Stereotactic body radiation therapy: an emerging technique for prostate cancer treatment

Abstract Purpose: Stereotactic Body Radiation Therapy (SBRT) is treatment using stereotactic techniques outside of the brain. SBRT involves accurate delivery of an extremely hypofractionated treatment which should be beneficial for tumours with a low α/β ratio. The focus of the review is on low risk localised prostate cancer due to the low α/β ratio and lack of research into the region. This will help to determine if further research into SBRT for prostate cancer is warranted. Methods: A review of the literature was performed to discover the history and current use of SBRT for various body sites. Results: SBRT has been investigated for lung and liver cancers with studies finding toxicity and survival outcomes equivalent to conventional radiation therapy. Research into the use of SBRT in other body sites has also been conducted. However, short follow up times, small patient populations and studies finding toxicity and survival outcomes equivalent to conventional radiation therapy. Conclusions: Despite these limitations, positive acute toxicity and survival outcomes were observed across five studies into SBRT for prostate cancer. There has been no published study into the use of SBRT for prostate cancer within Australia. Theoretical modelling suggests prostate cancer will respond well to the hypofractionated treatment provided by SBRT. Good clinical outcomes with reduced treatment times are possible with SBRT making it a more convenient treatment option for the patient. SBRT also allows greater patient throughput in radiation oncology departments.

Keywords: extra-cranial stereotactic, literature review, prostate cancer, radiation therapy, stereotactic body radiation therapy.

Introduction
Radiation therapy has been used to treat malignant and benign tumours since the late 1800s. It is the use of ionising radiation to achieve tumour cell kill. Ideally, there would be 100% cell kill within a tumour and 0% outside the tumour. The ideal 100% cell kill is not physically possible. This is because the radiation beams must traverse normal tissues surrounding the target. However, new techniques in radiation therapy have continued to allow reduced margins around target volumes and higher doses to be delivered to attempt to achieve this ideal goal.

Stereotactic body radiation therapy (SBRT) is one of these new techniques. It is the use of stereotactic techniques in regions outside of the brain. Stereotactic radiation therapy involves the precise positioning of a tumour in 3 dimensions (3D) allowing high doses to be delivered in few fractions. SBRT has been the subject of many trials assessing the survival outcomes and toxicity experienced by patients treated with this technique. It was first implemented in spinal tumours and also liver and lung cancers. Conventional radical radiation therapy treatments, where the intent is to cure, can take up to eight weeks of daily fractions to deliver the desired dose. SBRT allows curative treatment to be completed in less than two weeks in most cases. This is more convenient for the patient and also allows for treatment of a greater number of patients. The effect of the dose delivered using SBRT theoretically has the same or greater biologic effect as conventional treatment regimes. Due to the high doses delivered each day, SBRT requires accurate positioning to ensure there is not a geographical miss of the tumour. A geographical miss would result in the high dose meant for the tumour being delivered to surrounding normal tissue and a low dose entering the lesion. Image guidance techniques and specialised immobilisation should be used to ensure the accuracy of dose delivery for SBRT.

Theoretical models suggest that prostate cancer will respond well to radiation therapy delivered using high daily doses. Studies examining the use of SBRT for prostate cancer have positive acute toxicity outcomes and survival results are encouraging. However, these studies are primarily performed on a small sample size with limited follow up. A comparison of SBRT dosimetry with conventional radiation therapy dosimetry has not been performed. Therefore, further research is needed to confirm SBRT is an appropriate alternative radiation therapy treatment for prostate cancer.

Methods
A search of the ScienceDirect, Medline and SCOPUS databases was performed for this literature review. Searches were performed between February and May 2010. The search terms used were "stereotactic body", "extra-cranial stereotactic", "radiation therapy", "α/β ratio", "radiotherapy", "radiosurgery", "history", "introduction", "hypofractionation" and prostate. Peer reviewed articles relating to the history of radiation therapy, stereotactic body radiation therapy and stereotactic radiosurgery were retrieved. The majority of articles were from 2005 onwards. A number of older articles were retrieved to provide historical background.
A search of publications in *The Radiographer* using the same search terms was also performed. No articles in relation to SBRT were found in this journal.

**Stereotactic body radiation therapy – history and description**

A stereotactic method for treating spinal lesions was developed in 1993 by Hamilton, et al. This was the first introduction of extra-cranial stereotactic radiation therapy or as it is now commonly known, SBRT. Concurrently, Blomgren and Lax were developing a similar technique for the treatment of liver and lung lesions. SBRT is an extreme form of hypofractionation with doses of up to 23 Gray (Gy) per fraction. The planning target volume (PTV) is generally small with diameters often less than 5 cm. The aim is to deliver an ablative dose to the tumour while maintaining minimal toxicity to the surrounding tissues. An ablative dose is desirable as it will destroy all the tumour cells in the local region. SBRT delivers a high biologically effective dose (BED) in a short amount of time. This means there is a greater likelihood of tumour ablation, even in tumours historically thought to be radioresistant.

