TITLE: PATTERNS OF PRACTICE SURVEY FOR BRACHYTHERAPY FOR CERVIX CANCER IN AUSTRALIA AND NEW ZEALAND

Running title: Brachytherapy survey for cervix cancer

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12 **ABSTRACT**13 **Introduction**

14 The purpose of this survey was to explore the current patterns of practice for brachytherapy
15 in cervix cancer in Australia and New Zealand. The survey was also intended to explore
16 clinician attitudes toward image-guided adaptive brachytherapy (IGABT) and identify barriers
17 to the implementation of IGABT

18 **Methods**

19 Electronic surveys were sent to all radiotherapy centres in Australia and New Zealand under
20 collaboration with Australia New Zealand Gynaecology and Oncology Group (ANZGOG), in
21 order to identify patterns of radiotherapy practice. The survey was sent out in December
22 2013, with a reminder in February 2014.

23 **Results**

24 Of the 75 radiotherapy centres in Australia and New Zealand, 23 centres replied (31%
25 response rate). Twenty two responding departments treat cervix cancer with external beam

radiation (EBRT) (22/23; 96%). Fourteen responses were from departments that also use intracavitary brachytherapy (14/22; 64%). The remaining eight departments who do not offer intracavitary brachytherapy referred their patients on to other centres for brachytherapy. Ultrasound was used by 86% for applicator guidance. CT and MRI were used by 79%, and 50% respectively for planning. Optimisation was based on organs at risk (93%) and target volumes (64%).

Conclusions

Brachytherapy remains an integral component of definitive treatment for cervix cancer in Australia and New Zealand. There was increased use of soft tissue imaging modalities with emphasis on verification; high rates of volumetric planning, and adherence to a defined overall treatment period. Brachytherapy was not substituted with other EBRT modalities. Despite this there remain barriers to implementation of image guided brachytherapy.

Five key words:

Brachytherapy
Cervix cancer
Image guidance
Patterns of practice

Introduction

Brachytherapy plays an integral role in the curative treatment of inoperable cervix cancer, enabling tumouricidal doses of radiation to be delivered directly to the primary site of disease¹. Recent SEER data suggests that brachytherapy utilisation in cervix cancer has declined in the USA from 83% in 1988, to 58% in 2009, with a sharp decline in 2003 (43%)². This decline in brachytherapy usage has been shown to impact adversely on cause-specific and overall survival².

Brachytherapy has become more complex with advances in technology such as stepping source capabilities and the use of 3D imaging. It also requires more time and resources when delivering fractionated courses of treatment. The advent of image guided adaptive brachytherapy (IGABT) over the last decade has resulted in a paradigm shift in the treatment approach to cervix cancer from point based dosimetry to volume based dosimetry. This has resulted in significant improvements to local control and reduced toxicity, Table 1³⁻¹⁶.

Previous reports have demonstrated that centres in Australia are adopting image guided protocols with an increase in the use of 3D imaging in brachytherapy planning from 27% in 2005 to 65% in 2009^{17,18}. The purpose of this survey was to explore the current patterns of practice for brachytherapy in cervix cancer in Australia and New Zealand. The survey was also intended to explore clinician attitudes toward IGABT and identify barriers to the implementation of IGABT.

Methods

The survey was distributed electronically via email to all radiotherapy centres affiliated with the Royal Australian and New Zealand College of Radiologists (RANZCR) and Australian and New Zealand Gynaecology Oncology Group (ANZGOG) across Australia and New Zealand in December 2013 with a reminder in February 2014. Survey responses were collated and analysed using descriptive analysis.

Results

Overview

Responses were received from all states and territories of Australia and New Zealand except for the Northern Territory. There are 75 radiotherapy centres in Australia and New Zealand, 23 of which treat cervix cancer with brachytherapy. Overall, 23 departments replied to the survey (23/75 = 31% response rate). Twenty two responding departments treat cervix cancer with external beam radiation (EBRT) (22/23=96%). Fourteen responses were from departments that also treat intracavitary brachytherapy (14/22=64% response rate). The remaining eight departments who do not offer intracavitary brachytherapy all referred their patients on to other centres who do provide brachytherapy services.

None of the survey respondents reported substituting brachytherapy with intensity modulated radiotherapy (IMRT) or stereotactic body radiation therapy (SBRT). Radiotherapy related survey responses were supplied by radiation therapists (43%), and radiation oncologists (57%).

External beam radiotherapy (EBRT)

Over 95% of survey respondents used 3D conformal radiotherapy for the external beam component of treatment at the time of the survey. More conformal modalities such as IMRT, tomotherapy, volumetric arc therapy (VMAT) are also used but it is not clear in what clinical setting these were used (e.g. nodal boost).

