Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice (2011)
10, 85–90

doi:10.1017/S1460396910000178

Original Article

Post-operative accelerated hypofractionated radiotherapy for adenoid cystic carcinoma

Jennifer Sherriff[1], Urmila Barthakur[1], Paul Sanghera[1,2], Christopher McConkey[3], Christopher Rusius[4], Andrew Hartley[1,2], John Glaholm[1,2]

[1]*Hall-Edwards Radiotherapy Research Group, Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK,* [2]*Division of Cancer Studies, University of Birmingham, Birmingham, UK,* [3]*Clinical Trial Unit, University of Warwick, Coventry, UK,* [4]*Medical School, University of Birmingham, Birmingham, UK*

Abstract

Objective: To examine the outcomes of patients with adenoid cystic carcinoma (ACC) treated with post-operative accelerated hypofractionated radiotherapy (AHRT).

Methods: Patients treated with AHRT (50–55 Gy in 20 fractions over 25 days) between 1997 and 2008 were identified and retrospectively analysed. Data collection included site of primary and surgical excision margin. Primary outcomes were overall survival (OS) and local control (LC) calculated using the Kaplan–Meier method.

Results: A total of 37 patients meeting the above criteria were identified with a median age of 55 years (range 31–79). Distribution by anatomical site was as follows: parotid 9 patients; submandibular gland 8 patients; other salivary gland tissue 20 patients. Surgical excision margins were as follows: non-involved 25 patients; microscopic involvement 7 patients; macroscopic involvement 4 patients; unknown 1 patient. Median follow-up was 59 (range 14–126) months. Five patients had local recurrence, 4 distant recurrences, and 1 both local and distant recurrence. The 5-year LC and OS rates were 81.8% (95% confidence intervals (CIs) 60.9–92.2) and 78.5% (95% CI 58.0–89.8%), respectively.

Conclusion: Outcomes with post-operative AHRT appear comparable to those in the literature. However, until more is known about the radiobiology of this rare disease, a biological equivalent of 60 Gy in 2 gray fractions without correction for accelerated repopulation should be used.

Keywords

Accelerated hypofractionated radiotherapy; adenoid cystic carcinoma

INTRODUCTION

Adenoid cystic carcinoma (ACC) accounts for approximately 10% of salivary gland tumours. It is the most common tumour of the minor salivary glands and is the second most common tumour of the major salivary glands after

Correspondence to: Paul Sanghera, Cancer Centre, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK. E-mail: paul.sanghera@uhb.nhs.uk

mucoepidermoid tumours.[1] There is a propensity for perineural spread in addition to nodal and haematogenous spread. The tumours often have a slow, protracted natural history.

Surgery is well established as the definitive treatment modality for ACC. Local recurrence occurs commonly following treatment with surgery alone. This is thought to occur because of the infiltrative growth pattern and perineural spread associated with these tumours, hence radiotherapy is given post-operatively. The addition of post-operative radiotherapy has been shown in several retrospective reviews to enhance LC rates.[1–7] Radiobiological parameters for this tumour have yet to be fully established, and current treatment schedules are based upon clinical experience and small retrospective case series.

Current post-operative schedules used within the United Kingdom deliver at least 60 Gy in 30 fractions as there is evidence that doses less than this lead to inferior outcomes.[1–3] Little data exists regarding the use of accelerated hypofractionated regimes for ACC. In theory, this may offer both practical advantages to a busy radiotherapy department, alongside potential radiobiological advantages. The present study determines outcomes following the use of an accelerated hypofractionated regime in the post-operative setting for patients with ACC.

METHODS

All patients treated with accelerated hypofractionated radiotherapy (AHRT) between 1997 and 2008 were identified and retrospectively analysed. The dose delivered included 50 Gy, 52.5 Gy or 55 Gy given in 20 fractions over 25 days. Anterior and posterior oblique fields were used to deliver the treatment with an anterior matched neck field to treat uninvolved lymph nodes within levels III to V to a dose of 41.25 Gy in 15 fractions where appropriate.

A retrospective review of hospital notes was performed. Data collection included site of the primary tumour and surgical margin status: classified as clear, microscopically involved or macroscopically involved.