Normal tissue surrounding the target is spared high doses due to the high dose gradient produced by SBRT. These high dose gradients are similar to stereotactic radiotherapy performed on intra-cranial lesions and is created by the use of multiple beams. A study completed in the USA concluded that the optimal number of beams when treating liver or lung lesions with SBRT is 13–15. This number of beams provided optimal conformality and dosimetric distribution. Any more fields resulted in beam overlap and a consequential increase in high dose to surrounding tissues. Tight dose distributions necessitate high accuracy of treatment delivery.

Pre-treatment imaging will ensure the treatment field is in the planned position, which will avoid delivering unnecessary dose to the surrounding tissues or a geographical miss of the target. This will need to be done before the delivery of each beam to ensure the location of each field is precise. With the use of high doses per fraction and few fractions, treatment accuracy is imperative for SBRT. If a geographical miss occurs on one fraction, there is the possibility that tumour control will not occur because the target is not receiving adequate dose. The α/β ratio of normal tissues is approximately 2–3 Gy. Late toxic effects may occur within these tissues if they receive the high doses that have been planned for the PTV because they are sensitive to high doses per fraction. Online imaging corrections should be used to ensure the correct region is being treated to avoid these negative outcomes.

Extra-cranial lesions pose a further challenge of inter and intra-fraction motion of the PTV’s. Lesions outside of the cranium are subject to respiratory movement, digestive motion etc. These processes will cause the target position to vary between fractions and even within a fraction. During the respiratory cycle, diaphragm movement will cause not only the lungs to vary in position but also organs within the abdomen. The internal target volume (ITV) is a modification of the clinical target volume (CTV) to account for motion. It includes the position of the CTV at any position that it may occupy due to internal movements such as respiration. The margin around the CTV to form the ITV can be asymmetrical. The ITV is then expanded normally to form the PTV. This is often used for SBRT to ensure the tumour is within the treatment field at all times. The motion of extra-cranial lesions necessitates the use of specialised immobilisation and localisation techniques to ensure accurate dose delivery.

**Immobilisation and localisation techniques for SBRT**

A prototype immobilisation frame was developed by Hamilton and associates in 1993. It was a rigid frame that associated a three dimensional co-ordinate system. It consisted of flat pressure plates that were positioned on the spinous processes of the patient. It is not in use today. Blomgren and Lax introduced the Stereotactic Body Frame which was developed whilst they were experimenting with SBRT for the liver and lung. This immobilisation device utilises multiple means to localise the patient including an abdominal screw which applies pressure to the diaphragm. Oblique copper wires in the side walls are used for localisation on CT images. A vac-lok bag is used within the body frame to ensure the patient’s position within the frame is reproduced exactly for each fraction. Scales on the side of the body frame ensure accurate positioning of the device on the treatment couch and of the patient inside.

The position of tumours in the lower thorax or upper abdomen is influenced by the movement of the diaphragm. Since a high degree of accuracy is required, the movement of these tumours needs to be decreased to ensure they are within the small treatment field. It is not possible for patients to hold their breath during SBRT as the fraction takes many minutes to deliver. The abdominal screw on the stereotactic body frame is used to limit the diaphragm motion caused by breathing. This is done by applying pressure to the abdomen through a pressure plate at the end of the screw. Diaphragm movement in the caudal cranial direction is reduced from approximately 10–19 mm to 5–10 mm in most patients when using this immobilisation technique.

Stereotactic immobilisation for the prostate was achieved using a flex prone position by Madsen, et al. This involved placing a specially designed cushion under the patient’s pelvis. Patients were also instructed to follow a strict diet to minimise variations in bowel and bladder distension. Madsen, et al. monitored bladder position during treatment with images taken every 6 minutes for 24 minutes. The 47 patients in this study had prostate movement of 1.4 mm left/right, 2.0 mm superior/inferior and 1.9 mm anterior/posterior. King, et al. made use of gold fiducials within the prostate and an SBRT body cradle for immobilisation and localisation.

