Treatment of Parotid Gland Malignancies with Neutron Radiotherapy – Experience of a tertiary hospital in South Africa

by

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Declaration

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Abstract

Background: Success rates in the treatment of salivary gland malignancies are associated with completeness of surgical resection with or without postoperative radiotherapy. For patients with unresectable tumours, radiotherapy is an option to attempt to gain local control and improve survival. Different modalities of radiotherapy are available and fast neutrons represent a form of radiotherapy effective in controlling locally advanced salivary gland malignancies. We report on 22 patients treated for locally advanced parotid gland malignancies at iThemba Laboratory for Accelerator Based Sciences via a tertiary institution in Cape Town, South Africa.

Methods: Records of patients with unresectable parotid gland malignancies treated with neutron radiotherapy at a tertiary institution between January 1991 and December 2012 were reviewed retrospectively. Twenty-two patients were eligible for statistical analysis.

Results: Complete, partial and no response rates were 64%, 14% and 22%, respectively. Of the 14 patients with a complete response, 3 recurred with the earliest recurrence being at 18 months. Locoregional control was 80% and 69% at 2 and 5 years respectively. Twelve out of the 22 patients died post treatment. Overall survival at 2 years was 40% and at 5 years 35%. Seven cases of CTCAE grade 3 and above late toxicities were observed. These included bone necrosis, eardrum perforation and skin ulceration.

Conclusions: Treatment modality of this group of patients depends on availability. Response rates of parotid gland malignancy to neutron radiotherapy in this small cohort are comparable to historical controls.

Key words: neutrons, radiotherapy, salivary gland, parotid gland, irresectable, macroscopic residual disease

Abstrak

Agtergrond: Die suksesvolle behandeling van speekselklier maligniteite word deur die volledigheid van chirurgiese reseksie bepaal. Sukses is onafhanklik van adjuvante radioterapie. In gevalle waar 'n tumor nie-resekteerbaar is nie, is radioterapie 'n opsie om plaaslike beheer en verbeterde oorlewing te verkry. Verskeie radioterapie modaliteite is beskikbaar vir bestraling van hierdie maligniteite. Vinnige neutrone is 'n effektiewe opsie in die behandeling van plaaslik gevorderde speekselklier maligniteite. Hierdie verslag vervat die inligting van 22 pasiënte wat

vir lokaal gevorderde parotisklier malignitieite te iThemba Laboratorium, Kaapstad behandel is.

Metode: Pasiënt rekords is retrospektief nagegaan. Gevalle het gestrek vanaf Januarie 1991 tot-en-met Desember 2012. Slegs gevalle van nie-resekteerbare parotis maligniteit is ingesluit. Twee-en-twintig pasiënte het aan die kriteria van die studie voldoen en het deel van die statistiese analise uitgemaak.

Resultate: Volledige-, gedeeltelike- en geen respons koerse was 64%, 14% en 22% onderskeidelik. Drie van die veertien pasiënte wat aanvanklik volledig gerespondeer het, het herhaling van siekte ontwikkel. Die vroegste van hierdie herhalings was op 18maande. Plaaslike beheer was 80% en 69% teen twee- en vyf jaar onderskeidelik. Twaalf van die 22 pasiënte in die studie het na afloop van behandeling afgesterf. Algehele oorlewing teen 2 jaar en 5 jaar was 40% en 35% onderskeidelik. Graad 3 en hoër CTCAE chroniese newe-effekte is in sewe gevalle waargeneem. HIerdie newe-effekte het been nekrose, timpaniesemembraan perforasie en vel ulserasie ingesluit.

Gevolgtrekking: Gebruik van die behandelingsmodaliteit beskryf in hierdie studie, word bepaal deur die beskikbaarheid daarvan. In die betrokke kohort is die respons koers van parotis maligniteite tot neutron terapie vergelykbaar met dié van historiese kontrole groepe.

Introduction

Parotid gland malignancies are rare and constitute less than 1% of all cancers. In South Africa, they hold 32nd and 34th places in cancer incidence for men and women, respectively.[1] The cornerstone of management of salivary gland malignancies is surgery with or without postoperative radiotherapy.[2–4] However, the parotid gland has critical structures that traverse it, such that even tumours in their early stages can be deemed unresectable if they are intimately intertwined with these critical structures. For instance, when the facial nerve is in close proximity to a tumour, radical resection could lead to great morbidity.

There are currently various treatment options available for unresectable or macroscopic residual tumours to induce local control and improve survival. These include neutron radiotherapy (RT), photon RT, stereotactic RT, carbon ion therapy, brachytherapy and boron neutron capture therapy (BNCT).[5–11] The Radiation Therapy Oncology Group/Medical Research Council (RTOG/MRC) landmark trial of the 1980s showed a superior local control (56% vs. 17% at 10 years) for unresectable salivary gland malignancies if neutron RT was used versus photon RT, though this did not confer a survival advantage.[5,12] Other reports support the use of photon RT in this setting.[10,13]

The high relative biologic effectiveness (RBE) of neutron radiotherapy makes it favourable for use in radio-resistant tumours such as salivary gland malignancies.[14] One of the properties of neutron radiotherapy that enhances its RBE is its high linear energy transfer (LET). This means it has a dense pattern of ionisation and induces clusters of DNA double-strand-breaks in tumour cells, which are more difficult to repair. Neutron radiotherapy also has a low oxygen enhancement ratio (OER).[15] It is, therefore, able to effectively obliterate large tumours with hypoxic centres that are typically radio-resistant, as it is not dependent on oxygen to ‘fix’ the damage it causes. These properties make the lethality of neutron radiotherapy independent of cell cycle phase, which is known to vary radio-sensitivity.

The aim and objectives of this study was to review the treatment outcomes of a population treated for malignancies of the parotid gland with modern high-energy neutron RT at iThemba LABS via a tertiary institution in South Africa, describe the demographics and compare the local experience to that found in literature. It must be acknowledged that the majority of patients were part of a larger study of

335 patients on malignancies of minor and major salivary gland malignancies treated with neutron radiotherapy that was reported by Stannard et al[16] and the findings are described later in the discussion section.

Methodology

Patients and methods

Between January 1991 and December 2012, 25 patients falling under the drainage area of Tygerberg Hospital were documented as having been treated for malignancies of the parotid gland with neutron RT at iThemba Laboratory for Accelerator Based Sciences (LABS) in Cape Town. The indications for neutron RT, as per departmental protocol, were macroscopic residual and unresectable, as well as, inoperable patients due to various anaesthetic risks. A retrospective review of medical records of these patients was conducted. Patients were identified from the iThemba LABS database and verified with physical files in the Tygerberg Hospital's head and neck oncology clinic. Each patient file and radiotherapy treatment chart was reviewed to establish eligibility for inclusion in the study. The patients were restaged according to the 7th edition of tumour node metastasis (TNM) staging of the American Joint Committee on Cancer (AJCC)[17], and the toxicities were graded according to the Common Terminology Criteria For Adverse Events v4.0 (CTCAE).[18] Inclusion criteria were: Tygerberg patients with unresectable or macroscopic residual tumours or inoperable patients; patients referred from Tygerberg Hospital; at least 1 year post-treatment at the time of data collection; histologically confirmed malignant tumours of parotid gland. Exclusion criteria were: patients previously treated with photons for head and neck tumours; patients treated with mixed beam neutron and photon/electrons; children, defined as patients below the age of 18 years; patients' charts with vital information missing.

