Centre universitaire de santé McGill
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MINI HEALTH TECHNOLOGY ASSESSMENT

(Note: A mini HTA report consists of two parts. The first is completed by the applicant at the time the new technology is requested. The second consists of a commentary and possibly additional evidence provided by TAU)

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Fiducial markers for improving treatment margins in radiotherapy for prostate cancer

PART I: Request for HTA

REQUESTOR

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Technology (Name, Description, Purpose)
Name: Fiducial markers.

Description: A Fiducial marker is a metallic object inserted in the area of interest (organ or tumor to be treated with radiation therapy) and used as a point of reference to facilitate its visualization by an imaging system.

Purpose: Daily localization of the fiducial markers immediately before radiation therapy delivery allows for correction of inter-treatment organ motion, minimizing geometrical errors when small treatment margins are used.

Has it been used at the MUHC? What is the alternative?
It has been used for a single patient so far.

Currently we use a 3D transabdominal ultrasound system for daily localization of the prostate in our patients. However, in some situations, it is difficult to visualize the prostate gland due to many reasons, including small prostate sizes, obese patients and the use of hormonal therapy.

Health benefits (Give references)
The use of fiducial markers will allow an adequate assessment of organ motion for those patients who present poor quality ultrasound images. Without position

verification and setup corrections, small margins would be insufficient to account for position uncertainties during radiation therapy of prostate cancer[1,2,3,4,5].

Risks/complications (Give references)

Although pain and/or discomfort are reported during the insertion of the fiducial markers, the incidence of complications is low[2,6]. A recent study[7] assessing quality of life in patients who underwent fiducial marker implantation, the most common side effects were haematuria (15%), rectal bleeding (4%) and fever (2%), with no major toxicity necessitating any intervention. The rate of infection is very low[3], happening mainly in patients who have the transrectal insertion of the fiducial markers[2].

Unit costs (Direct costs of items requested)

It is proposed that each gold marker will be divided and two sections placed in each prostate at a net cost of approximately $200.

Usage (Quantity of drugs/expendables or number of procedures per year)

It is expected that a total of 30 patients, for whom it is difficult to visualize the prostate gland via ultrasound, will have the fiducial markers inserted in the first year of utilization of this technique.

Impact on hospital services (Bed usage,OPD, Etc)

This is a 10-minute procedure done under local anesthesia. It will be performed at the brachytherapy suite, in the Division of Radiation Oncology of the Montreal General Hospital.

References

1) Daily online localization using implanted fiducial markers and its impact on planning target volume for carcinoma prostate. Khosa R, Nangia S, Chufal KS, Ghosh D, Kaul R, Sharma L. J Cancer Res Ther. 2010 Apr-Jun;6(2):172-8.

2) Long-term experience with transrectal and transperineal implantations of fiducial gold markers in the prostate for position verification in external beam radiotherapy; feasibility, toxicity and quality of life. Moman MR, van der Heide UA, Kotte AN, van Moorselaar RJ, Bol GH, Franken SP, van Vulpen M. Radiother Oncol. 2010 Jul;96(1):38-42. Epub 2010 Mar 23.

3) Technique for implantation of fiducial markers in the prostate. Shinohara K, Roach M 3rd. Urology. 2008 Feb;71(2):196-200.

4) Influence of daily setup measurements and corrections on the estimated delivered dose during IMRT treatment of prostate cancer patients. van Haaren PM, Bel A, Hofman P, van Vulpen M, Kotte AN, van der Heide UA. Radiother Oncol. 2009 Mar;90(3):291-8. Epub 2009 Feb 3.

5) Dosimetric impact and theoretical clinical benefits of fiducial markers for dose escalated prostate cancer radiation treatment. Gauthier I, Carrier JF, Béliveau-Nadeau D, Fortin B, Taussky D. Int J Radiat Oncol Biol Phys. 2009 Jul 15;74(4):1128-33. Epub 2009 Jan 13

6) Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors. Langenhuijsen JF, van Lin EN, Kiemeney LA, van der Vight LP, McColl GM, Visser AG, Witjes JA. Int J Radiat Oncol Biol Phys. 2007 Nov 1;69(3):671-6. Epub 2007 May 23.

