Review Article

Boron neutron capture therapy in the treatment of lung cancer

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Abstract: Boron neutron capture therapy (BNCT) is a binary treatment based on the atomic interactions between epithermal neutrons and boron-10 isotopes, which can provide a means for specific molecular and cellular targeting of high energy radiation to tumour cells with the concurrent sparing of normal tissue. It has the potential to be the ideal form of treatment for many types of cancers. This paper begins with an overview of BNCT. It then explores the potential of BNCT in the treatment of lung cancer, specifically in the following areas: overcoming complex issues of respiratory motion, treating micrometastatic or diffuse treatment, treating tumours that are adjacent to or have invaded radiosensitive normal tissue, re-irradiation, and hypofractionated treatment. The paper concludes with a summary of the efforts and plans of the international BNCT community to make this treatment a widely adopted one.

Keywords: Boron neutron capture therapy (BNCT); lung cancer

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Introduction

Despite advances in cancer treatment, lung cancer is still one of the most common malignancies worldwide with a high mortality. Radiotherapy remains an important treatment modality in for lung cancer. When radiotherapy is currently employed in lung cancer, two major challenges exist. Firstly, as radiation is delivered, the path of photons traverse normal tissues before reaching the tumour, depositing unnecessary and harmful, but inevitable, radiation in these normal tissues, which are relatively radiosensitive and unable to tolerate high doses of radiotherapy. Secondly, movement of the thorax and its contents during respiration results in the intrafractional movement of the tumour, which in turn can lead to more normal tissue exposure. Together, they limit the radiation that can be received by tumour.

To further complicate matters, disease recurrence is the dominant cause of death after initial treatment of lung cancer. Recurrent lung cancer has been historically viewed as universally fatal as only rarely did efforts lead to tumour control, let alone cure. It is particularly challenging to attempt thoracic re-irradiation in patients where radiotherapy was used as part of their initial management. It has been generally assumed that once definitive radiotherapy has been administered, further radiotherapy cannot be given because the cumulative doses of radiation would likely exceed normal tissue tolerances, resulting in a higher incidence and higher grades of toxicities (1).

Boron neutron capture therapy (BNCT) has for close to a century been proposed as a novel form of radiotherapy that theoretically can be the ideal treatment for many types of cancers. This paper explores the potential of BNCT in the treatment of lung cancer, overcoming the challenges alluded to in the preceding paragraphs.

BNCT is a treatment centred on the atomic interactions between neutrons and boron-10 isotopes. A brief introduction into the reactant entities of this reaction is in order here. The neutron is a subatomic particle with no net charge. Together with protons, they constitute the nuclei of atoms which are the building blocks of all matter. Neutrons can be classified according to their kinetic energy, and the neutrons used in BNCT are those with a lower kinetic energy. Boron, on the other hand, is a metalloid element with the symbol B and atomic number of 5. The stable boron-10 isotope makes up about 20% of all naturally occurring boron. It has the unique property of "capturing"

neutrons—to merge with neutrons to produce a heavier nucleus.

BNCT relies on this capture reaction. In BNCT, inert boron-10 is first selectively taken up by cancerous cells. This is achieved by making use of the interplay between tumour characteristics and the pharmacology of boron-containing compounds. A full discussion of this topic is beyond the scope of this paper. We shall limit the discussion to the most commonly used boron-carrier, borono-phenylalanine (BPA). BPA is a modified version of the amino acid phenylalanine, and thus share very similar behaviour with it. Phenylalanine and other amino acids are transported into cells through transporter-mediated mechanism, one of which is the L-Amino Acid Transporter 1 (LAT1). Tumours have been known to over-express LAT1, which accounts for how BPA is selectively taken-up by them. Obviously, other boron-carriers will use other different mechanisms to be selectively taken-up by tumours, which makes BNCT a very exciting field in the years to come.

These boron-saturated tumours are then irradiated with epithermal neutron, which would be absorbed by boron-10, resulting in the production of unstable boron-11, which immediately undergoes nuclear fission to produce highly destructive alpha particles and recoiling lithium-7 (^{7}Li) nuclei (2).

These heavy charged particles have short pathlengths of approximately one cell diameter and deposit their destructive energy within the boron containing cell. Thus, the BNCT allows specific cellular targeting of highly destructive radiation to tumour cells while simultaneously sparing normal tissue.