Three patients were excluded based on the study criteria for the following reasons. The first patient was 13 years old at time of treatment, the second had previously been treated with photon radiotherapy, and the third was found to be a pleomorphic adenoma on file review. Data collection and analysis was performed for the remaining 22 patients.

The clinical neutron beam is produced by a p(66)/Be(40) source that is used in combination with a hydrogenous filter to remove the low-energy components of the neutron spectrum. The 66 MeV proton beam used for this application is obtained from a separated-sector cyclotron capable of accelerating protons to maximum energy of 200 MeV. Before 2000, a General Electric (GE) Target Planning system was utilised, and afterwards the 3-D treatment planning was done by a dose calculation system developed in-house.[19] The platform of this modern treatment planning facility is the VIRTUOS system developed by the Deutsches Krebsforschungszentrum (DFKZ).[20] Anterior and posterior wedged fields were used with an additional lateral field if the tumour growth was deep seated. The patients were treated 3 times per week as per availability of the neutron beam and received a total of 20.4 Gy with the exception of 1 patient who could not complete treatment and received 18.7 Gy. The organs at risk (and respective tolerances) were defined as spinal cord (12 Gy), brain (13 Gy) and lens (1 Gy, then 2 Gy in later years). Due to local clinical experience (i.e. patients that had a longer treatment period due to delays were noted to have fewer acute side effects) and results from radiobiological experiments, the fraction size was reduced from 1.7 Gy to 1.36 Gy in 2002 resulting in extension of treatment time from 4 weeks to 5 weeks (i.e. increase in number of fractions from 12 to 15).[21]

Patients were followed up at 6 weeks post completion of neutron RT, 3-4 months thereafter for 2 years, and then at 6-12 months. For some patients who came from geographically distant areas, there was a system of communication with patients and their local general practitioners for detailed clinical feedback. CT-scans of the treated region were done as clinically indicated.

Statistical analysis

Locoregional control and overall survival were computed and represented on Kaplan Meier graphs by the Stellenbosch University Biostatistics department using STATA 14 statistical package.

Results

Overview

In this chart review, there were equivalent numbers of patients above and below the age of 60 years (Table 1). Nine out of 22 patients were female. Only 36% of the patients had nodal involvement. Adenocarcinoma was the most commonly treated histological subtype. Half the patients had 7th cranial

nerve involvement. Follow up period ranged from 1 month (for a patient who died shortly after treatment) to a maximum of 232 months (for one patient who remained cancer free). There were no patients with recurrent tumours and it must be noted that they were not deliberately excluded.

Locoregional control and survival

As summarised in Table 1, the disease was localised in 9% (2/22) of the patients, with spread to regional nodes seen in 91% (20/22). Sixty-four percent (14/22) of the cohort attained complete response (CR) at the primary site (Table 2). For those with nodal involvement (N+) at baseline, 50% had a complete response of the nodes. Locoregional control was 80% and 69% at 2 and 5 years respectively (Figure 1). Twelve of the 22 patients died in the study period. The overall survival at 2 years was 40% and 35% at 5 years (Figure 2). Patients with persistent and recurrent disease had worse outcomes as would be expected.

Treatment-related side effects

Seven toxicity events of CTCAE grade 3 or above were observed in 6 patients (Table 2). One patient had both bone necrosis and skin ulceration. Two other patients had bone necrosis only and the remaining 3 had chronic otitis. One of the patients with bone necrosis of the mandible underwent reconstructive surgery.

Table 1. Patient and tumour characteristic

Characteristics n=22	%	n
Age (years)		
<60	50	11
≥60	50	11
Sex		
Male	59	13
Female	41	9
Target lesion		
Primary only	64	14
Primary and nodes	36	8
Histology		
Acinic cell carcinoma	9	2
Adenocarcinoma	44	9
Adenocystic carcinoma	9	2
Mucoepidermoid high grade carcinoma	5	1
Mucoepidermoid low grade carcinoma	5	1
Myoepithelial carcinoma	5	2
Undifferentiated carcinoma	18	4
Squamous cell carcinoma	5	1
7th cranial nerve involement		
Involved	50	11
Not involved	27	6
Status unknown	23	5
Tumour size (cm)		
0-2	27	6
2-4	9	2
4-6	27	6
> 6	37	8
T stage		
T1	0	0
T2	5	1
T3	9	2
T4a	81	18
T4b	5	1
N staging		
N0	9	2
N1	86	19
N2a	5	1
N2b-3	0	0
AJCC 2010 staging		
Stage II	5	1
Stage III	9	2
Stage IVA	81	18
Stage IVB	5	1
Surgical status		
Macroscopic residual	36	8
Irresectable	46	10
Medically inoperable	18	4

Table 2. Treatment outcomes

Parameter		%	n
Primary response	n=22		
Complete		64	14
Partial		14	3
No response		22	5
Node response	n=8		
Complete		50	4
Partial		13	1
No response		37	3
Late toxicities: CTCAE grade 3 or above	n=22		
Bone necrosis		14	3
Ear		14	3
Skin		5	1

