland carcinoma; (b) the pattern of treatment failure; and (c) the natural course of LELC.

Methods

Patient selection

All patients who had non-disseminated (stage M0) salivary gland carcinoma and whose primary treatment (surgery with/without postoperative radiotherapy, or radiotherapy alone) was performed at the Prince of Wales Hospital (PWH) from 1984 through 1993 were included in the study. From the case notes of the 50 patients, the following information was analysed: the sex and age of patient; the size and extent of the primary lesion; and the characteristics of the nodal metastasis (if present). Cancers were then classified according to the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer.[14] Also studied were the histological type of disease; the completeness of the primary surgery (resection margins close to or positive for tumour were classified as incomplete surgery); the date of the surgery; the use of radiotherapy; the disease status at and the date of the last follow-up visit of the patient; and in cases of relapse, the date of diagnosis and the site of occurrence of the relapse. During the study period, all patients who had a diagnosis of head and neck cancer (including parotid malignancies) were treated jointly by surgeons and radiation oncologists in a combined 'head and neck clinic', where the treatment decision (including whether to administer postoperative radiotherapy) was made. In general, patients with 'high-grade' tumours that had close or unclear resection margins, extended to adjacent organs, or had extensive extraparotid ramifications were considered appropriate candidates for postoperative radiotherapy. Cases in which patients died during follow-up were classified as either death due to cancer or cancer-related causes (including treatment complications), or death due to intercurrent illness without evidence of relapse.

Statistical analysis

The overall survival rate (OSR), relapse-free survival (RFS) rate, free from local failure (FLF) rate, and free from distant metastasis (FDM) rate were calculated by using the product limit method to analyse the frequency of death, locoregional failure, and distant metastasis. The OSR and RFS, FLF, and FDM rates were plotted against time to produce Kaplan-Meier curves. Different groups of patients (eg different histological types and stages) were compared by using the logrank test. Potentially significant prognosticators, such as the patient's sex and age, TNM stage, histological type, completeness of resection (clear of tumour versus positive for tumour), administration of postoperative radiotherapy, and the total dose of radiotherapy (≥60 Gy, ≤50 Gy, or 50-60 Gy), were further studied using Cox regression analysis. The cut-off level for statistical significance was taken as P=0.05. The 95% confidence interval (CI) was calculated for the risk ratios for each of the significant prognosticators.

Results

Fifty patients received primary treatment for non-disseminated salivary gland carcinoma at the PWH during the 10-year study period. The median age of the patients at the time of presentation was 55.5 years (range, 10-86 years) and the male to female ratio was 1:1. The majority of carcinomas were those of the major salivary glands (parotid, n=35 [70%]; submandibular gland, n=12 [24%]; sublingual gland, n=1 [2%]), and only two (4%) cases were carcinoma of the minor salivary glands in the hard palate. The distribution of histological types of carcinoma was as follows: 16 (32%) cases of adenocystic carcinoma, eight (16%) of mucoepidermoid carcinoma, eight (16%) of squamous cell carcinoma or adenocarcinoma not otherwise specified, seven (14%) of LELC, three (6%) of adenocarcinoma ex-pleomorphic adenoma, three (6%) of undifferentiated or anaplastic carcinoma, three (6%) of acinic cell carcinoma, and two (4%) of clear cell carcinoma.

One (2%) of the 50 patients had unclear tumour resection margins, but was not offered postoperative radiotherapy because of the patient's poor general condition. Forty-two (84%) patients received postoperative radiotherapy, the administration of which was not found to be significantly associated with the completeness of resection (positive or close resection margins versus negative and adequate margins), the histological type, the site of the primary tumour, or the cancer stage. Of the 42 patients, the majority (24; 57%) received a total dose of 60 Gy or more (range, 60-70 Gy) to the tumour bed. Ten (24%) of the 42 patients received 50 Gy or less (range, 40-50 Gy) and

the remainder (8; 19%) received a dose of between 50 Gy and 60 Gy. Two (4%) patients were treated solely by radiotherapy for palliation: one patient was given 16 Gy in two fractions and the other was given 22 Gy in five fractions; their T4-tumours were considered inoperable because of the patients' poor general condition and/or extensive infiltration of surrounding structures. Two (33%) of the six patients who were treated by surgical resection without postoperative radiotherapy experienced local failure, compared with seven (17%) of the 42 patients who received radiotherapy after surgical resection (P=0.312). The 5-year OSR and RFS rate for the 50 non-disseminated cases were 78.4% and 63.1%, respectively, and their 5-year FLF and FDM rates were 77.2% and 72.8%, respectively.