BNCT in clinical practice—an overview

If the "Holy Grail" of radiotherapy is to develop a technique that can maximize tumour cell kill while minimizing normal tissue radiation exposure and damage, then BNCT is a top contender for this title (3).

However, despite the potential of BNCT being first recognised in 1930s, technological limitations in the past decades could not make it a reality until the recent years. Over the past six decades, different neutron facilities and multi-disciplinary BNCT groups from different institutes all around the world, have studied the use of BNCT on patients suffering from a various cancer type. Most of these studies are phases I and II clinical trials, and the remainder are clinical procedures performed outside controlled clinical trial protocols (4).

These trials were performed in difficult-to-treat tumours whose standard optimal therapies do not provide satisfactory outcomes, in attempt to improve patient outcomes.

The difficult-to-treat tumour that been most extensively treated with BNCT is glioblastoma multiforme (GBM), which is a very aggressive brain tumour. Standard treatment consisting of surgery followed by external beam radiotherapy of 60 Grays (Gy) in 30 fractions with concurrent and adjuvant oral chemotherapy, temozolomide, confers a median overall survival of 14.5 months (5). BNCT has been compared to this standard treatment in two different studies and both have shown that it is at least equivalent, if not better than standard therapy (6,7). Both studies also demonstrated lower incidences as well as lower grades of toxicities sustained by patients. BNCT has also been demonstrated to be efficacious in recurrent GBM, which current standard salvage treatments yields a very dismal prognosis (8).

The second ground of tumour are locally recurrent previously irradiated inoperable head and neck cancers. For this group of patients, National Comprehensive Cancer Network guidelines recommends that "*the treatment approach is the same as that for patients with metastatic disease*", which consists of palliative measures including palliative radiotherapy, analgesia and systemic therapies (9). The phase III EXTREME trial demonstrated that addition of the monoclonal antibody cetuximab to platinum-based chemotherapy improved the overall survival of patients with locally recurrent previously irradiated inoperable head and neck cancers, conferring a median overall survival of 10.1 months (10). On the other hand, a phase I/II trial by Kankaanraata *et al.* of 30 patients with recurrent head and neck cancer treated with BNCT showed an overall survival of 13 months. This was comparable to the results of EXTREME, and like the GBM studies, it was once again achieved with lower incidences of toxicities (11).

With these impressive results, clinical trials have been done with many other difficult-to-treat tumour subsites, including melanoma, sarcoma, hepatocellular carcinoma and other brain tumours. From such a track record, the interest has expanded to the use of BNCT for lung cancer and other thoracic malignancies.

BNCT and lung cancer

The lung, which in the usual state consists of largely air, does not attenuate neutron as much as other normal tissue for which water is a major constituent. This means the

epithermal neutrons used in BNCT can traverse into the thorax to treat tumours at a greater depth than it normally could, which in turn makes BNCT for thoracic diseases an attractive option.

The interest in the use for BNCT in thoracic cancer were first reported in the 2006. Suzuki *et al.* (12) performed a dosimetric study to evaluate the feasibility of BNCT for malignant pleural mesothelioma. His results showed that BNCT has the possibility to be a promising treatment for these patients. Two years later, he went on to treat a patient with mesothelioma with good outcomes (13).

This prompted other groups to explore the use of BNCT in lung cancer. Farias *et al.* (14) reported dosimetric analysis of BNCT in three scenarios. The authors recognised that while there had been good outcomes reported when non-small-cell lung cancer (NSCLC) are treated with hypofractionated, high dose radiotherapy (e.g., stereotactic body radiotherapy, SBRT), there were also situations where such therapies were not possible because of proximity to tumours at risks. Using SBRT criteria for dose constraints, the authors went on to evaluate treatment plans of BNCT for three scenarios: a localised early stage NSCLC close to chest wall, a deep localised tumour close to trachea and bronchi, and oligometastatic disease encompassing the whole lung volume. All three treatment plans showed that BNCT could deliver adequate tumour dose without exceeding normal tissue constraints. A second dosimetric study by Yu *et al.*, confirmed the results of Farias *et al.*—that BNCT is feasible for the treatment of lung cancer (15). Both studies also demonstrated that tumour depth does not preclude BNCT in the thorax.

