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The Evolving Role of Particle Radiotherapy in the Treatment of Head
and Neck Cancer

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Abstract

Radiotherapy has a proven role in the management of most types of head and neck cancer but results are suboptimal in certain clinical situations. Particle radiotherapy offers the opportunity to improve outcomes in such cases. Fast neutron radiotherapy is a high linear energy type of radiotherapy and may be advantageous for many “radio resistant” tumors such as salivary gland malignancies, mucosal melanomas, and sarcomas. Proton radiotherapy offers greatly improved dose distributions compared to conventional photon radiation and this allows for higher radiation doses and potentially improved outcomes for tumors near critical structures such as the brain stem and optic structures and in the re-irradiation setting. The applicability of proton radiotherapy in other settings is also discussed. Heavier charged particles, such as carbon ions, offer both improved radiation dose distributions and the radiobiological advantage of fast neutron radiotherapy. While data is limited, it appears that carbon ions are advantageous in the same subset of tumors as fast neutron radiotherapy, but the improved dose distribution theoretically should result in reduced morbidity. Boron neutron capture therapy (BNCT) is a technique that has recently been used to treat recurrent head and neck tumors and new boron carrier compounds are being developed for this application. Clinical data on the use of each of these modalities in the treatment of head and neck cancer is reviewed and their current role in the treatment of head and neck cancer is summarized

Key Words: Neutron radiotherapy, proton radiotherapy, carbon ion radiotherapy, BNCT

1. Introduction/Background

There is considerable clinical data on the use of conventional photon and/or electron radiotherapy in the treatment of carcinomas arising from the epithelial surfaces of the aero digestive tract (HNSCC). These are fairly common tumors with there being about 62,000 cases per year in the United States alone (American Cancer Society, 2016). Radiotherapy has an established role either as definitive treatment or in an adjuvant setting with surgery, often in conjunction with chemotherapy. While the heavier nuclear particles can be used to treat such tumors, it is for other types of less common tumors such as sarcomas and salivary gland tumors that they may have their greatest utility. Particle radiotherapy may also have an important role to play in the treatment of recurrent HNSCC after conventional radiotherapy.

Photon and electron radiation are types of low linear energy transfer (LET) which produce ionization events distributed in space and time. Radio resistant tumors such as sarcomas and salivary gland tumors often are able to repair radiation damage caused by this type of radiation (Hall and Giaccia, 2006). Fast neutrons are a type of high LET radiotherapy which has approximately the same dose localization properties as photon radiotherapy. However, their greater energy deposition means that it is more difficult for tumors to repair radiation damage from this modality. Protons are a type of low LET radiotherapy but have a different basic physics in terms of their interaction with matter, allowing a much better dose localization than is achievable with standard photon radiotherapy. In many settings one can safely deliver higher radiation doses which, in principle, yields better tumor control with equivalent side effects, particularly in the setting of concomitant chemotherapy. Conversely, one can keep the radiation dose the same and the lower doses of radiation given to adjacent normal tissues should result in fewer side effects. Carbon, neon, and other “heavy” stripped ions, combine

the radiobiological properties of fast neutrons with the better dose localization properties of protons and there is burgeoning interest world-wide in their use to treat cancers.

The final type of radiotherapy I will discuss is boron neutron capture therapy (BNCT) which has been recently applied in the treatment of recurrent HNSCC. In this technique, a broad beam of slow neutrons is used, often from a nuclear reactor, and the dose localization properties come from a boron carrier that preferentially localizes in the tumor compared to surrounding normal tissue. Boron-10 has a high cross section for capturing a slow neutron and then undergoing a fission reaction releasing an α -particle and a lithium-7 nucleus which have ranges of 6-9 microns in tissue – approximately cellular dimensions. These are high LET particles and hence, can destroy a tumor cell “tagged” with boron without damaging nearby normal cells that are “untagged”. Since boron-10 is non-toxic this means that the carrier agents can be cleared via the liver and/or kidneys without damaging these organs, unlike the situation if the carrier compound utilized a radioactive nuclide or a cytotoxic moiety.

2. Neutron Radiotherapy

Fast neutrons typically deliver 20-100 times more energy along their path length than do the megavoltage photons used in conventional radiotherapy. This gives rise to a tissue and dose dependent relative biological effectiveness (RBE) factor compared to photon radiation (Hall and Garcia, 2006; Battermann et al, 1981; Laramore and Austin-Seymour, 1992). The dose distribution of fast neutrons in tissue is similar to that of photons as shown in Fig. (1) and it is the differential RBE between tumor and normal tissue that results in a therapeutic gain factor in certain clinical situations. For late effects in most normal tissues the RBE is in the range of 3.0 – 3.5, while for damage to the central nervous system, the RBE is in the range of 4.0 – 4.5. For the response of malignant tumors, the

RBE is in the range of 3.5 for squamous cell tumors, in the range of 4.5 for sarcomas, and in the range of 8.0 for salivary gland malignancies. Intuitively, one would expect improved clinical results in the situation where the tumor control RBE was higher than the RBE for normal tissue damage and in general, this has been borne out clinically.