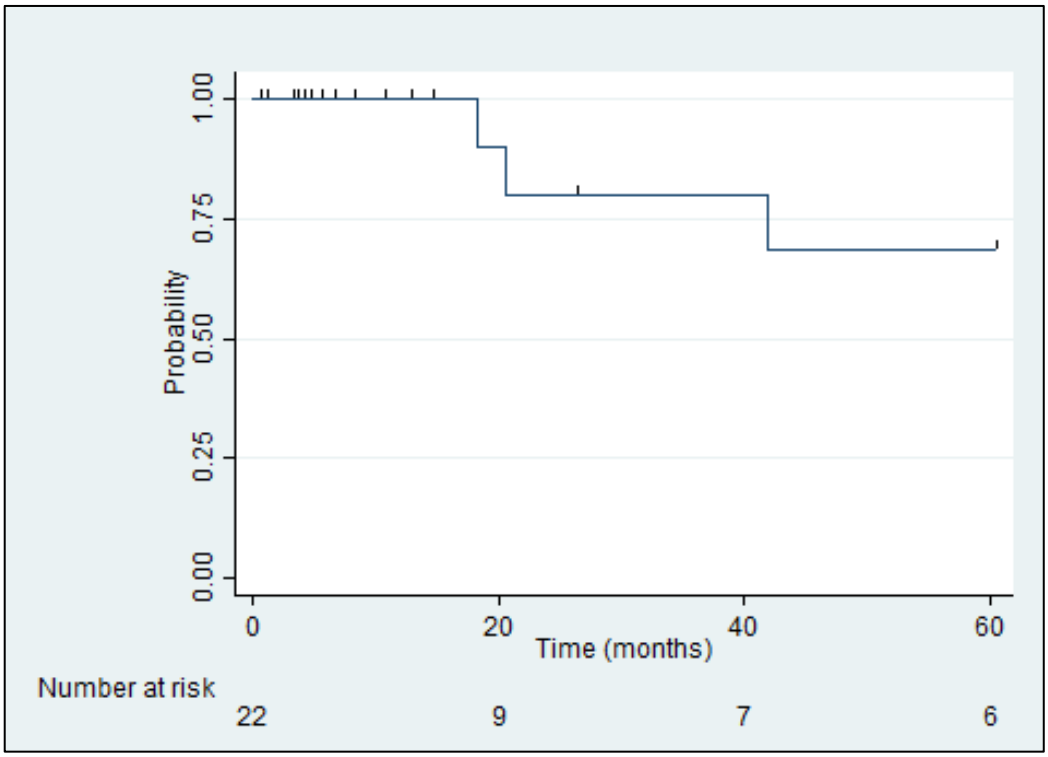

Figure 1. Kaplein Meier curve showing locoregional control

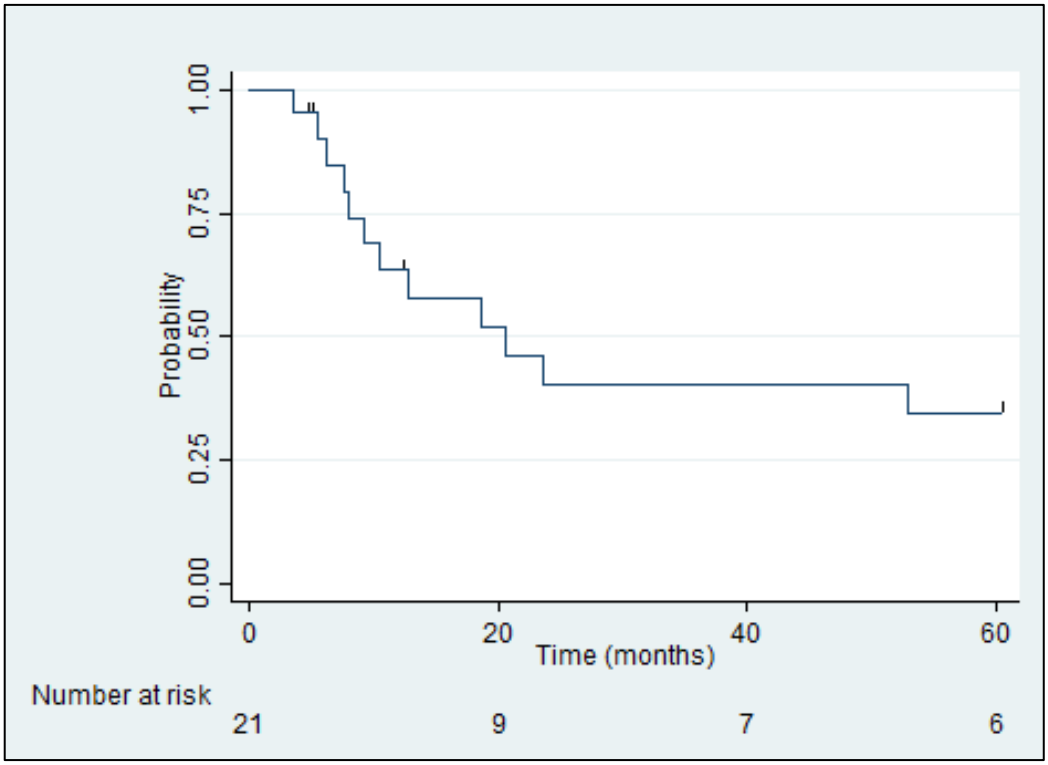

Figure 2. Kaplein Meier curve showing overall survival.
*Patient who died within a month of treatment not picked by STATA 14

Discussion

The aim of this study was to describe the outcomes of treatment of patients with parotid gland malignancies with neutron RT at iThemba LABS via Tygerberg Hospital over a 22-year period. Our objectives were to report patient characteristics, treatment response, locoregional control rates, survival and toxicity rates in our cohort of patients, and to review the findings of other studies on salivary gland malignancies published in the literature.

The majority of patients in this review, which included only patients with parotid gland malignancies, had adenocarcinoma. In the larger cohort of 335 patients reported by Stannard et al[16], to which most of the patients in this study belong, only 18% were adenocarcinomas whereas 32% were adenoid cystic carcinomas and 21% mucoepidermoid carcinomas. Rice[22], in a review of malignant salivary gland carcinomas, named mucoepidermoid carcinomas as the most common parotid gland malignancies with adenoid cystic as the second most prevalent. In a series of 279 patients reported by Douglas et al[23], the most prevalent histological subtype was adenoid cystic carcinoma (68%) followed by mucoepidermoid carcinoma (11%). Adenocarcinoma was represented in only 10% of the cases. Due to the fact that all but

2 of tumours of the minor salivary glands were adenoid cystic carcinomas, histological analysis was performed on the major salivary gland malignancies. Of these 142 patients, adenoid cystic carcinoma was still the most prevalent (37%) followed by adenocarcinoma (19.7%) and mucoepidermoid carcinoma (19%). Statistical analysis was not performed due to small numbers in other histological subtypes but it was noted that adenocarcinomas had highest rate of metastasis with associated poor survival, which manifested as excellent local control rates.

The landmark RTOG trial which established the superiority of neutron RT over photon RT for unresectable salivary gland malignancies found that the 2- and 10- year locoregional control was 67% and 62%, respectively, and the 2- and 10- year overall survival was 56% and 15%, respectively.[5,12] Despite the positive finding of this trial and other studies, neutron RT has not found worldwide use due to the high costs associated with establishing and maintaining such a centre. Douglas et al[24] published on the Seattle experience of the treatment of adenoid cystic salivary gland malignancies with neutron radiotherapy. They found a 5-year actuarial overall survival of 71% with the associated cause-specific survival of 77%. On multivariate analysis, base of skull involvement, positive lymph node status, limited biopsy only, recurrent tumour status were associated with poorer cause-specific survival. The five-year loco-regional control for the whole cohort was 59% whilst the five-year actuarial locoregional control rate for patients with gross residual disease was 57%. On multivariate analysis, resection status (biopsy only) and base of skull involvement were statistically significant for poorer loco-regional control.[24] A subsequent retrospective analysis was conducted by the group on 279 patients with salivary gland malignancies of all histological subtypes treated with fast neutron radiotherapy.[23] Their cohort of patients had all been treated with radical intent of which 263 had macroscopic disease. The 6-year actuarial cause-specific survival was 67%. Multivariate analysis revealed 1998 AJCC group stages I/II disease, minor salivary sites, lack of base of skull invasion and primary disease were statistically significant for superior survival outcomes. Six-year actuarial locoregional control was 59%. Factors, which were significant for superior locoregional control on multivariate analysis, were lack of base of skull involvement, size 4 cm or smaller, no previous radiotherapy and prior surgical resection. The 16 patients with no evidence of microscopic disease had 100% rate of local control. Stannard et al[16] reported on 335 patients with salivary gland malignancies treated with neutron RT. The 5- and 10-year locoregional control were 60.6% and 39.1% and overall