7) Implantation of fiducial markers for image guidance in prostate radiotherapy: patient-reported toxicity. Igdem S, Akpinar H, Alço G, Agaçayak F, Turkan S, Okkan S. Br J Radiol. 2009 Nov;82(983):941-5. Epub 2009 Jun 8.

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PART II: Additional comments of Technology Assessment Unit

Completed by: Dr. Nandini Dendukuri,
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Literature search

Methods: PubMed and EMBASE databases were searched for peer-reviewed articles, while the database of the Centre for Reviews and Dissemination was searched for systematic reviews or health technology assessments. In the medical literature databases, we limited articles to those including human, male participants. The keywords used were: ((“Fiducial Marker” or “fiduciary marker” or “gold marker” or “seed implant”) OR (“image” or “imaging” or “ultrasound”)) AND (“prostate”) AND (“therapy” or “radiotherapy” or “treat$” or “shift” or “precision” or “deviation” or “error” or “accuracy”) AND (“tumor” or “tumour” or “cancer” or “carcinoma”). Articles or reports were limited to those published in English or French. Bibliographies of relevant articles were further hand-searched.

Results: Our literature search did not identify any health technology assessments, systematic reviews or randomized controlled trials evaluating use of fiducial markers in radiotherapy of prostate cancer. There were also no studies on the impact of this technology on observed clinical outcomes (such as survival or decreased toxicity to surrounding tissue).

Health benefits

The health benefit of this intervention, compared to the currently used technology, is the decrease in risk of x-ray burns to the bladder and rectum. No studies have quantitated this benefit.

Radiation damage to surrounding structures associated with radiotherapy for prostate cancer is not uncommon. A review of 66 patients treated at the MGH from 2002 to 2004 found that 3 (4%) had grade 2 toxicity and 9 (14%) had grade 3 toxicity. [“Grade 2 effects are considered moderate, are usually symptomatic, and interventions such as local treatment or medications may be indicated. They may or may not interfere with specific functions but not enough to impair activities of daily living. Grade 3 effects are considered severe and very undesirable. There are usually multiple, disruptive symptoms. More serious interventions, including surgery or hospitalization, may be indicated” [2]]. While these were "average" patients, the risk of toxicity in patients in whom the prostate can not be accurately located by ultrasound would be greater. How much this increased risk of toxicity could be reduced in such patients by use of fiducial markers markers must be conjectural, but there is every reason to anticipate that it would be reduced.

Health risks/Adverse effects

A number of studies report complication rates following use of fiducial markers. Reported adverse events include marker migration, hematuria, urinary tract infection and rectal bleeding. In a cohort of 914 patients, Moman et al. found that 2 patients developed urosepsis and in 5 patients the marker-based treatment had to be discontinued due to marker migration[3]. It is reported that complications are more likely to be seen in patients with advanced tumor stage, younger age, and shorter duration of hormonal therapy[4]. However, most studies have concluded that they are safe to use with a low risk of adverse events[3-5].

Budget and service impact

The only item that will significantly impact on budget will be the cost of the markers themselves which should add up to approximately $6,000 per year for the anticipated 30 patients. Markers will be inserted in the brachytherapy suite in roughly 30 minutes (not 10 minutes as mentioned in the request). Given that this suite is currently not fully used there is no need for additional staff. Furthermore, the use of markers will eliminate the daily adjustment time of 5 minutes per patient that is currently needed with use of ultrasound. Thus the total budget impact of using fiducial markers for 30 patients per year will be roughly $6,000.

Conclusion

- **This intervention will in all probability diminish the risk of radiation damage to bladder and rectum for the approximately 30 patients per year in whom it will be used. The extent of risk reduction cannot be estimated. The estimated budget impact would be approximately $6,000 per year. It could be carried out without any impact on service, and at insignificant risk to patients.**

Note

These comments apply only to the use of fiducial markers when the prostate gland is difficult to visualize by ultrasound.

Acknowledgements

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Additional References

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(2) Trotti A, Colevas AD, Setser A, Rusch V, Jacques D, Budach V et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse events of cancer treatment. *Seminars in Radiation Oncology* 2003; 13(3): 176-181.

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(4) Langenhuijsen JF, van Lin EN, Kiemeney LA, van der Vight LP, McColl GM, Visser AG et al. Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors. *International Journal of Radiation Oncology, Biology, Physics* 2007; 69(3):671-676.

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