Initial reports from Hammersmith Hospital on the use of fast neutrons to treat locally-advanced HNSCC were encouraging (Catterall et al, 1975; Catterall et al, 1977) but other reports from European treatment centers did not confirm this efficacy and moreover, showed considerable treatment related morbidity (Duncan et al, 1984; MacDougall et al, 1990). The Radiation Therapy Group (RTOG) in the United States initially conducted a randomized trial using a combination of neutrons and photons (mixed beam) as the experimental arm that showed no improvement in either tumor control or survival (Griffin, 1989). The RTOG and the Medical Research Council (MRC) of Great Britain as part of the Neutron Therapy Cooperative Working Group conducted a follow-on study using second generation treatment facilities having considerably more technical sophistication than the first generation laboratory-based facilities used in the earlier trial (Maor et al, 1995). There was a suggestive improvement in control of neck adenopathy but this was not statistically significant. There was no improvement in either local control at the primary site or in terms of survival. There were more late complications graded "severe or greater" on the neutron arm than the photon arm (40% vs 17%, $P=0.008$). Currently fast neutron radiotherapy is felt to be of limited utility in the treatment of HNSCC.

Salivary gland tumors, on the other hand, appear to respond much better to neutron radiotherapy than photon radiotherapy. In retrospect this could have been anticipated from the early clinical radiobiological work of Battermann et al which showed an RBE of approximately 8 for adenoid cystic carcinomas metastatic to

lung (Battermann et al, 1981). To put this into perspective, it is possible to deliver approximately 20 Gy_{ny} to the head and neck region with acceptable side effects (by convention the dose from the γ -rays produced by neutron interactions is included in the specification of the physical dose). Thus the biological dose to salivary gland tumors would be in the range of 160 Gy-equivalent while the surrounding normal tissues would "see" a biological dose of 60-70 Gy-equivalent resulting in a therapeutic gain factor in the range of 2.3 – 2.6. Early single institution studies supported this and so the RTOG and the MRC of Great Britain conducted a randomized, clinical trial for patients with inoperable salivary gland tumors including cases that had recurred after primary surgery. This study was stopped at the 2-year point when there was both an improved local/regional control and survival on the neutron arm. A final report on the study continued to show improved local/regional control at 10 years in the neutron-treated patients, 56% vs. 17%, $P = 0.009$, but there was no long term survival advantage due to the development of distant metastases (Laramore et al, 1993). The final local/regional control curve from this study is shown in Fig. (2). Later single institution studies lend supportive evidence to this study. Huber et al reported on a large series of patients with salivary gland adenoid cystic carcinomas treated at the University of Heidelberg which showed 5-year local control rates of 75% treated with neutrons alone compared to 32% for patients treated either with photons or a "mixed beam" regimen (Huber, et al, 2001). Douglas et al reviewed outcomes for tumors of major salivary gland with a mix of histologies and found at 9 years the local control rate was 78% for tumors ≤ 4 cm compared with 40% for tumors > 4 cm (Douglas et al, 1999). Because of the relatively high RBE for late effects in the central nervous system, it was necessary to limit these structures to doses in the range of 12 Gy_{ny} which reduced the local control rate for tumors with skull base extension to around 39% (Douglas et al,

2008). A Gamma Knife boost to the skull base portion of the tumor increased the local control rate to 82% which is approximately the same as for tumors without skull base disease. Work is in progress to see whether a proton boost will accomplish the same thing with fewer side effects.

Adenoid cystic carcinomas can arise in other head and neck sites such as the minor salivary glands in the larynx, trachea, and lacrimal glands. Neutron radiotherapy has proven effective at treating these tumors as well as the more familiar salivary gland malignancies. Bittner et al reported on 20 patients with adenoid cystic carcinomas of the trachea treated with neutron radiotherapy and found the 5-year actuarial survival to be 89.4%, although the 5-year local control rate was only 54.1% (Bittner et al, 2008). Six of the patients were given a brachytherapy boost following the neutron radiotherapy but this did not statistically improve the local control rate. Gensheimer et al reported on 11 patients with lacrimal gland tumors who were treated with neutrons with gross residual disease present in 8 patients (Gensheimer et al, 2013). With a median follow up of 6.2 years the Kaplan-Meier local regional control rate at 5 years was 80% and the median overall survival was 11.1 years.

Neutron radiotherapy may have a role to play in the treatment of other radioresistant tumors in the head and neck region. Liao et al evaluated 14 patients with mucosal melanomas treated with fast neutrons (Liao et al, 2013). Local control was achieved in 79% of patients until death or last follow up. Unfortunately, 50% of patients developed distant metastases. Neutron radiotherapy has also been utilized to treat advanced thyroid malignancies in certain clinical situations (Chapman et al, 2016). Sixty-two consecutive patients with advanced thyroid cancers were treated with external beam radiotherapy between 1985-2015 with 23 receiving neutron radiotherapy and 39 receiving conventional photon irradiation. There was no overall survival difference between the groups but

interestingly, patients with low-grade subtypes (papillary and follicular) did better with standard photon radiation while there was a trend towards improved survival with fast neutrons for the more aggressive medullary and anaplastic histologies.