survival were 51% and 37.4%, respectively. Tumours > 6 cm, squamous carcinoma, irresectable tumours and positive nodes were statistically significant on multivariate analysis for poor locoregional control. The 5- and 10- year disease specific survival (DSS) were 66.8% and 53.7%, with tumours > 6 cm, high grade, squamous carcinoma and positive nodes bearing a negative influence. Of note, age, sex, site, dose, fractionation, initial or recurrent disease had no statistically significant consequence to locoregional control or disease specific survival.

The use of photon RT with adaptation of techniques and treatment delivery in the treatment of unresectable salivary gland malignancies has been reported.[10,13] One of these strategies is accelerated fractionation of photon RT, which increases the tumour cell kill yet improving normal tissue sparing. The results presented by Wang et al[10] are a good of example the success of accelerated fractionation of photon RT, obtaining 85% and 83% for 5-year actuarial local control and survival rates, respectively. The development of 3-D conformal radiotherapy (3-DCRT) and intensity modulated radiation therapy (IMRT) allowed photon RT to be delivered to higher doses for effective tumour control and more normal tissue sparing. Spratt et al[13] reported on 27 patients who were treated with photon RT (60 – 70 Gy), using conformal techniques. They attained 2- and 5-year locoregional control rates of 65% (CI: ±21.4%) and 47% (CI: ±21.6%), respectively. Median overall survival was 2.14 years, with 2- and 5-year survival of 50% (CI: ±19.0%) and 29% (CI: ±16.6%), respectively.

Carbon ion RT, which has the high tumourcidal properties similar to neutron RT and useful dose range advantage of proton RT is gaining favour.[8,25–28] Schultz-Ertner et al[28] reported on 63 patients who were treated with either photon RT (stereotactic radiosurgery or IMRT) alone or photon RT with carbon ion RT boost. The photon + carbon RT arm had better outcomes (4-year locoregional control of 77.5% *vs.* 24.6%), but this did not translate into a survival benefit (75.8% vs. 77.9%). The severe late toxicity profile was also good at a rate of 2%. Jensen et al[25] later reported on outcomes of 309 patients with adenoid cystic carcinomas of the head and neck treated with IMRT and carbon ion RT boost. Local control rates were 84% and 59% at 3 and 5 years, respectively, with a grade 3 or above toxicity rate of 1%. Table 3 summarises a few studies related to treatment of salivary gland malignancies with radiotherapy.[5,10–13,16,23-25,28–36]

While pioneering work conducted on earlier machines showed adverse toxicity outcomes with the use of neutron radiotherapy, subsequent studies showed modest toxicity rates when patients were treated in a clinical setting.[16,23,36] More conformal techniques have improved treatment outcomes. The toxicity rates between neutrons and photons are comparable whereas carbon ions have a superior toxicity profile.

Burmeister et al[37] reported on the commissioning of intensity modulated neutron radiotherapy (IMNRT) and found that plan quality was superior to conventional neutron radiotherapy, but still inferior to photon RT plans. Studies that utilised carbon ion and brachytherapy have shown low severe late toxicity rates.[11,25,28]

Study limitations

The study cohort was small and of the patients identified some were excluded due to incomplete records. Cause of death was also not established in some patients, as they died at sites peripheral to the study centre.

Conclusions

The experience of treating patients falling in the drainage area of Tygerberg Hospital, who have parotid gland malignancies with neutron radiotherapy, has been documented. The locoregional control and survival results achieved in this study are comparable to those found in literature, though no conclusions can be drawn due to the small number of patients in the study. There is evidence to support the efficacy and safety of different modalities of treatment of salivary gland malignancies. Depending on facilities present in the patient's vicinity, the best treatment option must be offered. More conformal techniques in neutron RT have been developed and they yield better results in the management of unresectable salivary gland cancers.

Table 3. Summary of outcomes of treatment of salivary gland malignancies with different modalities

Author, year	Cohort	Modality	Locoregional control	Local control	Overall survival	Grade ≥3 toxicity rate
Henry et al, [29]1979	65	Neutron Photon Mixed		33.3% (2/6) 63.2% (12/19) 100% (5/5)		
Kaul et al,[30] 1981	30	Neutron Mixed		73% (11/15) 27%(4/15) min. FU 1 year		
Saroja et al, [31]1987	113 61 major 52 minor	Neutron		5-year: 57% (major gland) 51% (minor gland)	5-year: 38% (major gland) 46% (minor gland)	17.7% (20/113) (RTOG/ EORTC)
Catterall et al,[32] 1987	65	Neutron		74% (48/45)		
Duncan et al,[33] 1987	28	Neutron		60.0% (15/25) long term	Median: 19.5 months (1-84 months)	24% (4/17)
Griffin et al,[34] 1988	32	Neutron	5-year: 69%		5-year: 33%	16% (5/32) (RTOG/ EORTC)
Griffin et al,[5] 1988	32	Neutron Photon	2-year: 67% 17%		2-year: 62% 25%	18.4% (12/65) Event taken per site (RTOG/ EORTC)
Wang et al,[10] 1991	24	Photon		5-year: 65%	5-year:83%	
Laramore et al,[12]1993	32	Neutron Photon	10year: 56% 17%		10year: 15% 25%	15.4% (4/26) 0% (RTOG/ EORTC)
Douglas et al,[36] 1996	72	Neutron	median 54months		5-year: 31-67%	13.9% (10/72) (RTOG/ EORTC)
Huber et al,[35] 2001	75	Neutron Photon Mixed		5-year: 75% 35% 35%	Median: 88 months 104 months 60 months	17%(5/29) 4%(1/25) 10%(2/21) (RTOG/EORTC)
Douglas et al,[24] 2003	279	Neutron		6-year: 59%	6-year: 71%	6 year: 10% (RTOG/EORTC)

