# THE ROLE OF NEUTRON RADIOTHERAPY IN THE TREATMENT OF ADENOID CYSTIC CARCINOMA

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## Background

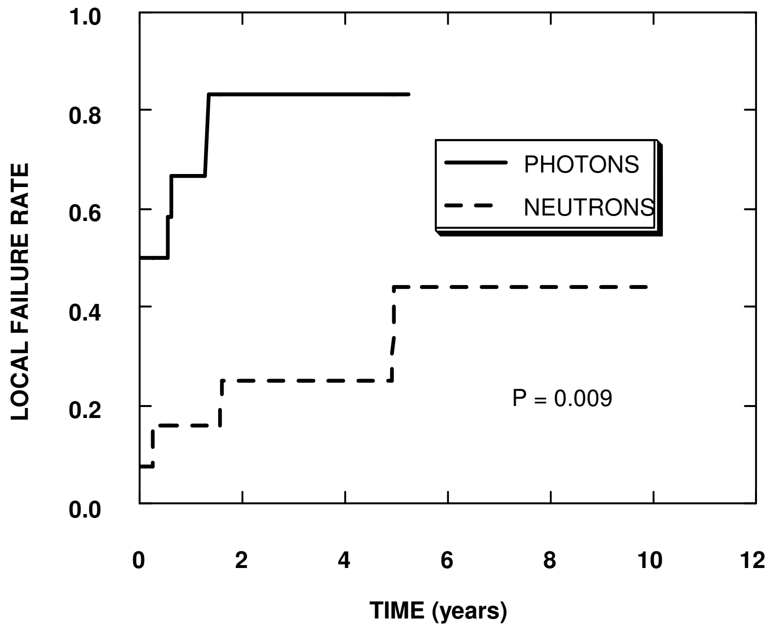
Adenoid cystic carcinomas most commonly arise in either the major (parotid, submandibular, or sublingual) or minor salivary glands. The minor salivary glands consist of clusters of secretory cells scattered throughout the upper aerodigestive tract. Examples of sites where such tumors arise are the palate, nasopharynx, tongue base, mucosal lining of the mouth, larynx, or trachea. Adenoid cystic carcinomas of non-salivary gland origin can arise in the lacrimal (tear) glands of the eye or in the breast. The later are quite rare. Regardless of location, these tumors have the same basic biological behavior in that they tend to spread along nerves (perineural invasion), rarely spread to the lymph nodes (although this does happen in about 5-10% of cases), and have a propensity for hematogenous spread (via the blood stream). The lung is the most common site where these distant metastases occur but they can also occur in the bones, liver, etc. Adenoid cystic carcinomas are generally considered to be resistant to conventional forms of radiotherapy (photons/x-rays or electrons) because of their ability to repair radiation damage. However, in the setting of low disease burden after surgery, conventional radiotherapy is effective in reducing the risk of local tumor recurrence.

## Why Use Neutrons?

Neutrons are an entirely different type of radiation which have different radiobiological properties than conventional radiation. A neutron is a constituent of the atomic nucleus and interacts directly with the atomic nuclei in tissue. Compared to conventional radiation, neutrons typically deposit 20-100 times more energy along their path length and so inflict greater damage in the cells -- damage which is less readily repaired. Neutron radiotherapy has been tested on many different types of tumors but salivary gland tumors, and in particular, adenoid cystic carcinomas, are where neutrons show the greatest benefit.

## Clinical Data

In the 1980s the Radiation Therapy Oncology Group of the United States and the Medical Research Council of Great Britain conducted a randomized, clinical trial comparing fast neutron radiotherapy with conventional radiotherapy for patients with either recurrent and/or inoperable salivary gland tumors. These patients were "high risk" in that they had bulky tumors at the time they were treated. This study was stopped early for ethical reasons when it became apparent that the local control rate was considerably better in the neutron-treated group. Because this is the only randomized neutron trial for salivary gland tumors, it is worth looking at the local control data from the final report which is shown below. The long term local control rate is 56% for the neutron-treated group compared to only 17% for the photon-treated group.




Probability of local failure for salivary gland patients as a function of the type of treatment. Data is from Laramore *et al.* Int. J. Radiat. Biol. Phys. 27: 235-240, 1993.

There were a mixture of different tumor types in this early study with about 25% being adenoid cystic carcinomas.