While used primarily to treat malignant neoplasms, a small number of patients with multiply-recurrent pleomorphic adenomas have also been treated with neutrons (Douglas et al, 2001). The 16 patients in the series had a median at-risk period of 98 months at the time of analysis and at 15 years a Kaplan Meier analysis showed a local control of 100% for patients with unifocal tumors and 72% for patients with multinodular disease. As this is a benign process, local control was defined as shrinkage and/or stabilization with no further growth. In terms of late side effects, 2 patients had RTOG/EORTC grade III or IV toxicities and 4 patients exhibited some degree of unilateral hearing loss. Neutron radiotherapy offers an acceptable alternative to further surgery in the recurrent, high-risk setting but in general, should not be offered as the initial treatment for pleomorphic adenomas.

3. Charged Particle Radiotherapy

3.1 Overview

Charged particles, protons and heavier, deposit little energy along their initial path. However, when they near the end of their range, the energy loss increases resulting in what is termed the Bragg peak. The energy loss profiles for protons and carbon ions are shown in Fig (3). The depth of the Bragg peak depends upon the energy of the particle beam, the particle charge and mass, and the properties of the material through which it travels. Hounsfield numbers obtained from computerized scans (CT) are generally used to convert the material path length to water equivalent path lengths for proton treatment planning and tissue inhomogeneity is taken into account. Currently high energy cyclotrons or synchrotrons are required to accelerate the particle to hundreds of MeV per nucleon in

order to effectively treat deeply seated tumors. Comparing Figs. (1) and (3) one can see intuitively how charged particles are better able to spare normal tissues than photons or neutrons. The Bragg peaks are very sharp and must be spread over the tumor volume during treatment. The simplest way of doing this for protons is to use scattering devices resulting in what is termed a spread Bragg peak. More modern techniques utilize what is termed “pencil beam scanning” to vary the position and the energy of the beam to paint out the 3-dimensional target volume. This technique is referred to as “intensity modulated proton therapy” or IMPT and gives a more conformal dose distribution, particularly at the proximal edge of the target volume. Note that the proton beam stops abruptly resulting in no down stream dose. However, unlike the proton case there is a distal tail for the carbon Bragg peak due to nuclear fragmentation effects.

Protons and α -particles are considered low LET particles, except at the very distal edge of their Bragg peaks and so for practical clinical purposes, their RBE is the same as for megavoltage photons, apart from trivial scaling factors of 1.1 for protons and 1.2 for α -particles. This allows the clinician to easily adapt the time-tested dose fractionation schemas of conventional radiotherapy to their use. The RBE corrected dose is termed “cobalt gray equivalent” (CGE). Carbon ions, on the other hand, are high LET particles with radiobiological properties similar to neutrons and so the clinician must take into account tissue dependent RBEs when designing treatment plans. This can be an advantage when sophisticated treatment planning models are utilized which allow greater biological effect in the Bragg peak area when there are comparable biological effects in the entrance channel (Elsasser et al, 2010).

3.2 Protons

Much of the early work in using charged particles to treat tumors of the head and neck involved skull base tumors such as

chordomas or chondrosarcomas. A prior review of the literature showed local control rates with protons or α -particles in the range of 75-100% with acceptable treatment related morbidities (Laramore, 2009). Using conventional photon radiotherapy with the tumor dose being limited by adjacent critical normal structures to the range of 55 Gy, the expected local control rates would be approximately 35% for these tumors (Munzenrider and Liebsch, 1999). Recent work on using IMPT for chondrosarcomas of the skull base showed 8-year actuarial control rates and survival of 89.7% and 93.5%, respectively, with RTOG/EORTC grade 3 or greater toxicities in only 7.8% of 77 treated male patients (Weber et al, 2015). At this point proton radiotherapy is an accepted standard treatment for primary skull base tumors.

HNSCC arising in the nasopharynx and paranasal sinuses are often close to dose limiting normal structures such as the brain stem, optic nerves, or optic chiasm and proton radiotherapy may offer the opportunity for dose improvement and better outcome. A comparative treatment planning study of IMPT vs IMRT for patients with nasopharyngeal tumors was conducted by Taheeri-Kadkhoda et al, 2008. Both techniques gave the same mean doses to target volumes but the IMPT plans had significantly better dose conformality and gave lower doses to avoidance structures such as the spinal cord, inner ear, and middle ear. Clinical outcome data is somewhat limited with Chan et al reporting on 17 patients with locally-advanced nasopharyngeal tumors treated at either the Harvard Cyclotron-Massachusetts General Hospital (HCL-MGH) proton facility or the Francis H. Burr Proton Center (FHBPTC) (Chan et al, 2004). With a planned median dose to the target volume of 73.6 CGE and 10 patients receiving induction and/or concomitant chemotherapy, the 3-year local/regional control rate was 92% and the overall survival was 74%. The treatment was delivered using first generation passive scattering techniques and 5 patients

exhibited MRI white matter changes in the temporal lobes and one patient developed an osteoradionecrosis of the mandible. It is thought that IMPT techniques will result in fewer side effects.

Ninety-one patients with advanced paranasal sinus tumors were given combined photon-proton radiotherapy at the HCL-MGH. The median prescribed dose was 73.6 CGE with only about half the dose being given with protons (Chan et al, 2004). There was a mixture of tumor histologies in this study with the 3-year local control rate being 88% for sarcomas, 86% for adenoid cystic carcinomas, 91% for neuroendocrine tumors, and 83% for squamous cell tumors. Distant failure was the dominant failure pathway. An accelerated fractionation schema with a median tumor dose of 70 CGE was utilized and the 5-year probability of late visual toxicity approached 20% (Weber et al, 2006). Nishimura et al have reported on 14 patients with esthesioneuroblastomas treated at the Chiba, Japan, proton facility (Nishimura et al, 2007). The prescribed dose was 65 CGE in 2.5 CGE increments and with a 40 month median time-at-risk, the 5-year Kaplan-Meier local control rate was 84% with an overall survival of 93%. Side effects were minimal with only one patient with extensive skull base disease having liquorrhea.