Correspondingly, EBRT was prescribed to International Commission on Radiation Units (ICRU) report 50 reference point in 64% of responses and to the 95% of the planning target volume (PTV) in 45% of responses¹⁹. It is likely that the proportion of departments using IMRT/tomotherapy/VMAT has increased since then.

The most common EBRT doses in use are 45 Gy in 25 fractions and 50.4 Gy in 28 fractions.

Brachytherapy

Overview

All respondents use high dose rate afterloaders, with one department also using pulse dose rate. Half the respondents commence brachytherapy after EBRT is completed, and half during week four or five of EBRT. The majority of respondents aimed to complete treatment in less than eight weeks (71%), with 14% aiming for less than seven weeks and 14% aiming for less than nine weeks. Most departments aim to treat with four fractions of brachytherapy (57%) although logistical considerations may cause treatment courses to be contracted, two departments treat with three fractions and one department treats with six fractions. Inter-fraction intervals range from one week, 43%; 4-5 days, 21%; 2-3 days, 43%; and 24 hours (7%).

One department also treats twice daily occasionally. The majority of applicator insertions occur in an operating theatre, (64%), with the remainder (36%) occurring in a dedicated brachytherapy suite. All respondents reported using general anaesthetic for applicator insertion. Spinal anaesthesia was also widely used (57%) and epidural anaesthesia less so (7%). The prescription dose range from 3.5 – 8.5 Gy per fraction. The most common dosages are 6 and 7 Gy per fraction.

Workload

The majority (71%) of respondents treat more than ten patients per year, 21% treat five to ten patients per year and one centre treats between 60 – 70 patients annually, Figure 1.

The number of radiation oncologists performing procedures per department, varies from one (14%), two (57%), three (21%) or four (7%).

Brachytherapy is offered to patients with metastatic disease by 79% of respondents. The most common scenarios where this would be offered are indicated in Figure 2. In the category “Other”, respondents indicated that brachytherapy is offered on a case by case basis, depending on patient Eastern Co-operative Oncology Group performance status (ECOG), severity of local symptoms or clinical response to chemotherapy. The dose and fractionation used in these scenarios are mostly identical to those used for radical patients, although 18% would use an abbreviated fractionation schedule depending on the scenario.

Use of Imaging

All respondents use some form of imaging at the time of brachytherapy to aid in treatment planning, although not all considered this image guided brachytherapy. The majority of centres offering brachytherapy use 3D imaging, Figure 3. Image guided brachytherapy is performed by 71% of respondents, with the remaining 29% of respondents indicating they would like to implement image guided brachytherapy in the future. Computed tomography (CT) is the most commonly used form of 3D imaging (79%) with 50% of the respondents using magnetic resonance imaging (MRI) and 29% using ultrasound. Many of the respondents use multi-modality imaging. Most planning imaging takes place in the radiotherapy department (79%). Ultrasound is used to guide applicator insertion by 86% of respondents. It is also used to aid planning by 29%. Twenty nine percent of respondents take intrafraction verification images after patient transfers and prior to brachytherapy treatment. Ultrasound is used by 21% and x-ray by 14% for intrafraction verification. CT and MRI are not used for intrafraction verification. Of the 71% of respondents who do not take intrafraction verification images, there is considerable reliance on skin markings to indicate applicator position. Twenty one percent of respondents who take intrafraction verification images adjust the applicator position if it is unsatisfactory, 7% replan based on the updated applicator position and 7% reimage and replan with CT. Use of 3D imaging is employed by 50% of respondents for every fraction of brachytherapy. Interfraction imaging is used for replanning by 57% respondents, while 29% back project the original plan onto the new image set. The purpose of interfraction imaging for those not replanning is to verify the applicator position, 36%; verify the target volume, 21%; and verify the organs at risk (OAR), 29%.

Applicators and fixation

The majority of respondents used intracavitary applicators, tandem and ovoids, 93%; tandem and ring, 29%; and tandem and cylinder, 86%. Use of combined interstitial and intracavitary applicators is 29%. A vaginal spatula (to move the rectum away) is used by 50% of respondents. Applicators are fixed in position by use of intravaginal packing by 93% of respondents. Perineal sutures are used by 43%, a perineal bar by 7%, and mesh underpants by 14%. Two departments also use fabric tape around the applicator to secure it in position.

Planning methods

All departments using brachytherapy to treat cervix cancer use imaging at the time of brachytherapy to aid treatment planning. 3D imaging is used by 79% (CT) and 50% (MRI) of respondents, with many using dual modality imaging. Brachytherapy planning methods range from plans based on applicator geometry, 36%; optimised plans based on OAR dose constraints, 93%; to optimised plans based on high risk clinical target volume (HRCTV) coverage, 64%. Various degrees of contouring are performed on the 3D image data sets. The gross target volume (GTV) is contoured by 21%, intermediate risk clinical target volume (IRCTV) by 29%, HRCTV 64%, rectum 93%, bladder 86%, sigmoid 79%, small bowel 29%, while the vagina is not contoured by any respondents.