Prognosticators

There was a significant difference in the OSR when comparing patients who had LELC or acinic cell carcinoma with those who had other histological types of salivary gland carcinoma (P=0.019). The OSR of patients with adenocystic carcinoma was also significantly different from that of the patients in the 'others' group (P=0.020)[Fig. 1]. After excluding the seven patients with LELC and the three with acinic cell carcinoma (whose prognosis was better than that of the other patients), the 5-year FLF and RFS rates were 74.8% and 57.4%, respectively, and the 5-year OSR was 73.0%. The prognostic significance of classifying salivary carcinoma as LELC, adenocystic carcinoma, or 'others' (which excluded acinic cell carcinoma) was maintained for the overall survival among the salivary gland carcinomas conventionally classified as 'high grade' (n=47; P=0.007).

The N-stage significantly governed survival (Fig 2) and the rate of distant metastasis (Fig 3). The prognosis of primary tumours that infiltrated surrounding structures (the b-substage of the T-stage) was worse than the prognosis of tumours that were confined to the salivary gland (the a-substage of the T-stage) [Fig 4]. By using univariate analysis, the b-substages of cancer taken as a whole group were found to have significantly more local failures (P=0.040) and distant metastasis (P=0.038) than the a-substages. On the other hand, the completeness of resection (positive or close margin versus adequate margin), the T-stage, and whether or not postoperative radiotherapy was used did not affect survival, local failure, or distant metastasis rates. There was a trend towards better survival rates of younger patients (<55.5 years) and female patients, although the difference in results was not statistically significant (P=0.1 in both cases).

According to the Cox regression analysis of the data, the N-stage (P<0.001; risk ratio=3.08; CI, 1.46-6.51) and the histological type (LELC/acinic cell carcinoma, adenocystic carcinoma, or others)[P=0.006; risk ratio=5.3; CI, 1.34-21.02] were the only significant prognosticators that governed overall survival. The N-stage was the only significant factor that determined