Oropharyngeal tumors are of increasing interest in proton radiotherapy. The changing demographics shows these tumors now being more commonly associated with the HPV16 virus than with tobacco and alcohol use. This is associated with better outcomes and proton radiotherapy may offer less long term morbidity in the longer-living patients. The clinical data on this is, however, mixed. The first reported study was from the Loma Linda University Medical Center which utilized a concomitant boost technique with the clinical target volume receiving 50.4 Gy with photons at 1.8 Gy per fraction and the gross tumor volume receiving 25.5 CGE with protons during the last 3.5 weeks of

therapy (Slater et al, 2005). The overall 5-year actuarial local control rate (primary and nodes) was 84% and the disease free survival rate was 65%. Although aggressive nutritional support and pain management were required, all patients were able to complete the planned course of therapy. RTOG/EORTC grade 3 late toxicity was observed in 3 patients. The Loma Linda patients were treated using passive scattering techniques. Van de Water et al analyzed the benefit of IMPT compared to either 3-D conformal or IMRT photon irradiation in regards to salivary gland sparing (van de Water, 2011). Normal tissue complication probabilities were used to estimate salivary dysfunction and xerostomia. They found that 3-D conformal treatment was inferior to both IMRT and IMPT and that IMPT resulted in a reduced dose to the parotid glands but not the submandibular glands compared to IMRT. Theoretically this would translate into improved clinical outcomes through reduced xerostomia. Direct comparisons between cohort groups of oropharyngeal cancer patients treated with IMRT or IMPT have been reported by the MD Anderson Group. Sio et al did a matched, comparative study of 50 patients treated with IMPT and 100 patients treated with IMRT and found that the IMPT patients fared better in terms of reduced incidence of severe weight loss as defined as greater than 20% of pretreatment body weight and/or requirement of a feeding tube (OR = 0.44, P-value = 0.05 at 3 months; OR = 0.23, P-value = 0.01 at 1 year) (Sio et al, 2016). However, the same institution, using a patient reported outcomes instrument, surveyed 35 patients treated with concurrent chemotherapy and IMPT and 46 patients treated with concurrent chemotherapy and IMRT and found only a minimal difference in symptom burden (taste, xerostomia, swallowing/chewing, appetite, fatigue) during the subacute phase with this difference was lost with further follow-up (Blanchard et al, 2016). Thus the clinical data is clearly mixed thus far in terms of reduced side effects with IMPT.

Even after aggressive local/regional treatment, the recurrence rate for patients with HNSCC is in the range of 8-30% depending upon tumor site and stage with uncontrolled disease being a major cause of death. With palliative chemotherapy alone, response rates are in the range of 10-40% with median survival times being in the range of 5-9 months. Hence, there is an increasing trend towards treating these recurrences more aggressively with re-irradiation playing an important role in many cases. Proton radiotherapy, with its improved dose localization may play an important role in this arena. An early report using passively scattered protons to retreat recurrent nasopharyngeal carcinomas showed a 2-year actuarial local control rate of 50% and a 2-year actuarial overall survival rate of 50% as well (Lin et al, 1999). Additional tumor doses of 50.0 – 88.2 CGE were given with the doses to critical structures kept below 22 CGE. It was found that the tumor control outcome correlated strongly with the dose-volume histogram analysis. No central nervous system side effects were noted. Romesser et al reported on a group of patients with recurrent head and neck cancer entered onto a multi-institutional data base, NCT01255748, managed by the Proton Cooperative Group (Romesser et al, 2016). Ninety-two patients were treated with curative intent with 76 having had one prior course of radiotherapy and 16 patients having had two prior courses of radiotherapy. Thirty-nine percent of patients had salvage surgery prior to proton re-irradiation. On a Kaplan-Meier analysis with death as a competing end point, the local regional control was 75% and the overall survival rate at 1 year was 65.2%. Grade 3 acute mucositis, dysphagia, and esophagitis were between 9-10%. In terms of late toxicities, 8.7% of patients had a grade 3 skin reaction and 7.1% of patients had grade 3 dysphagia. Two patients died of post treatment hemorrhage. The outcomes and toxicity are similar to that reported by Takiar et al for a group of 227 head and

neck cancer patients re-irradiated with IMRT (Takiar et al, 2016). McDonald et al reported on the outcomes of 61 patients with recurrent tumors treated with curative intent at the Indiana University Proton Center (McDonald et al, 2016). These patients had tumors primarily involving the skull base and therefore were not thought to be candidates for treatment with conventional radiotherapy. A spectrum of histologies was represented with the main tumor types being squamous cell tumors (52.5%) and adenoid cystic carcinomas (16.4%). Salvage surgery was utilized in 47.5% of cases but gross tumor was present in 70.5% of patients overall. The 2-year local control rate with death as a competing risk was 80% and the 2-year overall survival was 32.7%. The median re-irradiation dose was 66 CGE with cumulative radiation doses being in the range of 120 – 140 CGE. Grade 3 or greater toxicities were 14.7% in the acute time frame and 24.6% in the late setting with there being 3 treatment-related deaths.

