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Expanded view

# Boron neutron capture therapy as a novel modality of radiotherapy for oral cancer: Principle and antitumor effect

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ABSTRACT

Radiotherapy is essential for the treatment of oral cancer, especially in advanced cases. There has been marked progress in this field due to the prevalence of intensity-modified radiation therapy and introduction of particle radiotherapy using protons and carbon-ions. However, these treatments are still non-selective. Boron neutron capture therapy (BNCT) is a unique modality in which neutron beams destroy only boron compound-bearing tumor cells while leaving the surrounding normal tissues intact. Thus, BNCT is a selective form of radiotherapy, if high tumor/normal tissue ratio in boron concentration could be achieved. The principle of BNCT, and the basic study of the mechanism by which BNCT exerts antitumor effects using oral squamous cell carcinoma (SCC) cells and oral SCC xenografts in mice are described.



**Contents**



## 1. Introduction

Oral cancers account for 30% of head and neck cancers and treatment is dependent on the stage of the disease [1]. In stages I and II, either surgery or therapy with external or internal irradiation is recommended. In stages III and IV, radiochemotherapy is recommended as a first step. Thereafter, remaining tumors can be removed by surgery [2]. In advanced cases, however, surgical treatment causes severe cosmetic and functional disturbance, lowering quality of life. Radiotherapy is usually applied to tumors alone or in combination with chemotherapy [3]. Indeed, the best studied concurrent chemoradiotherapy regimen involves radiation and cisplatin, and is well-established as a standard of care in the management of patients with unresectable head and neck cancer, and oropharyngeal cancer and post-operative patients with positive margins, extracapsular nodal extension, lymphovascular invasion, and perineural invasion (Fig. 1) [2,4]. It was also reported that cetuximab, an IgG1 monoclonal antibody against the ligand-binding domain of epidermal growth factor, enhanced the cytotoxic effects of radiation in squamous cell carcinoma (SCC) [5,6]. Thus, radiotherapy is essential for the treatment of oral cancer.

The radiotherapeutic management of oral cancer has changed significantly over the past 10 years, as intensity-modulated radiation therapy (IMRT) has become the de facto standard treatment [7,8]. In contrast to conventional radiotherapy, particle therapy using carbon-ions or protons is also gaining importance worldwide [9,10]. Compared with photons such as X-rays and gamma rays, the in-depth dose distribution of particles allows a more accurate administration, resulting in an increased therapeutic ratio (Fig. 2). Nevertheless, it remains unclear, mainly because of the absence of randomized trials, whether particle therapy is superior to radiotherapy with photons in cases of head and neck cancer.

In spite of these developments, in principle, radiotherapy is still non-selective. Although the effect is dependent on the dose, most

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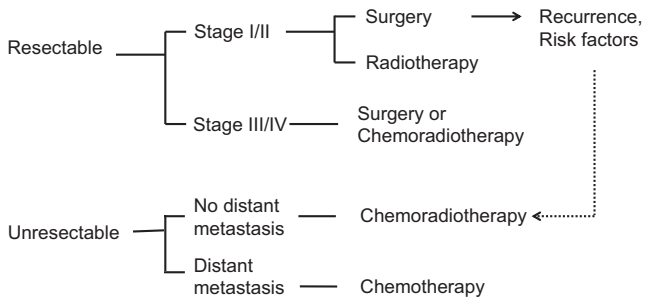


**Fig. 1.** Treatment plan for oral cancer with surgery, radiation and chemotherapy. In stages I and II, either surgery or treatment with external or internal irradiation is recommended. In stages III and IV, radiochemotherapy is recommended as the first step. Thereafter, remaining tumors can be removed by surgery. Usually, radiotherapy is applied to tumors singly or in combination with chemotherapy.

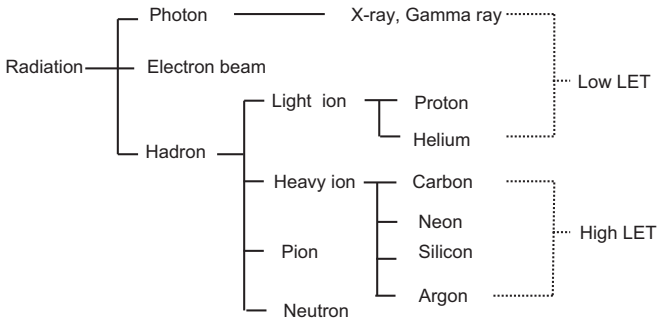


**Fig. 2.** Types of radiation. X-rays, gamma rays, protons, carbon-ions and neutrons are used for cancer therapy. LET, linear energy transfer.

cells exposed to radiation are damaged in a similar fashion. In this respect, boron neutron capture therapy (BNCT) is unique in its selectivity in appropriate conditions [11–13]. Oral cancers can be accessed relatively easily. This makes oral cancer a candidate for treatment by BNCT [14–17]. In this paper, we review the introduction of the principle of BNCT and the mechanism by which BNCT exerts antitumor effects on oral SCC.