Selective dose delivery at a cellular level is attained because the cell destruction in BNCT is confined to cells where neutrons are captured. This allows the BNCT to achieve the following in the treatment of lung cancer:

(I) to circumvent the issues surrounding complex techniques currently used to overcome respiratory motion during conventional external radiotherapy, while not requiring the irradiation field to tightly conform to the shape of the target;
(II) the ability to treat micrometastatic or diffuse treatment, while sparing intervening normal tissues;
(III) the ability to treat tumours that are adjacent to or have invaded radiosensitive normal tissue e.g., superior sulcus tumour;
(IV) re-irradiation;
(V) the possibility of delivering a hypofractionated or single treatment.

These situations described above that would benefit from BNCT shall be discussed in details in the following sections.

Overcoming motion effects of respiration

Lung tumour generally move with respiration. Thus, to be able to treat the tumour throughout the entire respiratory cycle, all the possible positions of the tumour during the cycle are considered, resulting in a larger treatment field, which leads to irradiation of a large volume of normal surrounding tissue, resulting in possible increase in the risk of complications, and consequently putting a limit on the possibility of dose escalation. Five main strategies are currently used to reduce respiratory motion effects: integration of respiratory movements into treatment planning, forced shallow breathing with abdominal compression, breath-hold techniques, respiratory gating techniques, and tracking techniques. *Table 1* summarises the characteristics of each of these techniques (16).

According to International Commission on Radiation Units and Measurements (ICRU) (17,18) recommendations, tumor motion and positioning uncertainties are considered by adding a specific margin around the clinical target volume to create the planning target volume (PTV). However, this strategy has its limits as the addition of such safety margins leads to irradiation of a large volume of healthy tissue, which in turns increases the risk of complications, and therefore limiting the possibility of dose escalation.

However, because of the tumour selectivity of BNCT at the cellular level that greatly minimises normal tissue exposure, such an integration of respiratory movements into treatment planning by using a large margin is a simple and viable plan. This is because only the boron-concentrated tumour within the treatment field irradiated by neutron receives the high radiation dose—the normal tissue that is devoid of boron have minimal interaction with neutron. This in turn negates the need for complex equipment and techniques needed by the other strategies to overcome respiratory motion.

Treatment of metastatic and disseminated disease

The ability of BNCT to selectively target and destroy cancer cells, while leaving normal cells relatively unscath, provides the promise of using radiotherapy to treat

Table 1 Strategies used to reduce respiratory motion effects

Technique	Description	Advantages	Disadvantages
Integration of respiratory movements into treatment planning	Tumour motion and positioning uncertainties are considered by adding a specific security margin around the clinical target volume to create the PTV	Patients set up and treatment duration not affected	Potentially large PTV—increased dose to the organs at risk
Forced shallow breathing with abdominal compression	A plate is pressed against the patient's abdomen; the pressure plate is attached to a stereotactic body frame by a rigid arc.	Decrease tumor motion during radiation treatment, and thus decrease tumour position uncertainties	Causes discomfort; may be stressful to patients with compromised pulmonary function; increased length of treatment; patient training required
Breath-hold techniques	In active breath-hold techniques, the airflow of the patient is temporarily blocked by a valve; in passive techniques, the patient voluntarily breath-holds; during the period of breath holding, irradiation is performed	Decrease normal tissue exposure by not irradiating outside of breath hold when greater volume of normal lung tissue is within treatment field	May be stressful to patients with compromised pulmonary function; increased length of treatment; patient breathing patterns may be erratic after a period of breath hold; patient training required
Respiratory gating techniques	Real-time monitoring of patient free-breathing with triggering the CT scan acquisition and/or linear accelerator at a specific respiratory phase	Decrease normal tissue exposure by not irradiating outside of the specific respiratory phase when greater volume of normal lung tissue is within treatment field	Increased treatment duration; patient training required; specialised equipment required
Tracking techniques	Real-time localization of, and real-time beam adaptation to, a constantly moving tumor	Potential reduction of PTV margins, as beam adapts to tumour position, leading to decreased normal tissue exposure	Increase treatment duration; specialised equipment and treatment machine required

PTV, planning target volume; CT, computed tomography.

disseminated disease. In the past radiotherapy in such a scenario was impossible when the intervening normal tissue was exposed to radiation that would exceed the overall tolerance, as would be in the case of most situations. Though it may sound unusual, it should be noted that metastatic lung disease has been treatment with photon irradiation in patients with Wilm's and Ewing's tumour.