3.3 Carbon Ion Radiotherapy

Currently large synchrotrons or cyclotrons are required to accelerate heavy ions to energies high enough to be clinically useful and the greater momentum of these ions compared to protons means that higher magnetic fields are required to bend the beams. This makes ion gantries considerably more massive than proton gantries and means that a heavy ion facility is 2-3 times more expensive than a proton facility with an equivalent number of treatment rooms and gantries. Heavy ions, such as neon and argon, were first used to treat patients at the Lawrence Berkeley National Laboratory using the BEVALAC facility (Linstadt et al, 1990). Due to limited beam time, the majority of the patients received a substantial amount of their treatment with photons or α -particles and only a small number of head and neck cancer patients were treated. The 5-year local control rates were 61% for 18 patients with salivary gland tumors and 69% for 12 patients with paranasal sinus tumors. The great majority of current work is for fully-stripped, carbon

ions (C-ions) and this will be the subject of the remainder of this section.

A phase I/II dose escalation study for patients with locally-advanced head and neck tumors was conducted at the HIMAC facility in Chiba, Japan (Mizoe et al, 2004). A mixed set of histologies was treated with the overall 5-year local control rate being 75% in 34 analyzed patients. The authors stated that the treatment toxicity was acceptable and that there were improved outcomes for patients with non-squamous histologies such as melanomas and salivary gland tumors – the same subset of tumors where fast neutrons show an improved result compared to photon radiotherapy.

Skull base tumors are also of interest for C-ion radiotherapy. Schulz-Ertner et al have reported on 37 patients with skull base tumors treated at the Gesellschaft für Schwerionenforschung mbH (GSI) with C-ions (Schulz-Ertner et al, 2002). A constant RBE of 3 was assigned to the beam and 60 Gy-equivalent was given to the primary target volume. The 2-year progression free survival was 100% for patients with chondrosarcomas and 83% for patients with chordomas which is about the same as reported in the proton literature. Only mild toxicity was reported meaning that dose escalation is possible.

Koto et al have reported on C-ion therapy for patients with locally-advanced parotid tumors who were given 57.6 – 64 Gy-RBE in 16 fractions at the HIMAC facility (Koto et al, 2016). The overall survival at 5-years was 70.1% and the local control rate at 5-years was 74.5% with the failures being primarily at the skull base or in the lymph nodes. Treatment side effects were appreciable with 5 patients having treatment related facial nerve palsies, 2 patients having hypoglossal nerve injury, 1 patient having ipsilateral blindness, 1 patient having osteoradionecrosis, and 5 patients having grade 2 brain injuries. The use of a constant RBE of 3 to set the dose may have accounted for some of these side effects.

Jensen et al recently reported on 309 patients with adenoid cystic carcinomas who were treated with a C-ion boost followed by conventional IMRT therapy (Jensen et al, 2016). Tissue and spatial variations in the biological effectiveness of the C-ion beam were incorporated in the treatment planning process. Patients with both microscopic-only and gross residual disease were included in the analysis. At 10 years the local/regional control was about 40%. This is lower than would be expected with neutron radiotherapy and may be because a significant fraction of the radiotherapy was given with IMRT, thus diluting the effect of the high LET C-ions.

4. Boron Neutron Capture Therapy (BNCT)

Shortly after the discovery of the neutron by Chadwick in 1932, Locher proposed treating malignant tumors with low-energy thermal neutrons via a capture process involving ^{10}B nuclei (Locher, 1936). This process is shown in Fig. (4) with the resulting fission fragments having ranges comparable to cellular dimensions. Conceptually BNCT is a “magic bullet” approach as boron is an innocuous substance having limited toxicity and so would not affect tissues outside the area where it is activated by the low-energy neutrons. Since many of the carrier agents are cleared from the body by the liver and/or kidneys it is advantageous to use an intrinsically non-toxic compound rather than tag the compound with a toxic substance such as ricin. The low-energy neutron beam is broad and so tumor selectivity comes almost entirely through the B-carrier which must be chosen both to have high tumor selectivity and to accumulate in significant amounts in the tumor cells. Although there is considerable laboratory work taking place towards developing appropriate carrier agents, at this time only 3 boron carrier compounds have been approved for human clinical trials: sodium mercaptoundecahydro-*closo*-dodecaborate (BSH), (L)-4-dihydroxy-borylphenylalanine

(BPA), and sodium decaborane (GB10). Unfortunately, with the possible exception of BPA being concentrated in cells which synthesize melanin, these compounds do not exhibit tumor specific uptake. The low-energy neutron beams used in BNCT are currently produced using nuclear reactors although there is increasing interest in developing accelerator-based sources suitable for hospital environments. The earliest clinical BNCT studies were for high grade gliomas and did not demonstrate a significant benefit over alternative “standard” treatments. The depth-dose properties of epithermal neutron beams limits their effective treatment depth to around 10 cm which means that most head and neck cancers are within range, if appropriate B-carrier agents could be developed. In calculating the dosimetry for BNCT, it is necessary to take account of each radiation component (BNCT reaction, fast neutron, γ -ray, nitrogen capture reaction, hydrogen capture reaction) as well as the boron distribution on a cellular level which is both tissue and compound dependent (Coderre and Morris, 1999).