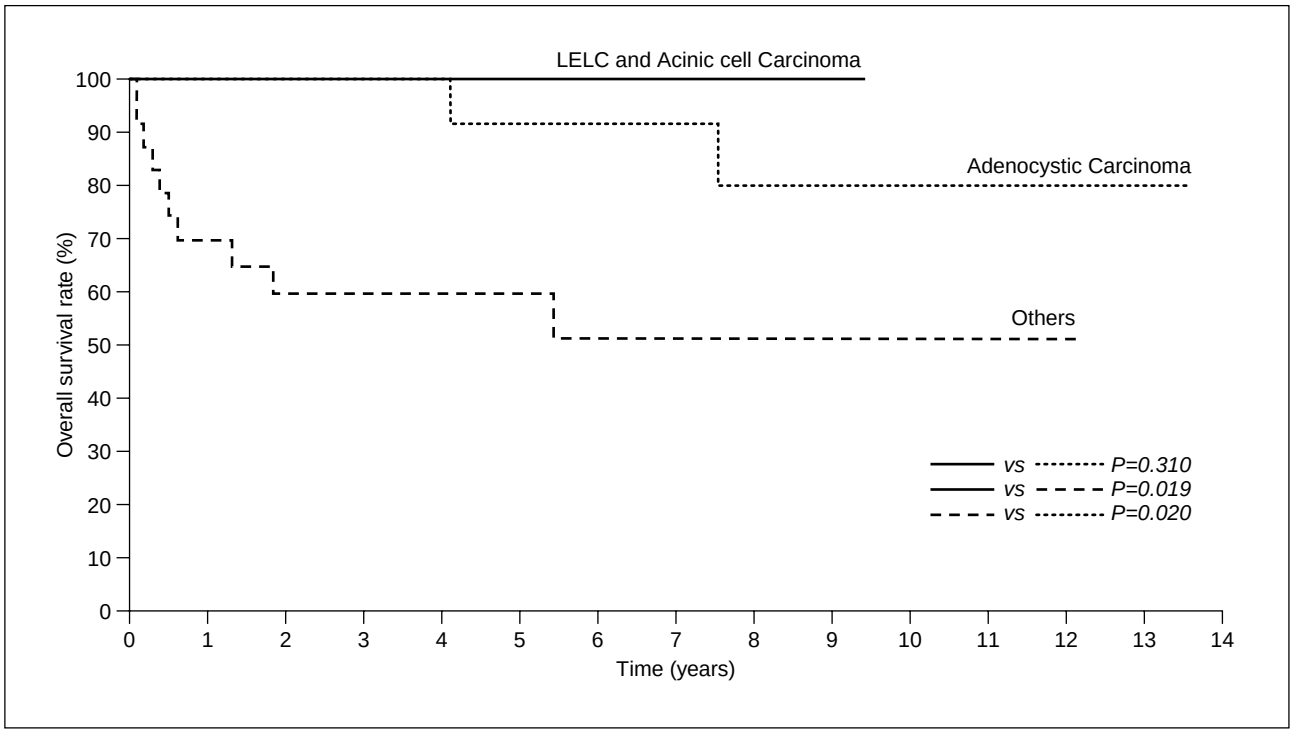

Fig 1. Comparison of overall survival rate between patients with different types of salivary gland carcinoma

