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Original Article

Radiotherapy for Tracheal–Bronchial Cystic Adenoid Carcinomas

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Abstract

Aims: Primary tracheal–bronchial adenoid cystic carcinoma (thoracic adenoid cystic carcinoma; TACC) is a rare and aggressive malignant tumour. Radiotherapy results have not been previously individualised in this setting.
Patients and methods: Records of 31 patients with TACC (74% tracheal and 26% bronchial) who received radiotherapy between February 1984 and September 2014 were retrospectively analysed.
Results: Surgical removal of the primary tumour was carried out for most (71%) patients, and 13/22 (59%) had R1 or R2 (1/22) margins. The mean tumour size was 4.1 cm, 10 (32%) had associated lymph node involvement and 13 (41%) had perineural invasion (PNI). Adjuvant and definitive radiotherapy were delivered for 22 (71%) and nine patients, respectively. The mean delivered dose was 62 Gy (40–70 Gy) and eight patients had a radiotherapy boost (mean 19 Gy, range 9–30 Gy, two with endobronchial brachytherapy). At a median follow-up of 5.7 years, the 5 year overall survival and progression-free survival (PFS) rates were 88% and 61%, respectively. There were three local relapses and 10 metastatic relapses (mean delay 3.2 years), resulting in 5 year local and metastatic relapse rates of 10% and 26%, respectively. The prognostic factors in the univariate analysis for both decreased overall survival and PFS were: age $\geq$50 years (hazard ratio 6.2 and 3.8) and the presence of PNI (hazard ratio 10.3 and 4.1); and for PFS only: a radiotherapy dose $\leq$ 60 Gy (hazard ratio 3.1). Late toxicities were: tracheotomy due to symptomatic tracheal stenosis ($n = 5$), G3 dyspnoea ($n = 4$), hypothyroidism ($n = 5$) and pericarditis ($n = 4$).
Conclusion: Radiotherapy dose may affect local control and the presence of PNI should be considered as an adverse prognostic factor. TACC irradiation conferred good local control rates, when comparing these results with historical series.

Key words: Cylindroma; Thoracic irradiation; Thorax; Trachea

Introduction

Tracheal–bronchial adenoid cystic carcinomas (thoracic adenoid cystic carcinomas; TACC) are rare tumours from the seroma glands of the bronchial wall. Primary tracheal tumours are rare and TACCs are, in order of frequency, the second most common tracheal malignant tumours after squamous cell carcinomas [1–4]. There is no known predisposing factor and the age at diagnosis varies between 20 and 70 years, with a peak incidence around 50 years [5,6]. These lesions are most often discovered late, while the endotracheal lumen is reduced by 75% or more. Submucosal extension may be important and perineural invasion (PNI) is common, which may partly explain late relapse occurrence, including pulmonary metastases [7]. Surgical resection is the backbone treatment for malignant tumours of the trachea, whenever possible. Complete resection is only achieved in 42–57% of cases and is associated with better survival [7–10].

In the absence of a randomised clinical trial, the benefit of irradiation is not formally proven. However, adjuvant

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radiotherapy is generally approved in TACC, especially if resection is not complete [8,11–16]. In the case of a tumour deemed unresectable or contraindication to surgery, definitive radiotherapy is proposed. Long-term complete responses have been observed and seem to be dose-related [17–19]. It is important to notify that most retrospective series are very heterogeneous, evaluating several tracheal tumour types (especially squamous carcinomas) treated by definitive irradiation with palliative or curative aim [9,17–21]. Specific thoracic TACC results are often not individualised. We report here our experience of TACC curative radiotherapy at our institution.

Patients and Methods

Patients

The details of 65 TACC patients were found in our centre's database. Patients were not included in this study if they had the following exclusion criteria: radiotherapy delivered outside our centre ($n = 14$), relapse or synchronous metastases ($n = 10$), absence of radiotherapy ($n = 6$) or extrathoracic location ($n = 4$). The data of 31 irradiated patients between February 1984 and September 2014 for a histologically proven tracheal or bronchial TACC were finally retrospectively analysed.