There is a small body of work using BNCT to retreat recurrent head and neck tumors using BPA as the B-carrier. Kankaanranta et al have reported on 29 patients with recurrent head and neck tumors treated at the FiR 1 TRIGA reactor in Helsinki, Finland, with a single radiation fraction (Kankaanranta et al, 2012). ^{18}F -L-BPA PET imaging was used to determine the tumor-background normal tissue boron levels and it was determined that ~ 91% of the tumor dose came from the BNCT reaction. With a median follow-up of 31 months, the 2-year local control was 27%, the 2-year overall survival was 30%, and the 2-year progression free survival was 27%. Acute side effects included mucositis and oral pain in 54% of patients and fatigue in 32% of patients. Late effects included grade 3 osteoradionecrosis in 3 patients and grade 4 soft tissue necrosis in 1 patient. A subsequent report by the Finnish group on 9 patients treated with BNCT for recurrent or

persistent laryngeal cancer showed a median time to progression after BNCT of 6.6 months with a median overall survival of only 13.3 months (Haapaniemi et al, 2016).

Wang et al treated 17 patients with recurrent head and neck tumors at the TRIGA CONV reactor in Taiwan using 2 radiation fractions spaced 28 days apart (Wang et al, 2016). Again ^{18}F -L-BPA PET imaging was used to determine the tumor-background normal tissue boron levels. With a median follow-up time of 19.7 months, there were 6 patients with partial tumor responses and 6 patients with complete tumor responses and at 2-years the Kaplan-Meier plots showed a local control rate of 28% and an overall survival rate of 47%. There was a 29% incidence of acute grade 3 mucositis and 1 patient had grade 4 laryngeal edema and carotid hemorrhage. Late effects included 2 patients with grade 3 neuropathy, 1 patient with grade 3 soft tissue necrosis, and 1 patient with grade 3 local pain.

The overall results using BPA based BNCT in the retreatment setting appear to be about the same as with other retreatment methods. What is encouraging is the development of a different class of compounds based upon liposomes that shows efficacy in an animal head and neck model. Kueffer et al describe a MAC-TAC liposome that contains boron in both the bilayer membrane and in the aqueous core (Kueffer et al, 2013). Using the EMT6 tumor model in BALB/c mice, they were able to demonstrate a 67 $\mu\text{g/g}$ boron accumulation in the tumors with a tumor/blood boron ratio of 5.68. Heber et al then tested this agent on the hamster cheek pouch model showing a boron concentration in the tumor of 67 \pm 16 $\mu\text{g/g}$ with accumulations in the surrounding precancerous tissue of 11 \pm 6 $\mu\text{g/g}$ and a 10:1 tumor/normal tissue boron ratio (Heber et al, 2014). Giving 21Gy-equivalent to the tumor resulted in only 5 Gy-equivalent to the surrounding precancerous tissue. At 4 weeks the overall tumor response was 70%. Work is in progress to obtain FDA approval to use this compound clinically with

recurrent head and neck tumors being among the first to be studied.

5. Summary and Conclusions

Particle radiotherapy is of increasing interest in the treatment of head and neck cancers, both for the common HNSCC and the less common salivary gland tumors, mucosal melanomas, and skull base tumors. Fast neutron radiotherapy is a mature field with well established clinical indications based upon tumor radiobiology. It is particularly useful in the treatment of salivary gland tumors and also has applicability in the treatment of “radioresistant” tumors such as sarcomas and mucosal melanomas. Currently the most active area of clinical investigation involves proton radiotherapy where the improved dose localization allows higher radiation doses to be safely given. Proton radiotherapy is a recognized treatment for skull base tumors. While there have been multiple dosimetric studies showing

improved tumor coverage and dose reduction to avoidance structures in the treatment of HNSCC, the clinical data is relatively sparse and randomized studies are lacking. There is an ongoing randomized clinical trial, NCT01893307, comparing IMRT and IMPT for patients with oropharyngeal cancer that hopefully will address this matter. Carbon-ion radiotherapy is available at only a relatively few centers throughout the world but this modality is especially intriguing in that it offers the radiobiological benefits of fast neutron radiotherapy and the dose localization advantages of proton radiotherapy. Carbon-ion facilities are extremely expensive and it will be important to thoroughly evaluate their clinical utility. BNCT for head and neck cancer represents the repurposing of an older technology and is of interest because of the development of newer boron carrier compounds that yield high boron concentration in HNSCC.

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Figure Captions

Figure 1: The neutron depth-dose curve for the University of Washington neutron treatment facility which utilizes a 50.5 MeV proton beam on a semi-thick,

beryllium target (solid line). A depth-dose curve for a 6 MV photon beam from a linear accelerator is shown for comparison (dashed line).