Wilkinson (19) in 2003 described a patient treated with BNCT in Pavia, Italy, whose liver was filled with metastases from colon carcinoma. The patient was first injected with a boron-carrying compound that was taken up by rapidly dividing cancer cells 2 hours before his operation. The liver was then removed, placed in a teflon bag, and irradiated with neutrons for only 11 minutes, before the liver was autotransplanted into the patient. Due to the selective uptake of boron in tumors, even small metastases that could not be diagnosed by the imaging methods were also treated. The patient, who had exhausted all possible conventional treatments and whose prognosis was predicted to be in the order of a few months, was remarkably able to live a normal life for 44 months after the BNCT treatment (20).

Thus, researchers have begun performing similar studies in patients with multiple lung tumour. As the lung is a radiosensitive tumour, irradiation of a large volume such as hemi-thorax or whole thorax with conventional radiotherapy techniques are expected to lead to fatal radiation pneumonitis. While the non-BNCT techniques in *Table 2* may be able to treat a few lung tumours, it is impossible to treat patients with diffuse tumours or multiple lung tumours. Using BNCT, a large volume of the thorax

can be irradiated with the aim of delivering curative dose to multiple or disseminated tumours. Farias *et al.* described their biodistribution studies to evaluate the feasibility and therapeutic potential of ex situ BNCT for lung tumours. The results were promising, suggesting that whole lung irradiation is a feasible technique that may increase overall survival and quality of life in patients with metastatic lung disease without extrapulmonary spread (21).

Suzuki *et al.* reported a pilot study of two patients, one with malignant pleural mesothelioma and one with malignant short spindle cell tumour, who were treated with BNCT. In both cases, the tumours responded to BNCT for a period of 3 to 6 months, with no adverse side effects greater than grade 2 observed (13). Further case

Table 2 Techniques employed for re-irradiation of tumours

Technique	Description	Advantages	Disadvantages
IMRT	IMRT subdivides each large radiation beam into smaller beamlets using small 'leaves' that move across the beam's path at different speeds and patterns while the beam is on; this results in parts of the radiation beam are selectively blocked for a portion of the treatment time, with the consequent effect that certain regions of the radiation beam deliver a high dose, while other regions deliver a low dose	Combining seven to nine beams allows the delivery of complex treatment plans that deliver high doses to the gross disease while sparing the normal surrounding OARs; has potential to allow dose escalation in patients with lung cancer	Longer treatment duration; radiation leakage through multi-leaf collimators; IMRT contouring is time consuming; higher integral dose to the lung; following exposure to low dose radiation there is a theoretical increased risk of radiation-induced second malignancies years or even decades following treatment
VMAT and tomotherapy	Both VMAT and tomotherapy involves the rotation of the source of the radiation beam with respect to the patient	Target dose distributions are improved, and hot spots are reduced in normal structures; allows increased dose to the tumour	Higher integral dose to the lung; following exposure to low dose radiation there is a theoretical increased risk of radiation-induced second malignancies years or even decades following treatment; specialised equipment and machines required
IGRT	IGRT is the use of imaging during radiation therapy to improve the precision and accuracy of treatment delivery; IGRT is used to treat tumours in areas of the body that move, such as the lungs	Reduction of set-up error and of volume of healthy tissues in PTV; change of shape and volume of tumour and healthy tissues can be measured and corrections applied; increased precision of treatment delivery and thus early and late effects caused by radiation should decrease	There is no single technology or strategy that can be employed for every clinical scenario; increase in precision of delivery of dose increases also places increased emphasis on accurate tumour detection and delineation errors; treatment time longer and might be problematic to patients with breathing difficulties
SBRT	SBRT gives radiotherapy from many different positions around the body; the beams meet at the tumour; so, the tumour receives a very high dose of radiation and the tissues around it only receive a low dose	Beneficial for early stage lung cancer patients who cannot undergo surgery; high local control rate for relatively small lung tumours; low treatment-related toxicity; allow for re treatment of infield recurrence; fewer fractionations	Long set up and treatment delivery—potential for intrafraction motion and error; suitable only for small, well defined tumours