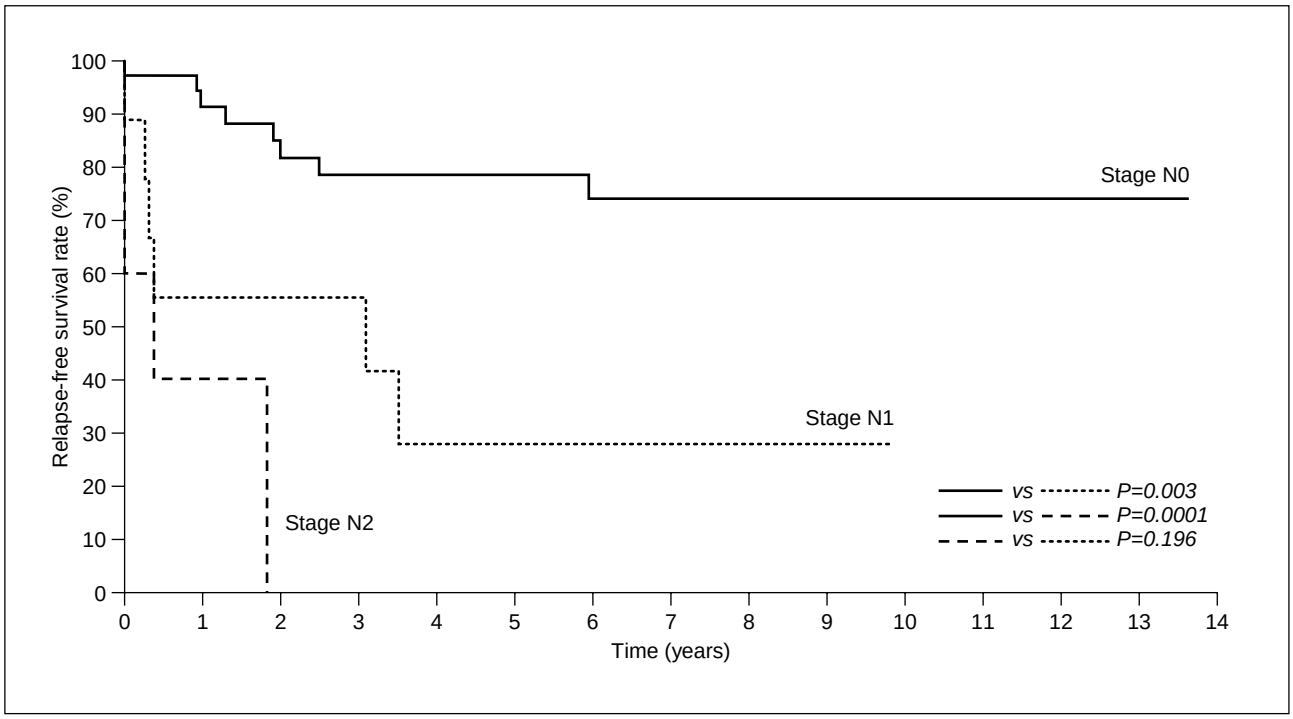

Fig 2. The effect of the N-stage on the relapse-free survival rate

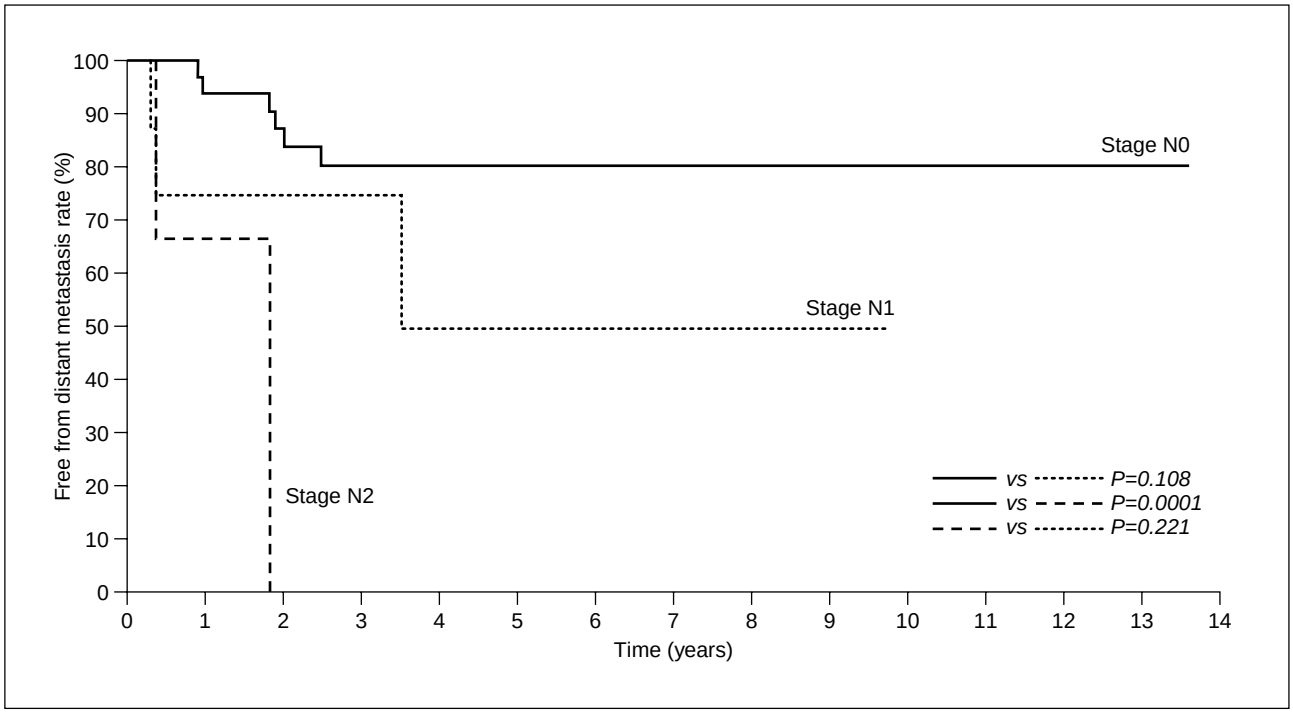

Fig 3. The effect of the N-stage on the free from distant metastasis rate

the rate of distant metastasis (P<0.001; risk ratio=3.67; CI, 1.55-8.65), as well as the rate of locoregional failure (P=0.002; risk ratio=3.26; CI, 1.43-7.44). For patients without cervical nodal metastasis (36; 72%), there were no significant factors that determined any of the clinical end-points. Whether or not radiotherapy was administered postoperatively and the total radiation dose (≥60 Gy, ≤50 Gy, or 50-60 Gy) were not significant in determining the survival or relapse rates. There were significant associations between the N- and T-stages (P=0.005, Fisher's exact test), between the N-stage and the a- and b-substages of the T-stage (P=0.001, χ^2=15.3), and between the N-stage and the age of the patient (<55.5 years versus 55.5 years) [P=0.002, χ^2=9.92]. There was no significant association between the histological type (LELC/acinic cell carcinoma, adenocystic carcinoma, or others) and the other potential prognostic factors.