Schultz-Ertner et al,[28] 2005	63	Photon Photon + Carbon	2- / 4-year: 72%/25% 78% / 78%		2- / 4-year: 78% / 78% 87% / 76%	2%(1/63) (CTCAE,V3.0)
Stannard et al,[16] 2013	335	Neutron	5-year: 60.6%(CI 53.0-67.2) 10-year: 39.1%(CI 30.2-47.9)	5-year: 58.6%(CI 51.1-65.4) 10-year: 45.9%(CI 36.5-54.8)	5-year: 51%(CI 44.3-57.3) 10-year: 37.4%(CI 29.8-44.9)	6year: 11.1% 8.9% (30/335) (RTOG)
Spratt et al,[13] 2014	27	Photon	2-year: 65%(CI +/-21.4%) 5-year: 47%(CI+/ -21.6%)	2-year: 69%(CI +/- 21%) 5-year: 55%(CI+/- 24.2%)	2-year: 50%(CI+/- 19.0%) 5-year: 29%(CI+/- 16.6%)	11%(3/27) (CTCAE, v4.0)
Zhang et al,[11] 2014	60	Brachy-therapy (Iodine-125)		Surg+brach 1-year: 87.5% 3-year: 82.4% 5-year: 78.6% Brachy alone: 1-year: 81.5% 3-year: 67.5% 5-year: 53.8%	Surg+brachy 1-year: 97.5% 3-year: 86.5% 5-year: 86.5% Brachy alone: 1-year: 82.7% 3-year:70.0% 5-year:61.2%	3%(2/60) (RTOG/ EORTC)
Jensen et al,[25] 2015	309	Photon + Carbon		3-year:83.7% 5-year: 58.5%	3-year: 88.9% 5-year: 74.6%	1%(3/309) (CTCAE, v4.0)
Current study	22	Neutron	2yr 80% 5yr 69%		2yr 40% 5 yr 34%	27% (6/22) (CTCAE, v4.0)

Abbreviations: CI = confidence intervals; RTOG = The Radiation Therapy Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; CTCAE = Common Toxicity Criteria for Adverse Events; Max. FU = maximum follow up period

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Ethics approval

Ethics approval was obtained from Stellenbosch University Health Research Ethics Committee 1, Ethics reference number S14/09/197, and facility permission was obtained from Western Cape Department of Health South Africa.

Ethics, consent and permissions

Waiver on consent was granted based on the retrospective nature of the study and difficulty in accessing patients.

Competing interests

None of the authors have competing interests with relation to this study.

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Literature Review

Treatment of Parotid Gland Malignancies with Neutron Radiotherapy – Tygerberg Hospital Experience

Thesis submitted in partial fulfilment of the requirements for the degree of Master of Medicine
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Search methods

EBSCO host, PubMed and Scopus were the search engines utilised in the literature search as they cover a wide database of peer-reviewed work.

The key words/phrases were: *parotid gland, malignancies, cancer, neutron radiotherapy* and *photon radiotherapy.*

Selection of Articles

Articles reporting studies or trials on the use of neutron radiotherapy in general, neutron radiotherapy in head and neck cancers, neutron and photon radiotherapy in parotid gland malignancies were selected and reviewed for relevance pertaining to the study question. Reports from conferences were also included in the review. Statistical methods and their suitability, as well as, the significance of reported results were appraised. A total of 88 articles, book chapters, reports and websites were reviewed and 56 were selected for inclusion in the literature review. Information from the body of literature was organised into the following themes associated with the subject question:

1. Introduction;
2. Rationale for the use of neutron radiotherapy in salivary gland malignancies;
3. Evidence supporting the use of neutron radiotherapy in salivary gland malignancies;
4. Other radiotherapy modalities used in the management of salivary gland malignancies; and
5. Conclusion/Summary of literature review

1. Introduction

Malignancies of the salivary gland (ICD-10 O-2 C7.0, C8.0-C8.9)[1] are rare and constitute less than 1% of all cancers. According to the latest report of the South African National Cancer Registry, they hold the 32nd place in cancer incidence for men and 34th place for women, and

constituting 0.36 and 0.28% of all cancers for each sex, respectively.[2] Globally, a similar frequency ranging from 0.2 - 0.5% is seen for both sexes.[3]

According to the World Health Organisation (WHO) classification of salivary gland tumours[4], there are 17 named different epithelial types of carcinoma, of which the most common are mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinomas, acinic cell carcinoma, squamous cell carcinoma, basaloid carcinoma and malignant mixed tumour (carcinoma in pleomorphic adenoma). The tumours are also grouped into grades depending on how similar in architecture they are to the native cells, namely low, intermediate and high grade and this is reflective of the inherent nature of the tumour.[5] Mucoepidermoid carcinomas have been described as the most common subtype of salivary gland malignancies with adenoid cystic being the second most common.[6] Classically, mucoepidermoid carcinomas are divided into low and high grade. In large series of 279 patients reported by Douglas et al[7] and 335 patients reported by Stannard et al[8] adenoid cystic carcinoma was the most prevalent subtype followed by mucoepidermoid and adenocarcinoma, not otherwise specified (NOS) respectively.

Tumours amenable to surgery are best managed by total excision. Those with microscopic residual disease and minimal volume of macroscopic residual can be successfully controlled with post-operative photon radiotherapy doses of 60 – 66 Gy.[5,9,10] Unresectable, large volume macroscopic residual and recurrent diseases pose a challenge for locoregional control. It has been established that conventional photon radiotherapy is not effective in this regard, but neutron radiotherapy due to its properties such as reduced oxygen enhancement ratio (OER) and higher relative biological effectiveness (RBE) overcomes radioresistance. This will be discussed in more detail below.

There are few places in the world that offer neutron radiotherapy, namely, South Africa, Russia, Germany and the United States, due to high establishment and maintenance costs. Neutron

radiotherapy in South Africa is offered at the Medical Radiation division of the iThemba Laboratory for Accelerator Based Sciences (LABS).[11] At iThemba LABS, the neutrons are produced in a 200 MeV cyclotron by reaction of 66 MeV protons on a 1.96-cm thick beryllium target.[12] The resulting neutron beam has the depth dose distribution of an 8 MV photon beam. The facility has an isocentric gantry with an approximately full 185° rotation, which is enabled by a moving floor to accommodate the full height of the gantry under the treatment bed. Field sizes range from 5.5 x 5.5 cm^2 to 29 x 29 cm^2 at a source axis distance (SAD) of 150 cm.[12] Conformal shaping is also possible by a 1-cm wide and 15-cm thick steel post collimator multi-blade trimmer.[13]

This review is intended to highlight the roles of neutron radiotherapy in the management of malignancies of the salivary gland.

2. Neutron radiotherapy – background and rationale of utilisation in clinical practice

The addition of photon radiotherapy to surgery for malignant salivary gland tumours increased local control in large, high-grade tumours and those with close margins or microscopic residual disease.[14–17] However, for certain tumour types, particularly advanced cancers with a high tumour burden and relative radioresistance such as macroscopic residual or irresectable salivary gland carcinomas, photon radiotherapy is not always effective. This has led clinicians to explore other forms of radiotherapy.