Table 2 (*continued*)

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Technique	Description	Advantages	Disadvantages
Proton therapy	A type of particle therapy that uses a beam of protons to irradiate diseased tissue, most often in the treatment of cancer	Lower dose to lung tissue and also to other organs at risk, than what is possible with photon therapy; dosimetric superiority compared to photons gives the promise of potentially lower side effects; doctors can control, to an extent, where the highest dose goes to; dose escalation is more feasible with proton therapy than with photon therapy; much reduced exit dose compared to photon	Aerated lung tissue is less dense than other soft tissues of the body, thus, the stopping region of protons is less precise in the lungs than in other tissues; limited clear published clinical benefits; higher cost; changes in patients, weight may affect dose and treatment plan
BNCT	Binary technique that allows cell-selective high-LET particle radiotherapy to tumor mass and the microscopic invasion while avoiding radiation damage to the surrounding normal tissue, based on the nuclear interaction of boron atoms with neutrons of appropriate energy (see main text)	Selectively delivery of high linear energy transfer radiation to tumour; selective therapy at a cellular level—even smallest malignant cell will be destroyed; radiation field does not have to be accurate; short fractionation and short treatment times	Current technology limits BNCT to nuclear reactors which can be distant from hospital; not widely available; large separation for with tissue that attenuate neutrons may decrease effective dose to tumour

BNCT, boron neutron capture therapy; LET, linear energy transfer; SBRT, stereotactic radiotherapy; IGRT, image-guided radiation therapy; VMAT, volumetric modulated radiotherapy; IMRT, intensity modulated radiation therapy; PTV, planning target volume; OAR, organs-at-risk.

reports by the same author presented at the recent 9th Young Researchers' BNCT Meeting have demonstrated the viability of such an approach by delivering sufficient radiation dose to the tumours without undue toxicities (22). We await the published results of Dr. Suzuki.

Treatment of tumour adjacent to organs at risk—e.g., superior sulcus tumour

Superior sulcus or Pancoast tumours are a subset of lung carcinomas located in the apex of the lung and with a tendency to invade into the surrounding structures of the thoracic inlet which includes the 1st and 2nd ribs, the 1st and 2nd vertebral bodies, the lower nerve roots of the brachial plexus, the upper sympathetic chain and stellate ganglion, and the subclavian vessels (23).

The invasion of these adjacent vital organs makes Pancoast tumours one of the most challenging thoracic malignancies to treat because attempts to deliver tumoricidal doses of radiation would exceed the normal tissue tolerances.

BNCT's ability to selectively destroy cancer cells with a sharp dose drop off makes treatment in such situation possible. BNCT can deposit a large dose of radiation while creating a steep dose gradient between the tumour and normal structures that have been invaded by the tumour. In fact, similar strategies have been employed in tumours elsewhere in the body. Kankaaraanta *et al.* (24) described a patient with a newly diagnosed inoperable head and neck poorly differentiated carcinoma that was abutting bilateral optic nerves, making it challenging to achieve a cure with conventional X-ray radiotherapy while maintaining a low risk of severe organ damage. This patient was first treated with BNCT which shrunk the tumour away from these organs at risk. Then the patient completed treatment with photons to the remaining tumour. When evaluated 9 months post treatment, there was no evidence of disease and the patient's vision remained normal.

At the 9th Young Researchers' BNCT Meeting, Suzuki described a case series of three patients with superior

sulcus tumour who were salvaged with BNCT (22). The accompanying dosimetric studies and reported clinical responses presented there were proof of concept of the utility of BNCT in the treatment of superior sulcus tumours.

Re-irradiation

Cumulative normal tissue exposure to radiation becomes the biggest limitation for re-irradiation. Various techniques have been employed and tried to irradiate recurrent tumours without excessive normal tissue exposure:

- Intensity modulated radiotherapy;
- Tomotherapy;
- Volumetric arc therapy;
- Image-guided radiotherapy;
- Stereotactic body radiotherapy;
- Proton therapy.

Table 2 summarises the characteristics, advantages and disadvantages of each of the above treatment. BNCT, with its sparing of non-cancerous cells that do not take up significant boron and thus allowing tumours to receive further doses, is yet another technique that can be used for re-irradiation. Re-irradiation with BNCT has been performed at other tumours sites, notably head and neck cancers, with good clinical response and minimal toxicities (25).