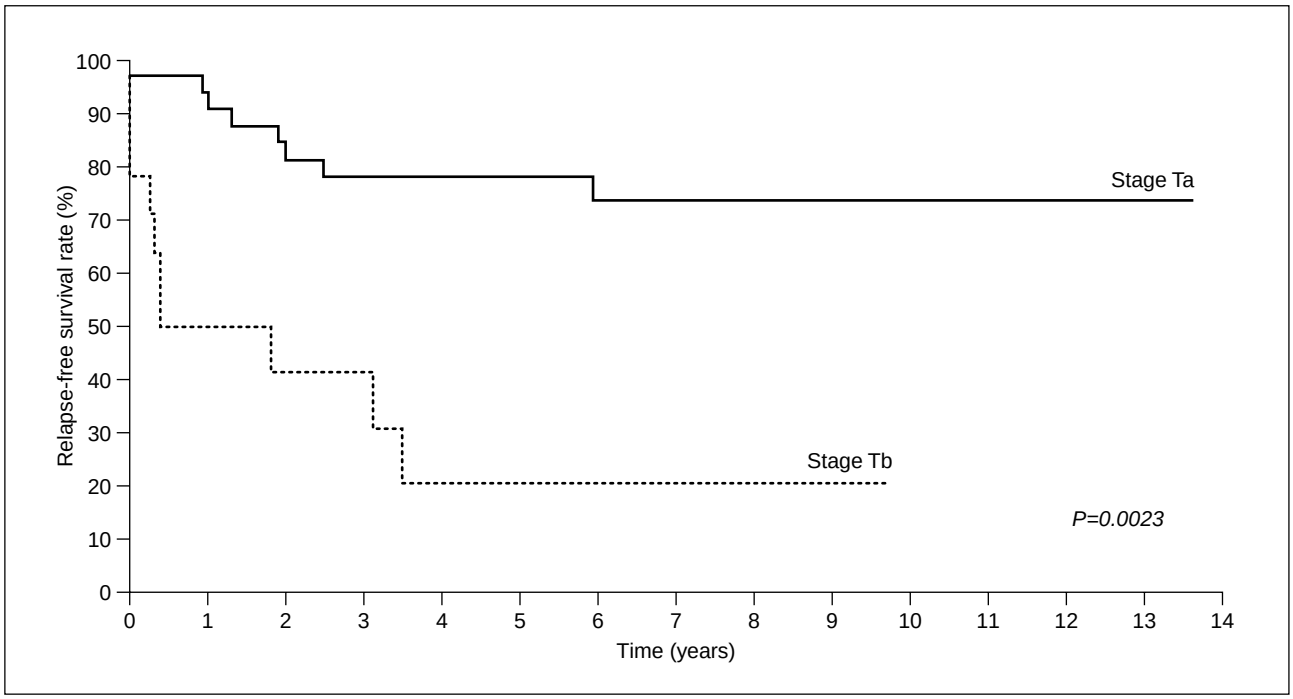

Fig 4. Comparison of relapse-free survival rates between a- and b-substages of the T-stage

Pattern of failure

Three types of treatment failure occurred: seven (14%) patients had locoregional failure only, seven (14%) patients had distant metastases only, and four (8%) patients had both locoregional failure and distant metastasis. There was no difference in the time to relapse after primary treatment between the three types of failure. In addition, there was no predisposition to a particular type of failure between the different histological types. Of the 11 patients who had locoregional failure with or without distant metastasis, one (9%) had regional failure, six (55%) had local failure, and four (36%) had both local and regional failures. The case of regional failure occurred in a patient with LELC of the parotid gland, whose the neck was not given elective irradiation. All five cases of regional failure (with or without local failures) occurred on the side of the neck ipsilateral to the primary tumour.

Among the 11 patients in whom distant metastasis developed with or without locoregional failure, the main site of metastasis was the lung (4; 36%), followed by bone (2; 18%), and liver (2; 18%). In four (36%) patients, distant metastasis developed between 0.24 and 6.48 months after the diagnosis of local and/or regional failure. Eight (73%) of the 11 patients were given palliative chemotherapy, which consisted of either epirubicin (75 mg/m^2, D1) [n=3], or cisplatin (100 mg/m^2, D1) with 5-fluorouracil (1 gm/m^2, D1-D4) [n=5] every 3 weeks. The median survival time after distant metastasis was 21.8 months (range, 4.6-90.0 months) despite the low response rate to chemotherapy (2/8; 25%).