A recent report [Douglas *et al.* Head Neck 21:255-263, 1999] from the University of Washington dealt strictly with adenoid cystic carcinomas. This showed a long term local control rate of about 80% for tumors that were less than 4 cm in size. Even for tumors larger than this, a 35% long term local control rate was achieved. While neutrons are more effective than photons, it is clear that on a statistical basis we obtain better results with the smaller tumors. Hence, there is a role for a conservative surgical resection to be followed by neutron radiotherapy.

As far as I can tell, all adenoid cystic carcinomas, even those arising in the tear glands, respond well to fast neutrons. To my knowledge, there is no reported data on the use of neutrons to treat adenoid cystic carcinomas arising in the breast. While breast adenoid cystic carcinomas would likely respond well to neutron radiotherapy, their location tends to make primary surgery a better choice.

Side Effects of Neutron Radiotherapy

Neutrons deposit greater amounts of energy in all tissues through which they pass -- not just the tumor cells. Hence, they generally give rise to more severe side effects than conventional radiotherapy. There is a much more severe mucositis reaction (sore mouth and throat) that may make it difficult for the patient to swallow. While any form of radiotherapy to the head and neck can cause xerostomia (dryness of the mouth), at the University of Washington we have worked out ways that often allow us to keep the dose to the parotid gland located on the opposite side as the tumor low enough that it recovers function. Agents such as Saligen can then stimulate this gland resulting in an acceptable saliva output. We are also studying the use of Amifostine to further protect tissues during radiotherapy. A final side effect that we have noticed in patients treated for tumors of the parotid glands is about a 10-15% incidence of hearing loss on the treated side.

## Indications for Neutron Radiotherapy

Because of the increased side effects, neutron radiotherapy is generally utilized for patients with inoperable or recurrent disease. We also use it in the post-surgical setting if there are multiple positive margins (indicating a considerable amount of residual disease), if there is perineural invasion noted in the operative specimen, or if there is tumor spread to the regional lymph nodes. On occasion we use neutrons as a "salvage treatment" for patients with tumors that have recurred in areas that have been previously treated with conventional radiotherapy. Such cases must be evaluated individually as the side effects associated with an aggressive retreatment of this type tend to be severe. It is not possible to use neutrons to treat large areas of the body for metastatic disease but occasionally we do treat isolated metastases when they are causing problems such as pain, causing blockage of part of the lung, are pressing on the spinal cord, etc.

## Treatment Approach

Given the reduced ability of both the tumor and the normal tissue to repair neutron radiation damage, it makes sense from a tumor proliferation point-of-view to treat as rapidly as possible consistent with keeping the side effects during treatment to an acceptable level. This also minimizes the time that a patient is in therapy. In the case of tumors located in the head and neck region, this generally means giving 16 treatments over a 4 week period (conventional radiotherapy generally takes 7-8 weeks). If the tumor is located elsewhere in the body, it may be necessary to give the treatment over a longer time.

At the University of Washington we utilize 3-dimensional conformal techniques for all our neutron patients in order to both target the tumor accurately and to minimize side effects to normal tissue. We make an immobilization device (generally a plastic mask) and perform a special CT scan with the patient immobilized in the treatment position. We then make a 3-dimensional computer model of the patient's anatomy and define the tumor relative to critical structures such as the eyes and spinal cord. This process typically takes several days. Generally a patient who comes to the University of Washington for treatment should plan on staying about 5 weeks.

## Location of Neutron Treatment Facilities in the United States

At the present time there are only 3 neutron treatment facilities in the United States. Because of the rarity of salivary gland tumors, it is possible for these facilities to care for the majority of patients who can benefit from neutron radiotherapy. These facilities produce neutron beams for therapy by accelerating protons or deuterons and impacting them onto a beryllium target.

There is a facility located at Fermi National Laboratory in Batavia, Illinois, that utilizes the proton injector for a large physics-research device to produce the neutrons. This is the least sophisticated of the three facilities having only a fixed, horizontal beam and a set of fixed collimators for shaping the neutron beam.

There is a facility located at the Harper Hospital in Detroit, Michigan, that utilizes a small, superconducting cyclotron to accelerate deuterons. This cyclotron rotates about the patient which makes for a compact therapy system. This facility has a variable collimator that can be used to shape the neutron fields.

The University of Washington facility is located within the University of Washington Medical Center in Seattle, Washington. It is based upon a room temperature cyclotron and utilizes beam optics and a rotating gantry to direct a proton beam to the target. It also has a computer-controlled collimator for shaping the resulting neutron beram. This facility has the greatest experience in treating salivary gland tumors.