Suzuki *et al.* (26) reported the use of BNCT in the treatment of a 62-year-old male with recurrent lung cancer in a previously irradiated chest wall. Two fractions of BNCT, 1 month apart, were employed. No acute or late adverse reactions were observed, and the patient achieved tumour regression and relief from chest wall pain. As a substantial portion of patients with lung cancer will suffer local recurrence in the previously irradiated region, BNCT has the potential to become a promising treatment option for these patients.

Hypofractionation or single treatment

The alpha particle and lithium-7 ion produced in the BNCT reaction are highly destructive. Doses equivalent of up to 60–70 Gy can be delivered to Boron-10 containing tumour cells within an hour or less instead of 6–7 weeks for conventional external beam photon irradiation (27). To attempt to deliver the same dose of 60–70 Gy in the same period of time with photons would be impossible because of the inevitable fatal side effects from normal tissue exposure. All published case series report the use of one or, at most two, fractions of BNCT with excellent clinical outcome. In addition, by treating in multiple fractions, dose escalation is possible, especially to overcome radioresistant clones within the tumour.

There is another reason why the much shorter treatment times of BNCT is a huge advantage. For many patients who are treated with BNCT, their disease would have reached a stage whereby standard treatment is either no longer possible or merely only a means to prolong life slightly, and they progress relentlessly towards an inevitable demise. For these patients, time is not a commodity they possess in great abundance. The ability of BNCT to deliver a high dose of radiation safely in one fraction frees up valuable time which could then be used to spend time with their loved ones. At the same time, the paucity of side effects means less time is spent recuperating from the aftermath of treatment. Take for example patients with locally recurrent previously irradiated inoperable head and neck cancer. Standard treatment is a course of platinum-based chemotherapy and cetuximab lasting more than 6 months (10). On the other hand, two BNCT treatment, each less than an hour, 1 month apart, yields similar benefits, with much less toxicities (11). Simple arithmetic shows how much more quality time such patients gain with the hypofractionated treatment with BNCT.

Limitations of BNCT

Despite such potentials and track records, BNCT is still not a widely recognised treatment for a few reasons.

The first reason is the source of neutrons. Until recently, nuclear reactors were the main source of neutrons. These same reactors have also been the reason that limited BNCT from becoming a mainstream therapy. Notable problems with nuclear reactor-based neutron sources include: the inherent dangers involved during a meltdown on the scale of Chernobyl or Fukushima; that a reactor is usually used for many other applications besides neutron capture therapy, thus conflicts or limitations on neutron capture therapy work could potentially arise; and lastly, most reactors are separated from hospitals.

Thus, as nuclear reactors are virtually never installed within the hospital environment, the scientific community, over the years, have strived to create thermal and epithermal collimated neutron beams using charged particle accelerators.

There is a general perception that the development of

BNCT into a standard clinical therapeutic modality would depend on these accelerator-based neutron source (ABNS). These ABNS has obvious advantages over reactor-based neutron sources. Firstly, they can be turned off easily when the neutron field is no longer required. Second, they allow the production of a spectrum of neutron energy to allow optimal coverage of a patient's tumour. Third, the costs of installing an accelerator-based BNCT system will be lower than those associated with installation of a reactor system. Lastly, accelerators have been used in radiotherapy departments in hospital and it is deemed easy to site the hardware for BNCT within an existing radiotherapy room with addition of shielding.

Yanch and Blue (28) describes the basic components of BNCT: (I) a particle accelerator to produce a high-current charged particle beam, (II) a neutron-producing target with a cooling system, and (III) a moderator to modify the neutron produced suitable for patient irradiation. Over the past decade, various groups have begun manufacturing their own versions of each of these components and an increasing number are now reporting about their ABNS systems.

Kreiner in 2016 reported that there are eight ABNS systems built or under construction around the world (29). Two of these were intended for clinical use. The first was a cyclotron-based neutron source has been installed at the Particle Radiation Oncology Research Center of Kyoto University in Kumatori, Japan. A second ABNS has been constructed for use at Tsukuba University in Japan. Since the publication of that paper, three other ABNS systems for BNCT have been constructed. The first one is being built the National Cancer Centre Japan in Tokyo. A second accelerator is installed at the Southern Tohoku BNCT Research Center in Japan. The third one is an accelerator designed and fabricated by Neutron Therapeutics in Danvers, Massachusetts, and one of these is current being installed in Helsinki, Finland.