Lymphoepithelioma-like carcinoma

All cases of LELC arose from the parotid gland. Only two (4%) patients experienced relapses; one of the patients had not received elective neck irradiation and isolated regional relapse developed 6 years after parotidectomy and postoperative radiotherapy of the primary tumour bed. The second patient had a local recurrence in the parotid gland despite total parotidectomy and postoperative radiotherapy (50 Gy) 3.5 years after the primary treatment. Both cases of relapse were successfully salvaged by further treatments. The regional recurrence was treated by performing radical neck dissection and giving postoperative regional radiotherapy. The parotid recurrence was treated by a second course of radical radiotherapy (60 Gy for 30 fractions for 6 weeks) using 3D-conformal methods to avoid exposing the spinal cord and the contralateral parotid gland to radiation.

Discussion

Factors affecting the prognosis of salivary gland carcinoma

Tumour stage

The N-stage was the only independent prognosticator of the RFS and FDM rates. The prognostic significance of the N-stage has also been highlighted in many previous reports.[3,4,6-10,15] In contrast, the T-stage, its a- and

b-substages, the completeness of surgery (close or positive margin versus adequate margin), and the administration of postoperative radiotherapy did not affect the relapse or RFS rates. One possible reason is that postoperative radiotherapy was given very liberally: only six (12%) of the 48 patients who had surgical resection did not receive postoperative radiotherapy.

The policy at the PWH is to select high-risk patients (high-grade tumour, inadequate resection margin, or extensive disease) to receive radiotherapy. The lack of significant association between the administration of postoperative radiotherapy with the completeness of resection (resection margin close or positive), T-stage, or histological type implies that the administration of radiotherapy was in fact not limited to the established indications of advanced-stage, high-grade cancer, and incomplete surgery. Although postoperative radiotherapy was not found to affect local control or survival by either univariate or multivariate analysis, the overall rate of its administration (42/50; 84%) was apparently higher than the rate found in other series.[3,6] The rates of local failure in this study (crude rate, 22.0%; 5-year actuarial rate, 22.8%) is more similar to the reported local failure rates after the administration of postoperative radiotherapy for high-grade tumours (14%-30%)[1,2,5] than to the reported local failure rates after surgical resection alone (43%-50%).[1,2,5] Even after excluding cases of LELC and acinic cell carcinoma, the 5-year actuarial local failure rate of 25.2% and the 5-year RFS rate of 57.4% were among the lowest and highest, respectively, in the literature; most studies have reported a 5-year RFS rate between 31% and 58%.[1,5,6]

The liberal administration of postoperative radiotherapy may also have contributed to the satisfactory locoregional control, which led to improved survival. The lack of significant difference in locoregional control between patients who were given postoperative radiotherapy and those who underwent resection alone is more likely a consequence of the small number of patients (n=6) and events among the latter. In addition, radiotherapy could have nullified the prognostic impact of some of the potentially significant factors, such as the incompleteness of surgical resection, the T-stage, and the a- and b-substages. In other words, the lack of prognostic significance of these well-known prognosticators in this study could be a consequence of the liberal administration of postoperative radiotherapy to the majority (42/50; 82%) of the patients. The findings concur with those of Parsons et al,[5] who showed that the best local control was achieved by the combined approach of performing radical resection and then giving radiotherapy.

Histological type

All salivary gland carcinomas, except the three acinic cell carcinomas, were classified as being 'high-grade' carcinomas.[1-3,6,7,9,11] Even acinic cell carcinomas, which are considered as being 'low grade' can behave rather unpredictably and can have significant rates of regional metastasis and relapse.[10] The cases of LELC have been conventionally classified as being 'high grade' because of their poor histological differentiation. However, LELCs are very radiosensitive and bear a better prognosis than the other high-grade salivary gland tumours.[11-13] In this study, there was no cancer mortality among the patients with LELC (n=7) or acinic cell carcinoma (n=3), hence justifying the grouping of these two histological types to analyse survival and relapse. Therefore, despite the poor differentiation and high-grade histological appearance of LELC, its clinical course and behaviour were benign in this study. The current classification of histological types of carcinoma into three groups—namely, LELC plus acinic cell carcinoma, adenocystic carcinoma, and 'others' was significant in predicting overall survival. In addition, when the acinic cell carcinomas were excluded from the analysis, the prognostic significance of the classification of patients into LELC, adenocystic carcinomas, and 'others' was maintained. It thus seemed justifiable to distinguish the LELCs and adenocystic carcinomas from mucoepidermoid carcinomas, the undifferentiated (or anaplastic) carcinomas, the squamous cell carcinomas, the adenocarcinomas expleomorphic adenoma, the adenocarcinomas not otherwise specified, and the clear cell carcinomas.