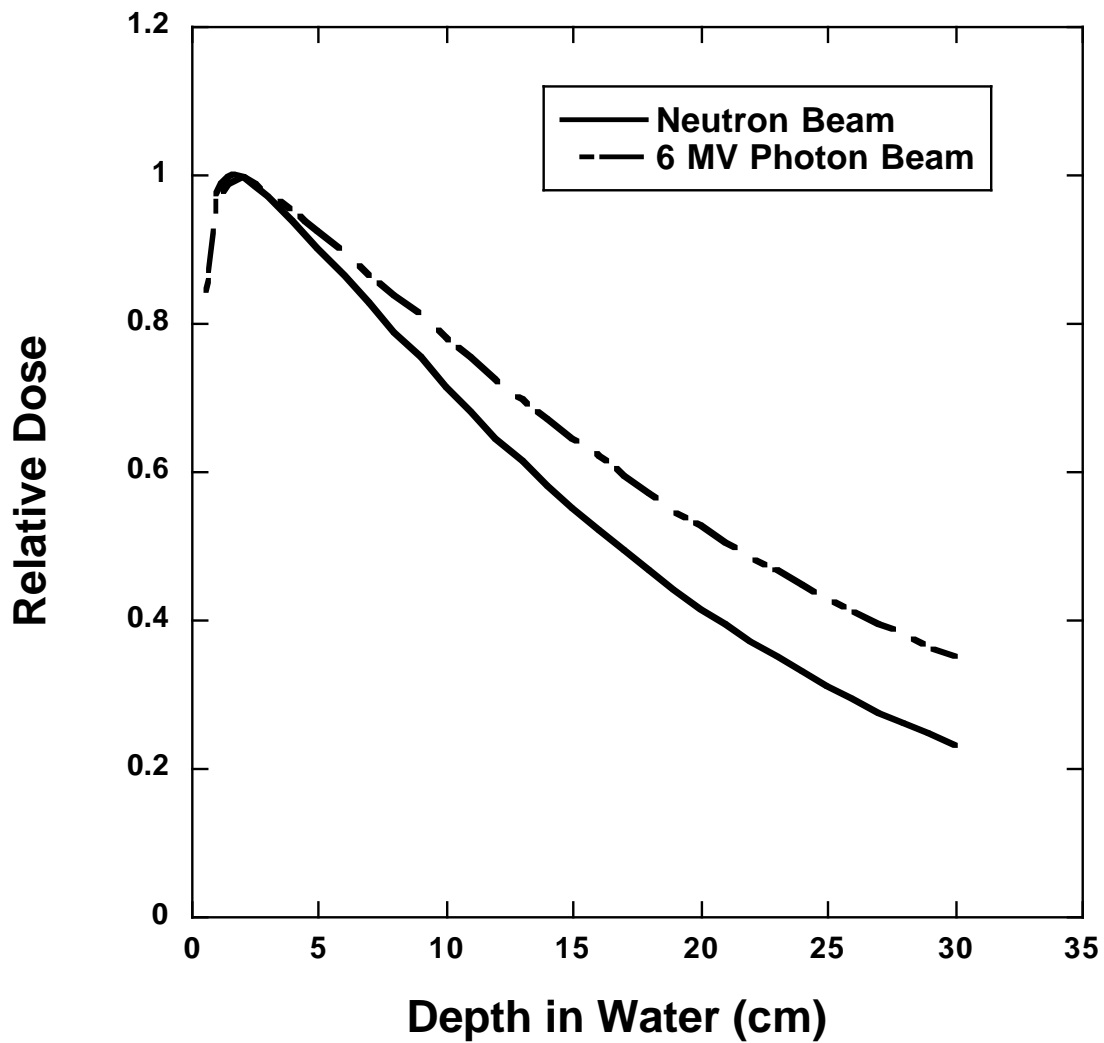


Figure 2: Probability of local/regional failure for patients treated on the two arms of the RTOG/MRC randomized clinical

trial. The photon arm is shown as the dashed curve and the neutron arm is shown as the solid curve. (Laramore, et al, 1993).