Some researchers have, on the other hand, continued to pursue reactor-based neutron sources by employing a small nuclear research reactor as a neutron source solely for BNCT use (30). Such reactors can be sited within the hospital compound, negating the issue of the great distance that separate hospitals from conventional reactors. The Chinese have developed such a small compact medical reactor, in-hospital neutron irradiator (INHI-1), and they have reported their success of treating melanomas with it (31).

The INHI-1 was constructed to be meltdown-proof. This low-powered reactor is designed such that do not require elaborate external cooling systems, the failure of which led to disasters like the ones on Fukushima in 2011. In INHI-1, once the interior temperature passes a certain threshold, the nuclear reactions slow, resulting in the cooling down the of reactor and thus in essence, making it self-regulating. This slowing down is a phenomenon called doppler broadening, where, as the temperature rises, the uranium nuclear fuel captures more neutrons without undergoing fission, resulting in less neutrons available for the normal function of the reactor. The researchers in INHI-1 have performed a power excursion experiment, confirming that the power will return to normal value after an initial surge.

Overall, neutron sources will become easier to obtain in the years to come. Thus solving the issue of resource availability of one component of BNCT, allowing researchers to focus their attention on the second component of the binary reaction—boron delivery agents.

Moss (4) explains the problems faced with the development of new, more selective boron delivery agents: while it is recognised that these agents are needed for the advancement of BNCT, both from the clinical and research points of view, this also requires the vital support of the pharmaceutical industry. Unfortunately, most pharmaceutical companies have not been interested in boron carriers. However, even if some of them were and managed to develop new boron compounds, there is still a need to undergo a very arduous and long investigative, approval and certification procedure. Thus, over the years, while there have been a multitude of reports of new compounds, in the majority of cases, the compounds never get beyond the laboratory bench. The reasons include tight requirements by the regulatory agencies, such as the FDA, as well as the financial burden that is necessary to carry out clinical biodistribution studies. Nevertheless, there are some promising candidates under development, one example of which is the incorporation of boron delivery agents into tumour-targeting molecules, which would target tumour cells more selectively to achieve a significantly elevated boron concentration in the tumour while at the same time avoiding surrounding tissues.

The third issue that is hampering BNCT from being widely accepted is the lack of dosimetry and the paucity of the knowledge of the exact dose delivered by the BNCT reaction. Current methods of determining this dose is by inferring from the measured neutron flux and the estimated boron concentration, which is in turn derived from uptake studies such as BPA-positron emission tomography (BPA-PET). While such an estimation may be sufficient for situations where BNCT is used as a last-ditch treatment in

patients in whom all standard treatment had failed, some radiation oncologists regard with great importance the need to know exactly how much dose is being delivered in each BNCT session to the tumour and to the organs-at-risk, and thus deem that such technique is insufficient, leading to the resistance of accepting BNCT as a standard treatment. As such, there is a need for a real-time, *in vivo*, non-invasive technique to measure the delivered BNCT dose. Over the years many innovative approaches have been proposed. The most common method is to use single photon emission computed tomography (SPECT) to measure the small amount of gamma rays that are produced during the BNCT reaction. By using tomographic reconstruction, a 3-dimensional image can be produced to provide both dosimetric information and tumour localisation. However, as the BNCT reaction only occurs when the neutron beam is applied, it stands to reason then that this method can only progress in tandem with the development of ABNS-BNCT, when other medical instruments can be integrated with much greater ease than BNCT facilities sited in a nuclear reactor.

Conclusions

Radiation oncologists today live in an exciting time, as technological advances abound and ever-increasing repertoire of radiation techniques appear to aid us towards achieving the "Holy Grail" of radiotherapy of maximal radiation dose in the tumour and minimal dose in the normal tissues. Admittedly, despite its clinical advantages, the potential of BNCT to become a mainstream radiotherapeutic modality is faced with hurdles and roadblocks highlighted in this article. However, when, and not if, they are conquered, then BNCT will become the next big thing in radiotherapy, not just for lung cancer, but for most cancers.

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