Pattern of failure

Local recurrence with or without regional recurrence (10; 20%) and distant metastasis (11; 22%) were the main causes of failure. Only a small proportion (4/18; 22%) of patients developed both locoregional and distant failures. The isolated regional relapse in the case of LELC might have been prevented had elective neck irradiation been given primarily. The other four regional failures were ipsilateral to and associated with local failures, which suggested that the uncontrolled primary lesion had given rise to the regional failures. In addition, their primary lesions were both high grade and advanced. Hence, the vigorous control of the primary cancer and administration of elective ipsilateral neck treatment are indicated by a bulky high-grade salivary gland tumour (stage T2) that infiltrates surrounding structures.

Four (8%) patients developed distant metastasis between 0.24 and 6.48 months after the diagnosis of locoregional recurrence. The uncontrolled locoregional disease may have eventually disseminated, and effective locoregional control may have reduced the rate of distant metastasis. Distant metastasis, however, remained the main cause of failure, and the majority (7/11; 64%) occurred without locoregional failure. In these patients, micrometastases that may have been present at the time of initial treatment would have caused the subsequent emergence of clinically overt systemic disease. Systemic treatment may have been indicated in addition to the primary treatment; those presenting with cervical nodal metastasis (4/14; 29%) were at particularly high risk of overt systemic disease occurring. However, effective systemic therapy is not available.[1-3] A low response rate to cisplatin 5-fluorouracil,[16] and epirubicin[17] has been reported in cases of recurrent/metastatic adenocystic carcinoma. The low response rate to chemotherapy in our experience also emphasised the need for the development of more effective drugs. On the other hand, the seven patients with LELC, including the two in whom local or regional recurrence developed, had no distant metastasis and did not require the adjunctive chemotherapy that has been advocated for nasopharyngeal carcinoma, which has a similar histological appearance.[18,19]

Lymphoepithelioma-like carcinoma

Lymphoepithelioma-like carcinoma can arise in the salivary gland, thyroid, tonsils, uterine cervix, and skin.[20] It constitutes a significant proportion of salivary gland carcinoma in Chinese and Eskimo populations[21,22] and is related to Epstein-Barr virus infection.[12,15,21,22] In this series, 7 (14%) of the 50 patients belonged to this histological group and all cases arose from the parotid gland. In agreement with other reports,[12,15] LELC was shown to have a better prognosis (Fig 1), and did not develop in any of the seven patients with LELC. Only two of patients had relapses after primary treatment: one regional and one local. The regional failure occurred ipsilateral to the primary parotid tumour because the neck was not electively irradiated. There was no evidence of local failure concurrent with or after the diagnosis of regional recurrence. Elective neck irradiation, which we now advocate for LELC of the parotid—if given ab initio—might have prevented the regional failure. This type of cancer drains primarily into the ipsilateral neck nodes, unlike nasopharyngeal carcinoma, which arises from a midline organ that has significant bilateral cervical lymphatic drainage, thus resulting in the frequent occurrence of bilateral nodal disease. Elective irradiation should therefore be confined to the neck ipsilateral to the primary lesion.

The single case of LELC that had local failure occurred 3.3 years after the patient had undergone total parotidectomy and postoperative radiotherapy (50 Gy). The surgical notes and reports from the pathological examination were reviewed and showed no evidence that gross residual tumour was present after the surgery. When the radiotherapy plan was reviewed, the 50 Gy isodose volume was considered sufficient to totally circumscribe the primary tumour bed. The 50 Gy dose, however, was unable to eradicate the microscopic residual disease. Although LELC has generally been considered to be very radiosensitive, and a significant number of gross tumours have been permanently controlled by using a radiation dose of 60 Gy,[11-13,15] treating microscopic residual disease after surgical resection with more than 50 Gy radiation to achieve adequate local control would appear safer.

Conclusion

From studying the patterns of failure, a significant proportion of distant metastases was shown to have arisen from uncontrolled locoregional disease, although the majority of cases were caused by micrometastasis. Preventing locoregional failure by giving more effective treatment and adjuvant chemotherapy should thus enhance systemic control. Furthermore, the N-stage is the main prognosticator governing the OSR and RFS, FDM, and FLF rates, whereas the classification of histological types of disease into LELC/acinic cell carcinoma, adenocystic carcinoma, and other high-grade carcinomas significantly determined the OSR. Finally, cases of LELC should receive elective ipsilateral neck irradiation; a dose higher than 50 Gy is required to adequately control microscopic disease.