The resistance of certain malignant tumours to photons can be attributed to a number of radiobiologic properties that favour neutron radiotherapy. These include relative biological effectiveness (RBE), dose per fraction, linear energy transfer (LET) and hypoxia, which for the most part, are related to the ionisation pattern of a given radiation type. RBE is the value achieved when comparing the effectiveness of other types of radiotherapy to photon radiotherapy (X-

rays).[18] The National Bureau of Standards gave the following definition 'The RBE of some test radiation (*r*) compared with X-rays is defined by the ratio $D_{250}/D_{r,}$ where D_{250} and D_r are, respectively, the doses of X-rays and the test radiation required for equal biologic effect.'[18] Factors that influence RBE are radiation quality (determined by linear energy transfer (LET)), radiation dose, number of dose fractions, dose rate and biologic system or targeted cells.[18] The relative biological effectiveness of fractionated neutron radiotherapy in salivary gland malignancies was described in the work of Battermann.[19] The RBE of adenoid cystic carcinoma of the salivary glands metastatic to the lung was found to range up to 8, and was significantly higher than that of the surrounding normal tissue.[19] The neutron RBE at iThemba LABS is taken as 3for normal tissue 3.

Tumour cell kill in radiotherapy is directly related to the ability ionising radiation to induce damage in the deoxyribonucleic acid (DNA) of the cells. Photon radiotherapy has a sparse ionisation density pattern (low LET) and predominantly induces single-strand-breaks in DNA, which can be readily repaired, whilst neutron radiotherapy has a dense pattern of ionisation (high LET) and creates DNA double-strand-breaks, which are more difficult to repair. An excess in unrepaired double strand breaks, therefore, leads to a higher tumour cell kill.[18]

Hypoxia is also an important radiobiological phenomenon. It plays an important role in creating an environment that confers cellular resistance to photon radiotherapy. Photon radiotherapy is a type of low LET radiotherapy and tends to interact with matter via a mechanism known as the indirect action of radiation. An electron is ejected from neighbouring atoms or molecules, which results in the formation of free radicals that in turn induce DNA damage of malignant cells. All the processes are highly dependent on the presence of oxygen to "cement" the damage, thus hindering DNA repair and resulting in the increased death of the malignant cells. Neutron radiotherapy on the other hand interacts directly with the DNA of the cells causing damage that is

predominantly permanent regardless of the presence of oxygen.[20] In a hypoxic environment, tumour cells would be sensitive to neutron radiotherapy, as biologic effects of radiation type are not mediated by oxygen. There are two main instances when a hypoxic environment can be created in a primary tumour:

1. Uncontrolled cell division resulting in a tumour outgrowing its blood supply. This creates an inner core of cells that adapt to the hypoxic environment and continue cell division; and
2. The quality of vessels in tumours tends to be poor and may collapse and interrupt oxygen supply.

In the case of locally recurrent tumours, the environment is usually fibrotic and lacking in blood supply. The thriving cells are, therefore, adapted to hypoxia. At the molecular level, hypoxia stabilises and activates hypoxia inducible factor (HIF), which encourages angiogenesis and causes an anaerobic shift of metabolism, thereby increasing survival and immortality of cancerous cells. In radiobiological terms, the dependence on oxygen for radiotherapy effectiveness can be expressed as oxygen enhancement ratio (OER).[20] The closer it is to 1.0, as is the case for high LET radiotherapy (e.g. neutron radiotherapy), the more effective the radiotherapy in hypoxic conditions.[20]

3. Evidence in support of the use of neutron radiotherapy in salivary gland malignancies

The indications for neutron radiotherapy for salivary gland malignancies include unresectable tumours, macroscopic residual tumours after surgery and tumours in patients who are not suitable to undergo surgery. In the first half of the 20th century, clinical use of neutron radiotherapy was attempted, but the resulting treatment toxicities outweighed the clinical benefit and further use was discouraged.[21,22] However, further studies revealed that excessively high doses might have been used in the earlier attempts. Modifications to dose schedules were made and neutron radiotherapy gained clinical momentum.[23,24] Subsequent analyses of published studies provided much needed answers and direction for the place of neutron therapy in the management of

cancer.[25,26] The quality of neutron therapy machines was also poor in earlier years, but has evolved to an acceptable clinical standard in the high energy neutron centres. Unfortunately, the development of highly conformal precise delivery techniques has not kept pace with photon radiotherapy machines.[12,13,27–29]

Based on favourable outcomes from work done by Catterall et al,[30] Battermann et al conducted a project to test neutron therapy on patients with locally advanced head and neck tumours, using a 14 MeV d+T neutron generator.[31] Although the authors conceded that the beam quality was not optimal and this may have resulted in some severe toxicity, tumours of the major salivary glands responded well. Henry et al[32] reported on malignancies of the major salivary glands, the majority being of parotid origin. Historical controls of patients treated with photons only were compared to those treated with neutrons alone or mixed with photons. Photon radiotherapy was delivered from a cobalt-60 machine to a total dose of 50.4 Gy – 69 Gy at 1.8 Gy per fraction 5 days per week. The neutron doses ranged from 18.5 to 21.5 Gy delivered over 7 weeks. For mixed beams, the total dose was equivalent to 56 – 67 Gy. All 13 patients with tumours less than 3 cm achieved local control regardless of treatment modality. For those with 3- to 6-cm tumours, neutron radiotherapy yielded better results with 100% local control compared to photons, which gave 33% local control. Tumours over 6 cm did poorly, with no modality achieving any local control. A small case series of 9 patients with parotid gland malignancies was reported by Geraci.[33] This report showed no advantage of neutron radiotherapy for stage III patients, and pointed to an increased incidence of severe late toxicities after 2 years. A major concern of this author was whether the benefit of neutron radiotherapy justified the late effects experienced by patients in the face of prolonged survival and superior local control.

Kaul et al,[34] at Fermilab in Illinois (USA), confirmed the efficacy of neutron radiotherapy in advanced salivary gland malignancies. In fact, unlike the report of a previous study[32] which

suggested that the efficacy of neutron radiotherapy was limited to tumours < 6 cm, this study concluded that tumour size did not influence efficacy of neutrons.[34] Of the 22 patients treated with neutron radiotherapy, 68% had malignant tumours arising from the parotid gland. Fifty percent of the patients with parotid gland malignancies achieved local control of the primary, 35% died of the disease of which 1 patient had anaplastic carcinoma. Two patients who were treated for recurrence also succumbed to the disease. The severe toxicity rate for the whole cohort was 13%, and included pigment alteration, subcutaneous fibrosis and necrosis. An update on the positive outcomes of treatment of salivary gland malignancies with neutron radiotherapy at Fermilab was confirmed by Saroja et al.[35] With a larger cohort of patients, there was a trend towards better overall local control of 63%.