Other methods of tumour localisation may also be used for SBRT. Tracking of the tumour for SBRT can also be achieved using active breathing control and respiratory gating. Active breathing control refers to controlled breath holds using devices to trigger and monitor respiration and the associated position of the tumour. Respiratory gating is a process by which the radiation beam only switches on when the tumour, whose position is represented by an external surrogate, is within a certain positional range. This ensures the target is receiving the planned dose at all times.

The following section examines the current uses of SBRT as found in the literature with a primary focus on the use of SBRT for prostate cancer.

**Current uses**

Current disease sites being treated with SBRT include lung, liver, spine, head and neck, kidney, pancreas, gynaecology cancers and prostate. Through a search of the literature most studies found were focussed on SBRT for primary or metastatic lung tumours with liver SBRT being the second most common body site.

Both inoperable primary and metastatic lung diseases have been the subject of many clinical trials to determine the efficacy and toxicity of SBRT. A multi-institutional retrospective study was conducted in Japan on lung lesions diagnosed as primary lung cancer on radiologic examination. There were 115 cases examined in this study with three
and five-year overall survival reported. For a group with tumour sizes of 5–10 mm, these figures were recorded as 100%. This is a very positive result since the five-year survival rate is approximately 22.2% when using conventional radiation therapy. Other results in this study were encouraging and Inoue, et al. concluded that, for patients with a tumour of less than 20 mm diameter, SBRT was “reasonably safe.” Toxicity was also examined by Inoue, et al. One treatment related death caused by interstitial pneumonia was reported in a patient with a tumour diameter greater than 20 mm. Another prospective trial of 45 patients in Japan, receiving four fractions of SBRT to a total of 48 Gy found that the results were as good as surgery with a median follow up time of 30 months. Nagata, et al. only experienced two cases of a grade 2 pneumonitis during their research which is a better outcome than Inoue, et al. although the total dose may have been different in each case of toxicity. Nagata, et al. treated each patient with 48 Gy in 4 fractions, whilst Inoue, et al. used a dose range of 30–70 Gy in 2–10 fractions. The dose and fractionation of the patient experiencing the grade 5 pneumonia was not reported and this may have been a contributing factor. Because SBRT is a relatively new technique, the follow up times on these studies is limited. Longer follow up is needed to monitor the appearance of late effects.

There is currently a Trans-Tasman Radiation Oncology Group (TROG) trial being conducted in Australia to determine if SBRT for stage 1 non small cell lung cancer is more effective, results in better life expectancy and has comparable toxicity results as conventional radiation therapy. This is a randomised trial so it is expected to provide reliable results. Further randomised trials need to be conducted to confirm the efficacy of SBRT for lung lesions.

Malignant liver disease is another cancer that has been the focus of many studies into the use of SBRT. Surgical resection is the standard of care for patients with liver metastases. On presentation however, 80–90% of these patients have unresectable disease. The use of SBRT has been documented as having a curative potential for lesions less than 5 cm in diameter. It achieves this outcome in a non-invasive manner with no need for anaesthesia or admission to hospital which makes it advantageous to surgery. A multi-centre phase I trial of dose escalation with 18 patients was conducted by Scheffer, et al. During the study, no dose limiting events were observed so the maximum planned dose was delivered to the final cohort of five patients. The maximum dose was 60 Gy in three daily fractions of 20 Gy. No patient experienced toxicity of grade 3 or above. Twelve patients survived the median follow up time of 7.1 months. While these results are very positive the limited participant numbers and short follow up time make the data less reliable. A further phase II study of SBRT delivered at 60 Gy in 3 fractions would be required to confirm the results. The limited toxicities experienced in the study by Scheffer, et al. indicates that dose to surrounding tissues is limited, even with an escalation of dose to the target.

Stereotactic body radiation therapy for prostate cancer

Advantage of hypofractionation

Different forms of fractionation may be used to increase the BED. The BED is a measure of the cell kill of a certain delivered dose on various tissues. It also allows the comparison of different dose regimes for the same cancer site. Hypofractionation is the use of fewer, large fractions to deliver a smaller total dose. Hence, this technique is useful for tumours that have a high sensitivity to the dose delivered per fraction. The α/β ratio is an indication of the dose response of the tissue. A low α/β ratio indicates that the tissue will be affected more by high doses per fraction. The α/β ratio, which can be seen upon examination of the equation;

\[
\text{BED} = (nd) + \left( \frac{nd^2}{\alpha/\beta} \right)
\]

Where \( n \) = number of fractions and \( d \) = dose per fraction.

Attempts have been made to theoretically model the effect of radiation on tissues. The linear quadratic model is currently the most accurate and widely accepted model. The α/β ratio is obtained from cell survival curves based on the linear quadratic model where \( \alpha \) is determined from the linear part of the curve and \( \beta \) the quadratic part. A tissue with a low α/β ratio will have a higher BED for a set dose than another with a higher ratio.