Primary outcomes were overall survival (OS) and local control (LC) calculated using the Kaplan–Meier method. The time to progression was defined as the date of starting radiotherapy until the documented date of failure for those who relapsed. Patients were censored at the date of death (if the patient died from other causes without relapse) or last follow-up date. Univariate analysis using Cox proportional hazards models was performed to assess the influence of the following variable on outcomes: involvement of resection margins, age, gender, and site of disease.

RESULTS

Thirty-seven patients were identified and reviewed. Of these, 13 were male and 24 were female. The median age at diagnosis was 55 (range 31–79) years. Nine patients had parotid ACC, 8 had submandibular ACC and 20 had minor salivary gland ACC. Minor salivary gland tumours included nine tumours within the oral cavity and the remaining 12 were from other sites.

Thirty six of the included patients had undergone surgical resection of their tumours prior to receiving radiotherapy. Histology reports were reviewed, 25 had clear margins, 7 had microscopic involvement of the margins and 4 had macroscopic involvement. Patient and tumour characteristics are given in Table 1.

Thirty-one patients were planned conventionally using the simulator. The remaining six patients, who were the most recent to be treated, were planned using computerized tomography. Table 2 shows the beam arrangements used. None of the patients were treated with intensity-modulated radiotherapy.

The median follow-up times for all patients was 59 (range 14–126) months. Ten patients had developed recurrence: 5 loco-regional, 4 distant recurrences and 1 both loco-regional and distant recurrence. The median time to

https://doi.org/10.1017/S1460396910000178 Published online by Cambridge University Press

Table 1. *Patient characteristics*

Patient characteristics	*n*	Percentage
Total entered	37	
Gender		
Male	13	35.1%
Female	24	64.9%
Age (years)		
Median (interquartile range)	55 (45–64)	
Range	31–79	
Site		
Parotid gland	9	24.3%
Submandibular gland	8	21.6%
Minor salivary glands	20	54.1%
T stage		
T1	4	10.8%
T2	14	37.8%
T3	7	18.9%
T4	7	18.9%
Unknown	5	13.6%
N stage		
N0	29	78.4%
N1	6	16.2%
N2	2	5.4%
Surgical excision		
Yes	36	97.3%
No	1	2.7%

Table 2. *Radiotherapy technique*

Beam arrangement	*n*	Percentage
Wedge pair	27	73.0
Parallel opposed	4	10.8
3 Field (anterior and 2 laterals)	5	13.5
Unknown	1	2.7

progression was 21 (range 4–85) months. The Kaplan–Meier plots for LC and OS for all patients are shown in Figures 1 and 2, respectively. The 5-year LC rate was 81.8% (95% confidence intervals (CIs) 60.9–92.2).

At the time of analysis, eight patients had died. Four of these had initially presented with T4 disease. OS at 5 years was 78.5% (95% CI 58.0–89.8%). No significant differences in the rate of LC or OS were found within the cohort when considering age, gender, T stage or site of disease. Figure 3 illustrates the survival curves when considering involvement of the surgical margin. Involved margins were associated with reduced OS ($p = 0.04$). Table 3 compares the results presented here to those available in the literature.

DISCUSSION

Radiotherapy is widely accepted as standard treatment in the post-operative setting for ACC. Several studies considering a combined approach of surgery followed by radiotherapy to a dose of at least 60 Gy (in 2 Gy per fraction over 39 days) have shown significantly greater LC than from surgery alone.[1,3,7]

The reported cohort shows a similar distribution of sites of ACC as compared to published data.[8,9] Garden et al. reported survival and disease-free rates for patients with ACC treated using combined surgery and post-operative radiotherapy.[2] Doses ranged from 50–69 Gy (median, 60 Gy) over 23–58 days (median, 42 days). Outcomes were significantly better in those who received a post-operative radiation dose of 60 Gy or more. The 5-year LC rate, freedom from relapse rate and OS were 95%, 68% and 82%, respectively.