Duncan et al[36] gave an account of the utilisation of neutron radiotherapy in Edinburgh in salivary gland malignancies which was in keeping with previously published studies. Of the 28 patients, 64% had parotid gland malignancies. Long-term local control was seen in 60% of the 25 evaluable patients. However, a more accurate rate of 72.2% in 22 patients may be justifiable as 3 of the patients had microscopic residual disease at the time of neutron radiotherapy. The ability of neutron radiotherapy to effect tumour control even in large locally advanced tumours was also documented by Griffin et al[37] who treated 32 patients with malignant salivary gland tumours that were either inoperable, recurrent or gross residual post operation. All patients with T3 tumours and 85% of T4 tumours had a complete response. The 5-year locoregional control and overall survival were 69 and 33%, respectively.[37]

The question of superiority of neutron radiotherapy in the management of unresectable salivary gland malignancies in comparison to photon radiotherapy led to the Radiation Therapy Oncology Group- Medical Research Council (RTOG-MRC) landmark trial in 1980.[38,39] Thirty-two patients with inoperable, recurrent, or unresectable salivary gland malignancies were randomised to

receive either neutron or photon radiotherapy. The study was discontinued prematurely, due to significantly superior outcomes of the neutron radiotherapy arm. Of the 25 patients with complete data, total tumour regression of the primary site was observed in 85% of patients in the neutron arm versus 33% in the photon arm. For nodal sites, complete response rates were 86% and 25% in the neutron and photon arms, respectively. The 2-year locoregional control and survival rates were 67% and 62% (neutron radiotherapy arm) versus 17% and 25% (photon radiotherapy arm), respectively. Though the differences in locoregional control had statistical significance ($p < 0.005$), the differences in survival were not significant ($p = 0.10$).[38] Ten-year locoregional control was 56% and 17% for neutron and photon radiotherapy arms, respectively ($p = 0.009$); and survival was 15% for neutron arm versus 25% for photon arm ($p = 0.50$).[39] As for late toxicities, there was a trend towards patients in the neutron arm experiencing more severe toxicities than those in the photon arm (9 versus 4, $p = 0.07$).[39]

The account of Catterall et al[40] on 65 patients with locally advanced or recurrent malignant salivary gland tumours suggested that recurrent tumours tended to respond worse than primary tumours. The neutron dose delivered in 4 weeks was 15.6 Gy. Forty-two of the 65 patients had received radical surgery and/or photon radiotherapy previously. Overall local control was 80% for tumours treated only with neutron radiotherapy compared to 35% for recurrent tumours. Over 90% of the tumours that were either greater than 6 cm in size or extending to skin, bone, facial or lingual nerves had a complete response. Of these, 19% recurred and 6 of these were second time recurrences. Histological subtype had no bearing on local control. Median survival times were 50, 60 and 36 months for tumours treated *de novo* by neutrons, recurrent after surgery and recurrent after photon radiotherapy, respectively.[40] The complication rate was 16% for patients receiving only neutron therapy and 21% for patients who had prior treatments. Notably, Catterall drew attention to the low quality of neutron beams as a partial explanation of the higher toxicity rate.[40]

It is well known that surgery in the form of complete excision of the tumour is the gold standard for cure in salivary gland malignancies, however results of a study by Buchholz et al[41] suggested that incomplete surgical intervention contributed to poorer outcomes and could be detrimental to tumour control. Their cohort of 53 patients included those with locally advanced cancers who had received definitive neutron radiotherapy and those with gross residual and recurrent cancers. Superior locoregional control was attained at 1 year follow up in the group of patients that were treated definitively with neutron radiotherapy (92%), compared to those with gross residual disease (79%) and recurrent cancers (60%). At 5 years, the locoregional control for the definitive group was at 92%, whilst for recurrent group it was 51% ($p = 0.01$). Comparison between the definitive group and gross residual disease at 5 years also showed a trend in favour of the definitive group, 92% versus 51%, respectively, although this was not statistically significant ($p = 0.12$). A paradoxical finding of poorer 5-year locoregional control in node negative patients than in node positive patients was seen (55% versus 75%, $p = 0.40$). The authors suggested that the smaller fields used in node negative patients, with the aim of sparing normal tissue could have compromised tumour coverage. This rationalisation is supported by the fact that 75% of node negative patients had out-of-field locoregional recurrences. However, the 5-year actuarial survival conformed more to expectation at 46% for node negative patients and 21% for node positive patients ($p = 0.12$).

Although surgery was suggested to be detrimental when all salivary gland malignancies were considered,[41] this may not be the case for slower growing sub group of adenoid cystic carcinoma. Douglas et al,[42] reviewed 159 patients with adenoid cystic carcinomas of both minor and major salivary glands and found that in both univariate and multivariate analyses, resection had a better prognosis for local control compared to biopsy only ($p = 0.02$ and $p = 0.03$, respectively). Of these, 151 had unresectable tumours and/or diffusely positive margins post resection. Sixty-two per cent were minor salivary gland malignancies, 29% were major and 9% were classified as

other sites. The 5-year actuarial locoregional control was 57%. The 5-year actuarial complication rate was 13.5%. Late grades 3 and 4 morbidities were seen in 15 patients. In this group, 5 patients were expected to experience severe late toxicities as the tumours were close to sensitive structures. In a similar study, Huber et al[43] analysed 75 patients with inoperable, recurrent or incompletely excised adenoid cystic carcinoma but compared photon, neutron and mixed beam radiotherapy. The 5-year actuarial and local control rates were 75%, 32% and 32% for neutron, mixed beam and photon radiotherapy, respectively. Multivariate analysis showed that postoperative radiotherapy ($p = 0.003$) and small tumour size ($p = 0.01$) were prognostic for better local control.[43] The severe late (grade 3 and 4) toxicity rate was 19% for neutrons, 10% for mixed beam and 14% for photons ($p > 0.1$).[43]

Subsequently, Douglas et al[7] looked at 263 patients with all histological subtypes of malignant salivary gland tumours. One hundred and forty-one tumours arose from major salivary glands of which 118 were parotid gland tumours. The 6-year actuarial overall survival, cause-specific survival and locoregional control were 59%, 67% and 59%. AJCC group stage I and II disease, minor salivary sites, no skull invasion and primary disease on multivariate analysis were advantageous to survival prognosis. For locoregional control, no base of skull involvement, size 4 cm or smaller, no previous radiotherapy and prior surgical resection were statistically significant on multivariate analysis for improved outcomes.[7]

In a contemporary study and the largest series on salivary gland malignancies treated with neutron radiotherapy, Stannard et al[8] reported on all salivary gland malignancies and the results were much in keeping with other international studies. They found 5- and 10-year overall survival of 51% (CI: 44.3 – 57.3%) and 37.4% (CI: 29.8 – 44.9%). Disease specific survival was 66.8% (CI: 59.8 – 72.9%) at 5 years and 53.7% (CI: 44.4 – 62.2%) at 10 years. Better locoregional control than primary local control was seen again with 5-year locoregional control and local control at 60.6% (CI: 53.0 – 67.2%) and 58.6% (CI: 51.1 – 65.4%), respectively. However, at 10

years local control stood at 45.9% (CI: 36.5 – 54.8%) whilst locoregional control was 39.1% (CI: 30.2 – 47.9%). Univariate analysis revealed, T4 tumours, size >4 cm, high grade, squamous carcinoma, irresectable tumours, and positive nodes were significantly worse for locoregional control and disease free survival. Unresected disease was significantly worse for locoregional control, but for disease specific survival outcomes improved with salvage surgery. Multivariate analysis showed that tumours > 6 cm, squamous carcinoma, irresectable tumours and positive nodes were significantly worse for locoregional control whilst tumours >6 cm, high grade, squamous carcinoma and positive nodes were worse for disease specific survival. The incidence of severe late toxicity was 8.9% (30/335) with a 6-year actuarial rate of 11%.

