Radiotherapy and Oncology 109 (2013) 262–268

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Neutron therapy

Malignant salivary gland tumours: Can fast neutron therapy results point the way to carbon ion therapy?

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ARTICLE INFO

Article history:
Received 18 January 2013
Received in revised form 12 June 2013
Accepted 7 August 2013
Available online 14 September 2013

Keywords:
Salivary gland tumours
Neutron therapy
High LET radiation therapy
Carbon ions
Head and neck cancer

ABSTRACT

Background and purpose: To evaluate the outcome of malignant salivary gland tumours treated with neutron therapy to assess the potential for other high linear energy transfer (LET) beams.
Materials and methods: Neutrons at iThemba LABS are produced by the reaction of 66 MeV protons on a beryllium target. A median dose 20.4 Gy, in 12 fractions in 4 weeks or 15 fractions in 5 weeks, was given to 335 patients with 176 irresectable, 104 macroscopically residual and 55 unresected tumours.
Results: Locoregional control was 60.6% at 5 years and 39.1% at 10 years and DSS was 66.8% and 53.7% at 5 and 10 years respectively.
In the univariate analysis T4, >4 cm, high grade, squamous carcinoma, unresected and irresectable tumours, and positive nodes were significantly worse for LRC. In the multivariate analysis tumours >6 cm, squamous carcinoma, irresectable tumours and nodes were significantly worse for LRC. Tumours >6 cm, high grade, squamous carcinoma and nodes were significantly worse for DSS. Neither LRC nor DSS was influenced by age, sex, site, dose, fractionation or for initial or recurrent disease.
Conclusions: Neutron therapy appears to be the treatment of choice for macroscopically incompletely excised and irresectable salivary gland tumours with improved survival rates. Further improvement may be achieved with other high LET modalities with a superior dose profile, such as carbon ions.
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The increasing number of hadron therapy centres around the world and their use of carbon ion beams have resulted in a growing interest in high-linear energy transfer (LET) radiotherapy. Carbon ions combine the advantages of high-LET radiation with the superior ballistic properties of charged particles. The most commonly used high-LET therapy to date is neutron therapy. The rationale for using it for salivary gland tumours is based on Battermann's observations of growth delay of pulmonary metastases treated with neutrons relative to cobalt-60 radiation [1]. He derived a relative biological effect (RBE) of 8 for fractionated therapy to adenoid cystic carcinoma metastases compared with 3 for most normal tissues, implying a significant therapeutic gain for salivary gland tumours. The safe application of high-LET hadron therapy requires biologically driven treatment planning that has to be based on clinical data. We contribute to this pool of data by reporting the results of salivary gland tumours treated with neutron therapy at iThemba LABS (formerly National Accelerator Centre), South Africa, over the last 20 years.

Materials and methods

iThemba LABS is the only heavy particle therapy facility in the Southern Hemisphere. The main accelerator is a 200 MeV separated-sector cyclotron. It is the only facility in the world where both high-energy neutrons and high-energy protons are used for patient treatment and also provides facilities for basic and applied research and the production of medical radionuclides. Neutron therapy is available on Tuesdays, Wednesdays and Thursdays each week. Most patients are referred through one of the two local university teaching hospitals; Groote Schuur Hospital (GSH)/University of Cape Town and Tygerberg Hospital (TBH)/University of Stellenbosch.

Technical and physical aspects

The neutron therapy facility incorporates an isocentric gantry – a moving floor permits full ~185° rotation [2]. Variable rectangular field sizes between 5.5 × 5.5 cm^2 and 29 × 29 cm^2 at a source–axis distance of 150 cm. are available. Neutrons are produced by the reaction of 66 MeV protons on a 1.96 cm thick beryllium target. Downstream of the target are several beam modification devices: steel flattening filters, tungsten wedge filters and a polyethylene

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http://dx.doi.org/10.1016/j.radonc.2013.08.013

hardening filter. This results in similar depth dose characteristics to an 8 MV X-ray beam. A novel 12-cm thick steel post-collimator multiblade trimmer is used for conformal field shaping [3]. The absorbed doses reported here are the total absorbed doses, neutron + photon. The photon component comprises less than 6% and can be neglected as the neutron RBE is about 3.

Clinical aspects

Patients eligible for neutron therapy are those with irresectable tumours, macroscopic residual disease after surgery and resectable tumours where the functional status associated with resection was considered to be suboptimal. From February 1989 until December 2008, 401 patients were treated with curative intent, and they have been followed up until 7 February, 2012. This retrospective analysis is confined to 335 patients with malignant tumours that received a full therapeutic dose to the whole of the target volume with neutron therapy only. There were 174 males and 161 females, with an age range from 8 to 96 years, median 58 years. Tumour characteristics are shown in Table 1. Squamous cell carcinomas of the parotid and submandibular glands were included if this appeared to be the primary site. The histology was reviewed by JH. Tumours of major salivary glands were classified according to the 2002 UICC/AJCC system. Tumours of minor salivary glands were classified according to the respective sites [4].