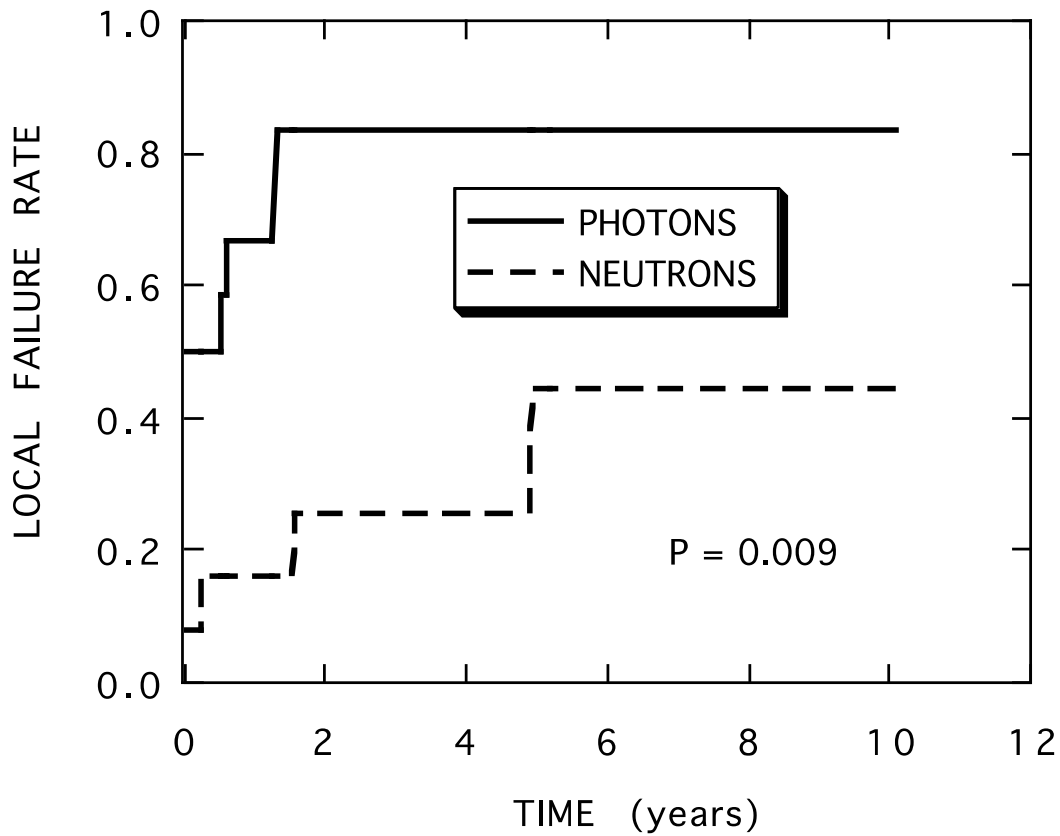


Figure 3: The proton energy distribution as a function of depth in water is shown in (a) and the carbon ion energy distribution as a function of depth in water is shown in (b). These curves have been taken from the general literature.

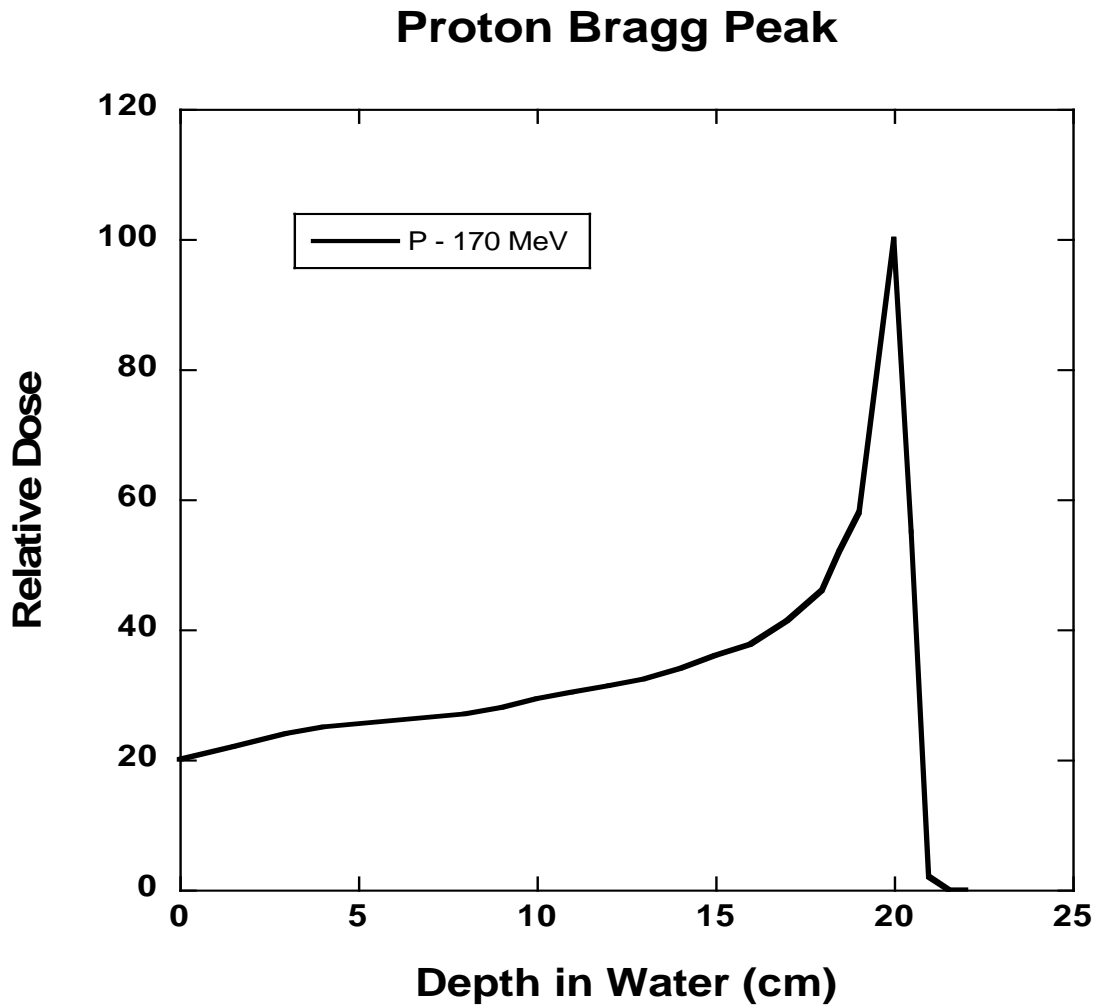


Figure 4: Schematic illustration of the BNCT process. The resulting α -particle and ${}^7\text{Li}$ nucleus are high LET particles having respective ranges in tissue of 10 μ and 6 μ , respectively.