4. Other radiotherapy modalities used in the management of salivary gland malignancies

Photon radiotherapy is also used in the management of salivary gland malignancies.[44–46] It is standard for photon radiotherapy to be used in the adjuvant setting for microscopic disease, high grade and large tumours.[14–17] Historically, photon radiotherapy has not offered good local control for macroscopic residual disease and irresectable tumours when compared to neutron radiotherapy,[38,39,47] but with appropriate fractionation schedules, taking into account radiobiological properties of salivary gland tumours and modern radiotherapy techniques comparable results are achievable.[46,48] Fu et al,[45] in their report on management of 100 salivary gland malignancies, treated 10 locally advanced parotid gland malignancies with photon radiotherapy (with 4 MV linac or cobalt-60). They achieved local control of the primary tumour in 3 out of the 10 cases (30%).

Mixed beams of photons and neutrons have been used in the past with contrasting outcomes.[32, 26,29] In the study by Henry et al,[32] the local control rates achieved by neutron radiotherapy, photon radiotherapy and mixed beam were 33.3, 63.2 and 100%, respectively, suggesting a better outcome for mixed modality. In the Fermilab report from Chicago by Kaul et al,[34] the local

control rate for neutron radiotherapy alone and mixed beam were 73 and 27%, respectively, suggesting a better outcome for pure neutron radiotherapy.

Treatment of recurrent parotid gland malignancies with brachytherapy using iodine-125 seeds was investigated by Zhang et al.[49] They retrospectively reviewed 64 patients, and found a local control rate of 76.6% and overall survival of 79.7%. Resection of tumours conferred a local control and survival advantage of 78.6 and 86.5%, respectively, at 5 years compared to 53.8 and 61.2% when there was no resection. The toxicity rate was 3%.

Carbon ion radiotherapy combines properties of high lethality and target precision made possible by the beam's high RBE and Bragg peak.[50] Several reports on its use in salivary gland malignancies have been published and results are favourable, especially in reducing toxicity rates.[50–53] In a retrospective review, Jensen et al[50] studied 309 patients with adenoid cystic carcinomas of the head and neck who were treated using a combination of intensity modulated radiotherapy (IMRT) and carbon ion boost. Local control rates of 83.7 and 58.5% were found at 3 and 5 years, respectively. Twenty per cent of their patients had parotid gland malignancies with the majority having undergone total or subtotal resection. In the whole cohort, T-staging had a prognostic value in outcomes. Only 3 out of 309 patients were reported to have had grade 3 toxicity and above.

Proton radiotherapy is also used in the management of salivary gland malignancies.[54,55] Pommier et al[54] used mixed photons and protons to treat adenoid cystic carcinomas of the head and neck which had extension to the skull base. Local control, disease free survival and overall survival rates at 5 years were 93%, 56% and 77%, respectively. The toxicity rate in this study was high with grade 3 toxicity being noted in 13 patients out of 25 (3 ocular and 10 neurologic) and 2 patients experienced grade 5 brain toxicity. The authors acknowledged this, stating they had

adjusted technical aspects of their treatment delivery to improve outcomes. Takagi et al[55] reported on 80 adenoid cystic head and neck patients treated with either proton or carbon ion radiotherapy at a single institution. No statistically significant difference was observed between the two modalities in the 5 year overall survival (63%), progression free survival (39%) or local control (75%). The toxicity rate for grade 3 and above was 26%.

Another modality is boron neutron capture therapy (BNCT).[56,57] It is a high linear energy transfer (LET) radiotherapy that utilises slow neutron beams. The potential of the non-radioactive isotope boron-10 to be selectively delivered in high concentrations to tumour cells and produce excited boron-11 ($^{11}B^*$) when irradiated with epithermal neutrons (n_{th}) is exploited to deliver high energy alpha particles and high energy lithium-7 nuclei. The excited boron-11 participates in nuclear capture and fission reactions by decay. The nuclear reaction is represented as follows:[58]

$$^{10}B + n_{th} \rightarrow [^{11}B]^* \rightarrow \alpha + {}^{7}Li + 2.31\ MeV$$

Radiobiologically, contribution to the dose is from:[58]

(i) high LET alpha particles and lithium-7 ions from thermal neutron capture and fission reactions;

(ii) high LET proton yielded from the scattering of fast neutrons and capture of the thermal neutrons by nitrogen atoms; and

(iii) low LET gamma rays yielded from the capture of thermal neutrons by normal tissue hydrogen atoms.

Doses of up to 60 – 70 Gy equivalent can be administered in one or two applications with high rate of normal tissue sparing.[58] The challenge of this therapy is to achieve a homogenous distribution of the boron isotope in the tumour volume and remains the limiting factor of its clinical application.[58]

Aihara et al[56] studied BNCT in 5 head and neck patients with locally advanced initial or recurrent salivary gland carcinomas not amenable to surgery. Complete response was attained in all the

patients at 6 months and median duration of local control was 24 months (range 22 – 32 months). Median overall survival was reported as 32 months (range 22 – 38 months). No patient developed toxicities of grade 3 or above. Notably, relatively superficial tumours were treated, as only patients with tumours whose deepest part was within 5 cm of the skin surface were eligible for inclusion.

Combination of modalities of fast neutron radiotherapy with a BNCT boost is also being explored.[57] Laboratory based work done by Laramore et al[57] investigated the feasibility of integrated BNCT and fast neutron beam. Their theory is based on the fact that a thermal neutron component is produced when fast neutrons traverse a medium. As such, the rationale was to manipulate the fast neutron beam utilised in the established hospital setting to yield therapeutically applicable thermal neutron beam for BNCT, hence relinquishing the need of a separate low energy reactor.[57]

5. Conclusion/ Summary of literature review

Good local control is consistently observed when neutron radiotherapy is used in the management of salivary gland malignancies. Early studies on the use of neutron radiotherapy showed high toxicity rates and this was mainly due to the use of low energy, inferior beam neutron radiotherapy administered with limited collimation. For salivary gland malignancies, high-energy neutron beams are adequate for treatment if the beam quality is equivalent to 4-8 MV. Currently, advances in neutron radiotherapy planning allows for better normal tissue sparing and results would be further improved with advances such as intensity-modulated neutron therapy.[59]

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