All patients had been referred to a multidisciplinary lung tumour board before treatment initiation. Radiotherapy dose prescription using 6 MV photons was adapted to the clinical situation (ideally, 45–65 Gy if adjuvant or 66–70 Gy if definitive). The gross tumour volume was expanded using 4–5 cm margins to generate their respective clinical target volumes. Radiotherapy was delivered through a 6 MV photon linear accelerator using two opposed beams fields with serial oblique 'off cord' cone-down fields. After radiotherapy completion, patients were assessed 3 months after the completion of treatment, with a physical examination and imaging studies every 3 months for 2 years, every 6 months until 5 years and every year after 5 years.

Toxicities

Patients were evaluated by chart review using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4) for acute toxicity and the Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scales (LENT SOMA) for late toxicity.

Statistical Analysis

The Mann–Whitney test was used to compare numerical values; the Fisher exact test was used to compare categorical variables. Follow-up was estimated using the reverse Kaplan–Meier method. Overall survival, progression-free survival (PFS), local relapse and distant relapse rates were estimated using the Kaplan–Meier method. Survival rates were defined as the time between the beginning of treatment and the first event. Survival curves were compared using the Log-rank test for the univariate analysis and in a multivariate ascending stepwise Cox regression for the multivariate analysis. Variables associated with a P value <0.2 were included in the multivariate analysis. In the Cox model, continuous variables were dichotomised. Statistical analyses were carried out using SPSS software, version 19. All reported P values are two-sided; $P < 0.05$ was considered significant.

Results

Patients and Treatments

Baseline patient and tumour characteristics are shown in Table 1. The median age was 49 years (range 25–70 years) and the patients were all in good general condition (more patients with a performance status of 1 in the non-operated subgroup). Most of the patients were women ($n = 24$; 77%) and were non-smokers ($n = 21$; 68%). The most frequent localisation was the cervical trachea (55%; $n = 17$). ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) was carried out for nine patients at diagnosis; 7/9 had primary tumour hypermetabolism.

Most (22/31: 71%) patients had a surgical resection. The resection margins were free (R0) in 36% (8/22, all tumours invading neighbouring structures) of the cases, microscopically invaded (R1) in 59% (13/22) and margins were macroscopically invaded in one case (R2). Lymph node dissection was carried out for 15/22 surgical patients (65%) and lymph node involvement was found in 66%. The mean tumour size was 4.1 cm (1.2–7 cm); 10 (32%) had associated lymph node involvement and 13 (41%) had PNI. Two patients had negative epidermal growth factor receptor (EGFR) tumour status.

Adjuvant and definitive radiotherapy were delivered for 22 (71%) and nine patients, respectively, at a mean dose to the gross tumour volume of 62 Gy (42–70 Gy) in 2 Gy fractions. Nine per cent received a dose ≤ 50 Gy, 26% a dose between 50 and 60 Gy and most (58%, $n = 18$) received a dose >60 Gy. Eight patients had a radiotherapy boost (mean 19 Gy, range 9–30 Gy), including two with endobronchial brachytherapy. Conformal three-dimensional radiotherapy was delivered to all patients except one, who received intensity-modulated radiotherapy (IMRT). There was no concurrent chemotherapy with radiation. Eight patients underwent endoscopic treatment to allow rapid clearance of the upper airway. One patient received adjuvant chemotherapy with adriamycin before irradiation.

Survival and Prognostic Factors

Eight patients had died at the last follow-up. With a median follow-up of 5.7 years (range 0.5–22.9 years), the 5 year overall survival rate was 88% (95% confidence interval 75–100%). The median overall survival was 13.5 years. In the univariate analysis, the presence of PNI and an age ≥ 50 years were associated with decreased overall survival, with

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