The accelerated hypofractionated regime reported here appears to be associated with similar LC and OS to conventional radiation schedules. At present, the radiobiology of ACC is poorly understood. Both the α/β ratio and significance of accelerated repopulation for ACC remain unknown. AHRT has been used successfully in squamous cell carcinoma of the head and neck cancer largely due to the shortened overall treatment time counteracting accelerated repopulation.[10] In prostate cancer, hypofractionated radiotherapy has also been used successfully but in this disease due to the postulated low α/β ratio.[11,12]

The small number of patients within this study limits conclusions with respect to variables analysed. However, consistent with other series, involvement of surgical margins was associated with a worse OS. With the exception of increasing T stage, other studies have failed to consistently identify any other significant prognostic factors.[4,6,8,13]

https://doi.org/10.1017/S1460396910000178 Published online by Cambridge University Press

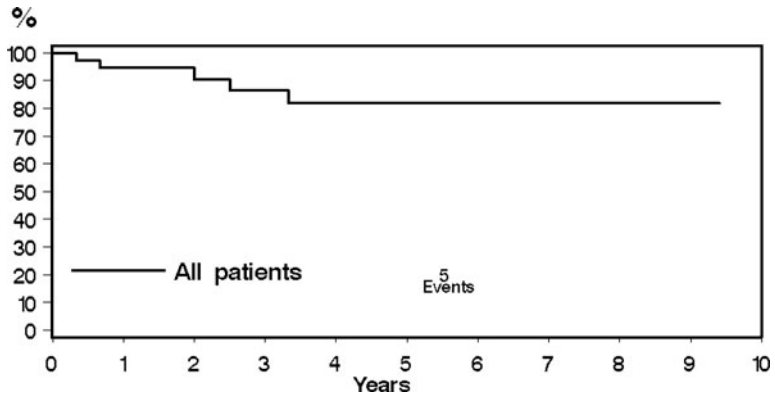

Figure 1. Kaplan–Meier plot of local control.

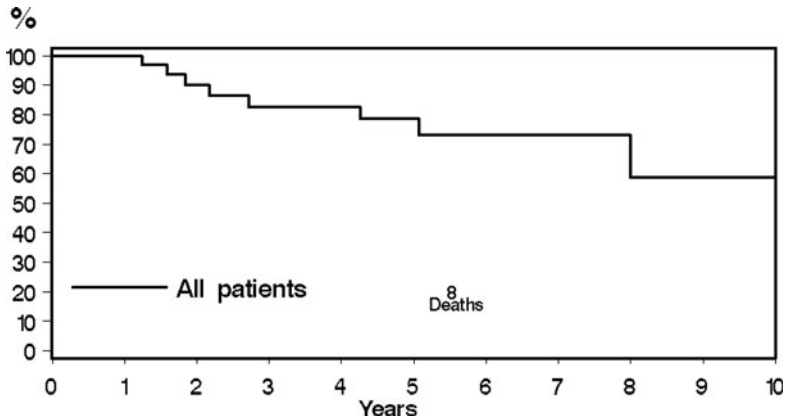

Figure 2. Kaplan–Meier plot of overall survival rates.

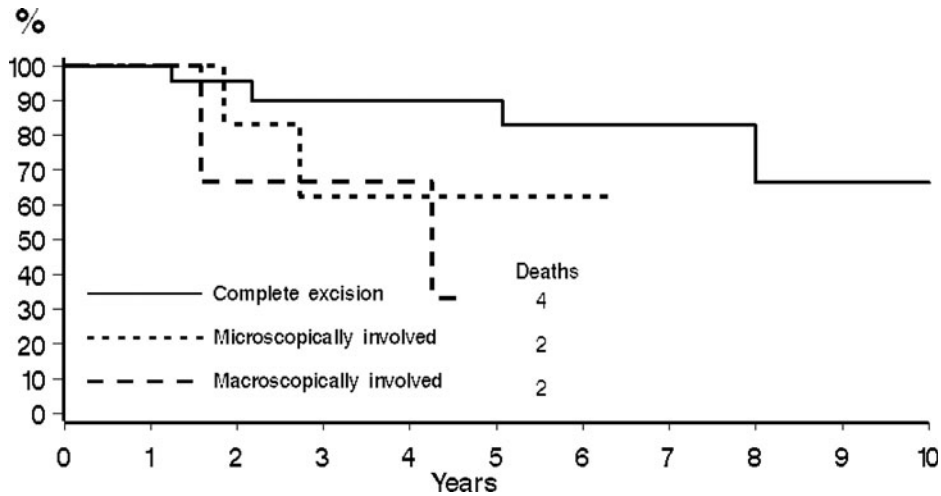

Figure 3. Overall survival by involvement of surgical margins.