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References

1. Rafla S. Salivary glands. In: Halnan KE, editor. Treatment of cancer. London: Chapman and Hall; 1982:269-94.
2. Sessions RB, Harrison LB, Hong WK. Tumors of the salivary glands and paragangliomas. In: DeViat VT Jr, Steven SH, Rosenberg JB, editors. Cancer principles and practice of

oncology. 4th ed. Philadelphia: JB Lippincott Company 1993: 655-72.
3. Spiro RH. Management of malignant tumours of the salivary glands. Oncology (Huntingt) 1998;12:671-80.
4. Beckhardt RN, Weber RS, Zane R, et al. Minor salivary gland tumours of the palate: clinical and pathologic correlates of outcome. Laryngoscope 1995;105:1155-60.
5. Parsons JT, Mendenhall WM, Stringer SP. Management of minor salivary gland carcinomas. Int J Radiat Oncol Biol Phys 1996;35:443-54.
6. Renehan A, Gleave EN, Hancock BD, Smith P, McGurk M. Long-term follow-up of over 1000 patients with salivary gland tumours treated in a single centre. Br J Surg 1996;83:1750-4.
7. Plambeck K, Friedrich RE, Schmelzle R. Mucoepidermoid carcinoma of salivary gland origin: classification, clinical-pathological correlation, treatment results and long-term follow-up in 55 patients. J Craniomaxillofac Surg 1996;24: 133-9.
8. Anderson JN, Beenken SW, Crowe R, et al. Prognostic factors in minor salivary gland cancer. Head Neck 1995;17:480-6.
9. Rodrguez-Cuevas S, Labastida S, Baena L. Risk of nodal metastases from malignant salivary gland tumours related to tumour size and grade of malignancy. Eur Arch Otorhinolaryngol 1995;252:139-42.
10. Napier SS, Herron BT, Herron BM. Acinic cell carcinoma in Northern Ireland: a 10-year review. Br J Oral Maxillofac Surg 1995;33:145-8.
11. Dubey P, Ha CS, Ang KK, et al. Non-nasopharyngeal lymphoepithelioma of the head and neck. Cancer 1998;82:1556-62.
12. Tsai CC, Chen CL, Hsu HC. Expression of Epstein-Barr virus in carcinomas of major salivary glands: a strong association with lymphoepithelioma-like carcinoma. Hum Pathol 1996;27: 258-62.
13. Borg MF, Benjamin CS, Morton RP, Llewellyn HR. Malignant lympho-epithelial lesion of the salivary gland: a case report and review of the literature. Australas Radiol 1993;37: 288-91.
14. American Joint Committee on Cancer, Salivary glands: parotid, submandibular, and sublingual. In: Handbook for staging of cancer from the manual for staging for cancer. 4th ed. Philadelphia: JB Lippincott Company; 1993:67-90.
15. Kuo T, Hsueh C. Lymphoepithelioma-like salivary gland carcinoma in Taiwan: a clinicopathological study of nine cases demonstrating a strong association with Epstein-Barr virus. Histopathology 1997;31:75-82.
16. Hill ME, Constenla DO, A'Hern RP, et al. Cisplatin and 5-fluorouracil for symptom control in advanced salivary adenoid cystic carcinoma. Oral Oncol 1997;33:275-8.
17. Vermorken JB, Verweij J, de Mulder PH, et al. Epirubicin in patients with advanced or recurrent adenoid cystic carcinoma of the head and neck: a phase II study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1993;4: 785-8.
18. International Nasopharynx Cancer Study Group. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in Stage IV (≥N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. Int J Radiat Oncol Biol Phys 1996;35:463-9.
19. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. J Clin Oncol 1998;16:1310-7.
20. Swanson SA, Cooper PH, Mills SE, Wick MR. Lymphoepithelioma-like carcinoma of the skin. Mod Pathol 1988;1: 359-65.
21. Leung SY, Chung LP, Yuen ST, Ho CM, Wong MP, Chan SY. Lymphoepithelial carcinoma of the salivary gland: in situ detection of Epstein-Barr virus. J Clin Pathol 1995;48:1022-7.
22. Saw D, Lau WH, Ho JH, Chan JK, Ng CS. Malignant lymphoepithelial lesion of the salivary gland. Hum Pathol 1986;17: 914-23.