Treatment details

Patients were CT scanned in an immobilising head cast with 5 mm thick slices at increments of 5 mm for 3D planning. Prior to 2000, treatment planning was done using a Theraplan planning system at GSH and a General Electric (GE) Target Planning system at TBH. After 2000 an in-house developed treatment planning system, using a pencil beam model, was used [5,6]. This system uses VIRTUOS, developed by Deutches KrebsForschungZentrum (DKFZ), as a front end for the bulk of the treatment planning tasks [7]. Treatment was delivered with source-skin distance (SSD) set-ups until 2000 and thereafter isocentric set-ups were used. Prior to the introduction of the multiblade trimmer in 2000, 12-cm thick tungsten blocks provided the final beam shaping.

All neutron doses were prescribed to a minimum tumour dose encompassing the planning target volume (PTV). Up until 2002 the majority of patients received a median total absorbed dose of 20.4 Gy in 12 fractions, over 4 weeks. For those patients who had a delay in completing the prescribed course it was noticed that acute morbidity was reduced. Based on this clinical observation together with the results from radiobiological experiments in our neutron beam which showed that there was in fact repair [8], the fractionation schedule was adjusted to 20.4 Gy in 15 fractions over 5 weeks in 2002. Node positive patients had levels II, III and IV included in the PTV and these levels were treated adjunctively, with 14–15 Gy in 3–5 weeks, in 25% of node negative patients. The dose to the spinal cord was restricted to 12 Gy to the lateral cord and since 1992 the brain dose has been limited to 13 Gy.

Complications were scored using the RTOG scoring system [9].

Statistical analysis

Loco-regional control and disease-specific survival rates by key variables were explored using the Kaplan–Meier life table analysis. Kaplan–Meier graphs are shown to 10 years of follow-up (this period covers approximately 90% of failures). The log rank test was used to evaluate statistical significance of differences between curves for the full dataset. Hazard Ratios (HR) and their 95% confidence intervals (CI's) were estimated using Cox proportional hazards modelling to examine the magnitude of associations between variables. All HRs labelled "crude" are adjusted for age in single years and sex and are referred to as univariate analyses throughout the text. For multivariate analyses, all clinically relevant variables (see Table 2) were included in the model. The 95%CI's for all proportions, rates and HRs are shown in parentheses. *P*-values were two-sided and considered significant if $p \leqslant 0.05$. All analyses were performed using Stata software, version 12.1 (Stata Corp LP, 4905 Lakeway Drive, College Station, TX 77845, USA).

Table 1
Characteristics of malignant salivary gland tumours.

Site		335
Parotid gland		160
Submandibular gland		26
Oral cavity and oropharynx		90
Hard palate	32	
Soft palate	19	
Tongue	17	
Floor of mouth	8	
Buccal mucosa	6	
Tonsil	3	
Alveolus/mandible	4	
Interalveolar space	1	
Paranasal sinuses, nose, nasopharynx		51
Maxillary antrum	35	
Ethmoid sinus	1	
Nasal cavity	9	
Nasopharynx	6	
Other		8
Trachea	6	
Larynx	1	
Lacrimal gland	1	
Histology		335
Low Grade		57
Low grade mucoepidermoid carcinoma	25	
Low grade polymorphous adenocarcinoma	22	
Acinic cell carcinoma	10	
Adenoid cystic carcinoma		108
High Grade		143
Adenocarcinoma NOS	60	
High grade mucoepidermoid carcinoma	47	
Undifferentiated carcinoma	13	
Myoepithelial carcinoma	14	
Carcinoma ex pleomorphic adenoma	9	
Squamous cell carcinoma		21
Other		6
Basal cell adenocarcinoma	1	
Carcinoma NOS	2	
Oncocytic carcinoma	2	
Ductal carcinoma	1	
Disease status		
Initial disease		279
Recurrent disease		56
Surgical status		
Irresectable		176
Macroscopic residual		104
Unresected		55

Classification				Size	All	Macroscopic residual
T1	4	N0	247	0–2 cm	48	40
T2	37	N1	42	<2–4 cm	80	37
T3	83	N2	41	<4–6 cm	88	14
T4	211	N3	5	>6 cm	119	13
Total	335		335		335	104

Results

Local control and survival

Local control (LC) is defined as no evidence of clinical or radiological progression of disease and loco-regional control (LRC) applies to both the primary and lymph nodes. Disease specific