Prostate cancer cells are thought to have a much lower α/β ratio than other tumour cells. The ratio has been derived by a number of studies and the values range from 1.0–8.3 Gy. Other tumour cells are thought to have an α/β ratio of 10 Gy. This high ratio indicates that they are early responding tissues and increasing the number of fractions will not reduce the cell kill. The prostate, with the low α/β ratio behaves more like a late responding tissue. Normal tissues are also late responding with an α/β ratio of 2–3 Gy. Using relatively small doses of 1.8–2 Gy per fraction and increasing the number of daily treatments is usually carried out to spare normal tissues surrounding the tumour. This is because a higher dose per fraction causes late toxicities in tissues with a low α/β ratio. Since all the current literature suggests the prostate has a low α/β ratio, SBRT should deliver superior control rates to conventionally fractionated treatments. As shown in the following section, multiple studies have explored the use of SBRT for low-risk localised prostate cancer.

Prostate studies

SBRT for localised, low-risk prostate cancer has been investigated by a number of researchers in the USA. All studies found during this literature review are non-randomised clinical trials indicating the evidence is not of the highest reliability that would be found with randomised trials. Table 1 presents

<table>
<thead>
<tr>
<th>Authors</th>
<th>Origin</th>
<th>Participants</th>
<th>Dose</th>
<th>Survival</th>
<th>Toxicity</th>
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<tbody>
<tr>
<td>Prostate Cancer</td>
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<tr>
<td>Madsen, et al.²⁴</td>
<td>USA</td>
<td>47 (NRCT)</td>
<td>33.5 Gy in 5 fractions</td>
<td>Not discussed</td>
<td>Generally mild. One grade 3 rectal toxicity, three grade 3 urinary</td>
</tr>
<tr>
<td>Madsen, et al.²¹</td>
<td>USA</td>
<td>40 (NRCT)</td>
<td>33.5 Gy in 5 fractions</td>
<td>4-year biochemically free from relapse: 70%</td>
<td>Generally mild. One grade 3 rectal toxicity, three grade 3 urinary</td>
</tr>
<tr>
<td>Friedland, et al.²</td>
<td>USA</td>
<td>112 (NRCT)</td>
<td>35–36 Gy in 5 fractions</td>
<td>Mean PSA: reduced from 6 to 0.78 ng/mL</td>
<td>Generally mild. One grade 3 rectal toxicity, three grade 3 urinary</td>
</tr>
<tr>
<td>King, et al.²⁵</td>
<td>USA</td>
<td>41 (NRCT)</td>
<td>36.25 Gy in 5 fractions</td>
<td>PSA reduced to &lt; 0.4 ng/mL</td>
<td>Generally mild. One grade 3 rectal toxicity, three grade 3 urinary</td>
</tr>
<tr>
<td>Wiegmans &amp; King,²⁶</td>
<td>USA</td>
<td>32 (NRCT)</td>
<td>36.25 Gy in 5 fractions</td>
<td>Not discussed</td>
<td>Generally mild. One grade 3 rectal toxicity, three grade 3 urinary</td>
</tr>
</tbody>
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[NRCT = Non-randomised clinical trial]
a summary of the prostate studies that have been reviewed. A standard treatment dose and fractionation schedule has not been proposed. Madsen, et al.20,21 have used 33.5 Gy in 5 fractions for both of their studies into various outcomes for SBRT of the prostate while King, et al.9 and Weigner and King14 made use of 36.25 Gy in 5 fractions. There was variation in the doses delivered to patients within the trial conducted by Friedland, et al.8 with a range between 35 and 36 Gy delivered in 5 fractions. While the doses are similar, there is a lack of evidence to explain why those schedules were chosen. A comparison of radiobiologic parameters such as tumour control probability (TCP) and normal tissue complication probability (NTCP) for a number of dose regimes may be helpful in explaining the choice. These researchers may have come up with their SBRT doses by using the same BED as their conventional prostate treatments. A calculation using 74 Gy in 37 fractions for the conventional prostate treatment produces a BED of 172.6667. This converts to 6.5 Gy in 5 fractions, or a total dose of 32.5 Gy which is a similar dose to those used for SBRT in the reviewed studies.