https://doi.org/10.1017/S1460396910000178 Published online by Cambridge University Press

Table 3. Comparison of the results from this study with those from the literature

Study	Number of patients	RT dose/fractionation	5-Year local control rate	5-Year overall survival
This study	38	50–55 Gy/20 fractions	81.8% 95% CI: (60.9, 92.2)	78.5% 95% CI: (58.0, 89.8)
Chen et al.[1]	90	64 Gy (range 54–71 Gy)/32 fractions	92%	Not reported
Garden et al.[2]	198	60 Gy (range 50–69 Gy)/30 fractions	95%	Not reported
Gomez et al.[4]	59	63 Gy (range 52–70 Gy)/32 fractions	91%	87%
Khan et al.[8]	41	57.3 Gy	Not reported	72%
Iseli et al.[14]	87	62 Gy (range 15–72 Gy)/31 fractions	73.4%	75.5%
Gurney et al.[5]	33	50.4–79.89 Gy	94%	85%
Mendenhall et al.[6]	59	50–72 Gy (in 2 Gy fractions either daily or twice daily in a hyperfractionated regime)	94%	77%
Silverman et al.[13]	50	59.8 Gy (range 45–72 Gy in 1.8–2 Gy fractions)	84.5%	79.8%
Chunying et al.[7]	28	58 Gy (range 50–60 Gy)	89.8%	Not reported

CI, confidence interval; RT, radiotherapy.

Other series used post-operative radiation doses ranging from 50 to 79.89 Gy, given in 2 Gy fractions (Table 3). Chen et al. reported 90 patients who received post-operative radiotherapy to a mean dose of 64 Gy, with a median follow-up of 66 months. Compared to our cohort, a greater proportion of patients had T3 (20%) and T4 (26%) disease and involved surgical margins (63%), yet a superior 5-year LC rate of 92% was achieved.[1] Furthermore, the series by Gomez et al. (mean dose 63 Gy) also contained a higher proportion of patients with T3 (14%) and T4 (34%) disease and a 5-year LC of 91% was reported.[4] Both these studies support the use of 2 Gy fractionation over accelerated hypofractionation. However, Iseli et al. reported 87 patients (median dose 62 Gy) and the 5-year LC rate was 73.4%. This cohort included 44.4% T3 or T4 disease.[14] Mendenhall et al. reported 5-year LC of 94% in a cohort of 59 patients treated with either pre- or post-operative radiotherapy with varying dose-fractionation schedules: pre-operative RT, 50 Gy (range, 45 Gy–61.3 Gy); and post-operative RT, 67.8 Gy (range, 10.5 Gy–76.8 Gy), in either 2 Gy per fraction or a hyperfractionated regime treating twice daily.[6] It is difficult to compare this series with ours in view of the heterogeneity of the dose-fractionation schedules.

The possibility that AHRT over 4 weeks is associated with inferior outcome cannot be excluded. To achieve radiobiological equivalence with a 60 Gy in 30-fraction regime, there would need to be a significant degree of accelerated repopulation to realise any benefit from the shortened schedule. Alternatively, in the complete absence of accelerated repopulation, an α/β ratio of 0.5 Gy would be required to give equivalence to 60 Gy in 30 fractions (see Appendix 1 for calculation). It is possible that a combination of moderate accelerated repopulation and a slightly decreased α/β ratio would also render the schedules equivalent. Multicentre prospective randomised trials are unlikely to be performed given the rarity of this disease and its long natural history. Therefore caution should be exercised when using altered fractionation for this disease. Following completion of this study, the local institutional policy for ACC has been revised. In the presence of involved margins, a dose of 65 Gy in 30 fractions over 39 days is administered. In the absence of margin involvement, a

https://doi.org/10.1017/S1460396910000178 Published online by Cambridge University Press

dose of 60 Gy in 30 fractions over 39 days is administered.