## 2. Principles of BNCT

The first theoretical account of the biological effects and therapeutic possibilities of BNCT was published by Locher [18]. BNCT is a two-component modality, in which boron-10 ($^{10}$B)-enriched compounds such as boronophenylalanine (BPA) and borocaptate sodium (BSH) are administered, prior to irradiation with a thermal neutron beam. $^{10}$B absorbs the neutrons and releases two linear energy transfer particles, an α($^{4}$He) particle and a lithium ($^{7}$Li) nucleus (Fig. 3). These products from the $^{10}$B (n, α) $^{7}$Li reaction have path lengths in water of 5–10 μm. This suggests that the effectiveness of BNCT depends on the maintenance of relatively high concentrations of $^{10}$B in the tumor compared with the surrounding normal tissues, and that BNCT potentially targets neoplastic tissue selectively [11–13]. Thermal neutrons are responsible for the boron capture reaction, but epithermal neutrons are now more generally used to improve the depth-dose profile. It should be also stated that boron captures thermal neutrons to produce two high linear energy transfer (LET) particles, i.e. α($^{4}$He) particle and lithium ($^{7}$Li) nucleus. However, they are also captured non-selectively by tissue nitrogen and hydrogen to produce high LET protons and low LET gamma rays which are by definition not tumor specific.

Thus, it is essential to elevate the intracellular boron concentration in tumor cells, while maintaining low levels of $^{10}$B in normal tissue. This results in a high tumor/normal tissue (T/N) ratio. Another important factor is the use of nuclear reactors, because the source of neutrons is limited to neutron beams derived from nuclear reactors. Thus, the treatment can be done only in certain countries and areas. Reactor-derived neutrons are classified according to their energies as thermal (En < 0.5 eV), epithermal (0.5 eV < En < 10 keV), or fast (En > 10 keV). Thermal neutrons are the most important for BNCT as they initiate the $^{10}$B (N, α)$^{7}$Li capture reaction. Because they have a limited depth of penetration, epithermal neutrons, which lose energy and fall into the thermal range as they penetrate tissues, are now preferred for clinical therapy. Several nuclear reactors with good neutron beam quality have been developed. These include the Massachusetts Institute of Technology reactor (MITR) in the USA, the clinical reactor at Studsvik

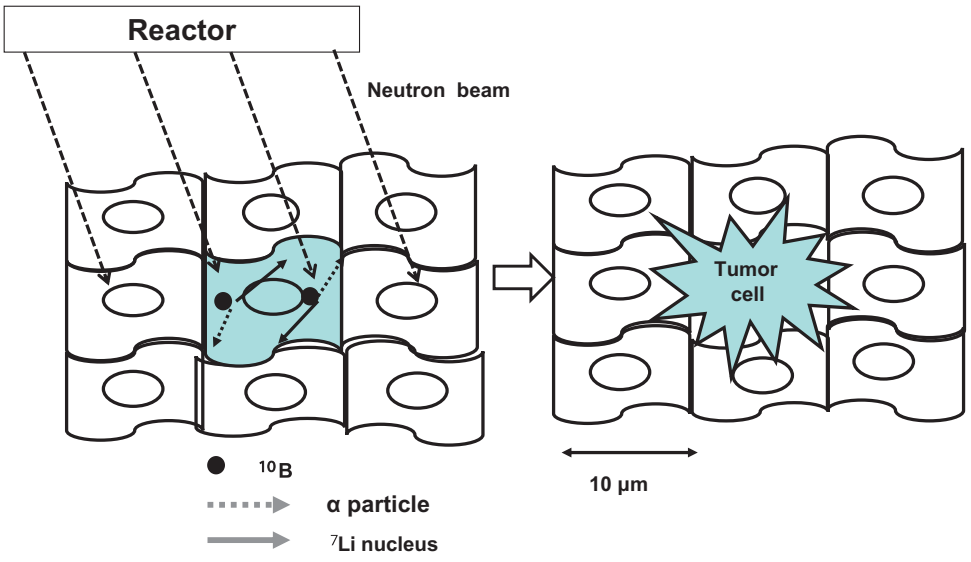


**Fig. 3.** The principle of boron neutron capture therapy (BNCT). BNCT is a two-component modality, in which $^{10}$B-enriched compounds are administered, prior to irradiation with a thermal neutron beam. $^{10}$B absorbs the neutrons and releases an α($^{4}$He) particle and a lithium ($^{7}$Li) nucleus. Since these products have path lengths in water of 5–10 μm, the effect depends on the maintenance of relatively high concentrations of $^{10}$B in the tumor compared with the surrounding normal tissue. Only tumor cells that incorporate $^{10}$B are destroyed.