Toxicity was discussed at length in all studies. It was found that the toxicities were generally mild. Across the five investigations there was one grade 3 rectal toxicity. This was experienced during the study conducted by Friedland, et al.8 and was reported as rectal bleeding. There were three cases of grade 3 urinary toxicities, two patients from King, et al.10 and the other was from Madsen, et al.13 which was recorded as urinary obstruction. These toxicity results are similar to those normally expected from conventionally fractionated radiation therapy for the prostate.10,11 However, there has been limited follow up periods in all of these studies with the maximum time being four years. There is the possibility that late toxicities have not been experienced at the time of reporting. A possibility for a future study is one that calculates theoretical BED to surrounding tissues and dose distributions. This may indicate if further late toxicities can be expected. A comparison of the doses to surrounding tissues in SBRT plans with conventional prostate treatment plans will indicate which treatment technique is more likely to experience toxic effects to surrounding tissues. No studies comparing SBRT treatment plans to 3D conformal radiation therapy techniques. Prostate cancer is a site of particular interest due to the sensitivity of the tumour to higher doses per fraction. While they are having radiation therapy. Outcomes from a number of trials have suggested that the prostate does respond well to SBRT. No comparisons of SBRT dosimetry with 3D conformal radiation therapy or IMRT for the prostate have been found in the literature. A study of this kind will indicate whether SBRT can provide equal or better cell kill and toxicity outcomes for patients with low-risk localised prostate cancer. If the outcomes of a dosimetry and radiobiology comparison are positive, this treatment will have greater potential of being implemented. SBRT

Survival was not discussed in two of the five studies located on SBRT for prostate cancer.20,21 Prostate specific antigen (PSA) levels were examined by two studies. Levels of PSA have been loosely linked to the volume of the prostate cancer.1 Decreased PSA levels occurred in the studies conducted by Friedland, et al.8 and King, et al.10 suggesting that the prostate cancer volume was reduced following treatment with SBRT. A brief statement confirming that no patient in the study died from prostate cancer was provided by Friedland, et al.8 Both Friedland, et al.8 and King, et al.10 recognised that protracted follow up is required to properly evaluate the PSA result. This indicates that there is not sufficient long term evidence to support SBRT treatments for low-risk prostate cancer. The four-year biochemically free from relapse rate was found to be 70% by Madsen, et al.13 There was no comparison of this rate to those commonly seen with conventional radiation therapy for prostate cancer. However, King, et al.10 commented that an estimated five-year biochemical control rate for 52 Gy is 40%. Thus, the relapse rate as defined by an increase in PSA reported by Madsen, et al.13 is superior to what may be expected from a conventional radiation therapy treatment regime of 52 Gy.

The most appropriate way to develop reliable and accurate results would be to complete a randomised control trial comparing SBRT with IMRT or 3D conformal radiation therapy. A larger number of 100 participants or more would be required and follow up times should extend for 10 years. Such a long follow up time is required for prostate cancer patients because they historically have good biochemical control and survival outcomes. Such a study would confirm the efficacy of SBRT for prostate cancer if the results were positive.

Conclusion

SBRT is a technique that allows higher daily doses to be delivered to tumours outside of the brain. It delivers these doses with an increased accuracy compared to conventional treatments. SBRT delivers a lower total dose over a shorter period of time compared to conventional radiation therapy treatments. The biologic effect of this fractionation is theoretically as high, or higher than traditional doses. While this is positive within the tumour volume, the effects on surrounding tissues may be increased. Image guidance technology and accurate immobilisation is required to ensure the correct location is receiving the high doses.

Recent trials into the implementation of SBRT have indicated that it has positive outcomes for a number of sites within the body. Survival rates and toxicities have been comparable or better than conventional radiation therapy techniques. Prostate cancer is a site of particular interest due to the sensitivity of the tumour to higher doses per fraction. Prostate cancer also accounts for a large proportion of all cancer patients in South Australia. SBRT has the potential to streamline patient treatment, reducing patient waiting times and also the inconvenience to patients while they are having radiation therapy. Outcomes from a number of trials have suggested that the prostate does respond well to SBRT. No comparisons of SBRT dosimetry with 3D conformal radiation therapy or IMRT for the prostate have been found in the literature. A study of this kind will indicate whether SBRT can provide equal or better cell kill and toxicity outcomes for patients with low-risk localised prostate cancer. If the outcomes of a dosimetry and radiobiology comparison are positive, this treatment will have greater potential of being implemented. SBRT
has the potential to provide better economic and patient outcomes due to the shorter treatment course. This is much more convenient for a patient and will have less effect on their day-to-day lives. It also allows for the treatment of more patients as the throughput is greatly increased.

References
5. Fowler JF, Tomé WA, Fenwick JD, Mehta MP. A challenge to traditional radiation treatment of more patients as the throughput is greatly increased.

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