It is possible that AHRT in the post-operative setting for ACC leads to an inferior outcome and we recommend using 2 Gy fractionation to a minimum dose of 60 Gy.

APPENDIX

To determine α/β of ACC if AHRT is equivalent to conventional fractionation in the absence of accelerated repopulation associated with ACC, the following equation is solved:

BED (biologically effective dose) hypofractionated regime without time correction = BED conventional regime

$$D_{\mathrm{h}}\left(\frac{1+d_{\mathrm{h}}}{\alpha/\beta}\right) = D\mathrm{c}\left(\frac{1+d_{\mathrm{c}}}{\alpha/\beta}\right)$$

where D_{h} = total dose hypofractionated regime = 50 Gy; d_{h} = dose per fraction hypofractionated regime = 2.5 Gy; α/β = unknown; D_{c} = total dose conventional regime = 60 Gy; d_{c} = 2 Gy

DISCLOSURE

P.S. received honoraria from Schering-Plough and A.H. received honoraria from Merck and meeting expenses from Roche and Sanofi-Aventis. The other authors declared no conflict of interest.

References

1. Chen AM, Bucci MK, Weinberg V, Garcia J, Quivey JM, Schechter NR, Phillips TL, Fu KK, Eisele DW. Adenoid cystic carcinoma of the head and neck treated by surgery with or without postoperative radiation therapy: prognostic features of recurrence. Int J Radiat Oncol Biol Phys 2006; 66: 152–159.
2. Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. Int J Radiat Oncol Biol Phys 1995; 32: 619–626.
3. Simpson JR, Thawley SE, Matsuba HM. Adenoid cystic salivary gland carcinoma: treatment with irradiation and surgery. Radiology 1984; 151: 509–512.
4. Gomez DR, Hoppe BS, Wolden SL, Zhung JE, Patel SG, Kraus DH, Shah JP, Ghossein RA, Lee NY. Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. Int J Radiat Oncol Biol Phys 2008; 70: 1365–1372.
5. Gurney TA, Eisele DW, Weinberg V, Shin E, Lee N. Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation. Laryngoscope 2005; 115: 1278–1282.
6. Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Hinerman RW, Villaret DB. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. Head Neck 2004; 26: 154–162.
7. Chunying S, Hu C, He S. The treatment results and prognostic analyses of 54 cases with adenoid cystic carcinoma originated from the major salivary glands. Proceedings of the 51st Annual ASTRO Meeting 2009. Abstract 2516.
8. Khan AJ, DiGiovanna MP, Ross DA, Sasaki CT, Carter D, Son YH, Haffty BG. Adenoid cystic carcinoma: a retrospective clinical review. Int J Cancer 2001; 96: 149–158.
9. Terhaard CH, Lubsen H Van der Tweel I, Hilgers FJ, Eijkenboom WM, Marres HA Tjho-Heslinga RE de Jong JM Roodenburg JL; Dutch Head and Neck Oncology Cooperative Group. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. Head Neck 2004; 26: 681–92; discussion 692.
10. Sanghera P, McConkey C, Ho KF, Glaholm J, Hartley A. Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2007; 67: 1342–1351.
11. Yeoh EE, Holloway RH, Fraser RJ, Botten RJ Di Matteo AC, Butters J, Weerasinghe S, Abeysinghe P. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a phase III randomized trial. Int J Radiat Oncol Biol Phys 2006; 66: 1072–1083.
12. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys 2002; 52: 6–13.
13. Silverman DA, Carlson TP, Khuntia D, Bergstrom RT, Saxton J, Esclamado RM. Role for postoperative radiation therapy in adenoid cystic carcinoma of the head and neck. Laryngoscope 2004; 114: 1194–1199.
14. Iseli TA, Karnell LH, Graham SM, Funk GF, Buatti JM, Gupta AK, Robinson RA, Hoffman HT. Role of radiotherapy in adenoid cystic carcinoma of the head and neck. J Laryngol Otol 2009; 123: 1137–1144.

https://doi.org/10.1017/S1460396910000178 Published online by Cambridge University Press