Prescription and dosimetry

Thirty six percent of respondents prescribe brachytherapy to Point A, with 1 respondent (7%) prescribing to Point M²⁰. The Groupe Européen de Curiethérapie and the European Society of Radiotherapy and Oncology (GEC-ESTRO) defined HRCTV is used by 43% while 14% of respondents prescribe to a self-determined target volume. One department that prescribes to the HRCTV stated they continue to report dose to Point A.

Planning constraints for the bladder range from 68 – 90 Gy in equivalent doses to 2 Gy fractionation (EQD2). Constraints for the rectum and sigmoid range from 64 – 75 Gy and 54 – 75 Gy respectively. Only one respondent indicated a vaginal mucosal constraint of 85 Gy. Only one respondent reported using a rectal probe to measure the rectal dose during treatment and commented that treatment is corrected if the dose is hotter than expected.

Moving toward and improving image guided brachytherapy

Twenty nine percent of respondents would like to move to image guided brachytherapy. The greatest impediment to implementation and improvement of image guided brachytherapy is

lack of access to MRI, 79%. The responses indicated that respondents using CT would like to improve image guided brachytherapy by accessing MRI. Similarly, respondents who use MRI would like greater access to it. Two respondents felt they had insufficient patient numbers to pursue the infrastructure needed for image guided brachytherapy. Other resource constraints include lack of access to anaesthetic and operating suite services, and lack of funds to finance training and equipment.

Discussion

The current survey results represent an update on the status of brachytherapy for cervix cancer throughout Australia and New Zealand. Important findings are the increased use of soft tissue imaging modalities, high rates of volumetric planning, and adherence to a defined overall treatment period. Most importantly, brachytherapy is prescribed for all patients regardless of the primary hospital's ability to deliver it. Patients undergoing radiotherapy in hospitals where brachytherapy is not available are referred to other institutions to receive brachytherapy. No departments in this survey reported using alternative boost modalities such as IMRT, SBRT or VMAT. This is a striking finding and is in stark contrast to recent data from the United States where Gill *et al* identified a 10.5% reduction in the use of brachytherapy for cervix cancer and a corresponding 10.3% increase in the use of IMRT or SBRT for boosting the tumour¹⁰. The use of an IMRT or SBRT boost was found to be associated with a significant increase in mortality risk.

Imaging

The use of 3D imaging has greatly expanded since the last survey conducted throughout Australia and New Zealand in 2009, Table 2^{17,18}. The high levels of CT use are to be expected as the majority of departments (79%) perform imaging in the radiotherapy departments using their own CT scanners. Use of MRI has increased from 15% to 50% in the intervening years. Only one department uses MRI exclusively. This department has an MRI scanner in the radiotherapy centre. Use and expansion of soft tissue imaging throughout Australia and New Zealand compares favourably to other parts of the world, with uptake exceeding most other countries and regions, Table 3^{17,21-27}. The most notable increase in soft tissue imaging has been in the use of ultrasound to aid applicator insertion (86%) and treatment planning (29%). While many practitioners have reported on the utility of using ultrasound for difficult

insertions Small *et al* recommend using ultrasound for all insertions as they felt uterine perforation was possible in any patient^{28,29}.

The use of intra-fraction imaging was asked for the first time in this survey. Intra-fraction imaging refers to imaging taken after planning imaging (and multiple patient transfers) and prior to brachytherapy treatment. The importance of intra-fraction imaging in modern image based protocols was described by Anderson *et al*³⁰. This group reimaged patients during a single insertion to ascertain intra-fraction changes to the position of OAR. The average time between planning MRI and pretreatment MRI was 4.75 hours (range 3.2 - 9.9 hours). During this time, the position of the OAR changed and dose constraint compliance reduced by 13.9%. The survey identified 21% of practitioners use ultrasound to verify the applicator position prior to treatment. While ultrasound verification cannot fully assess the position of OAR through the 2D keyhole view, it can confirm the target applicator relationship and ensure that isodose coverage beyond the target volume is safe for surrounding tissues³¹. This simple verification can reduce and correct applicator shifts that have been shown to result in mean changes to the bladder and rectum of 5% and 6% per mm for D_{2cm3} and $D_{0.1cm3}$ respectively³². Use of imaging to guide applicator insertion and verify applicator position improves the technical quality of implants which in turn improves local control.

Applicators

Conventional intracavitary applicators are used by the majority of practitioners, although the survey identified use of combined intracavitary interstitial applicators by 29% of respondents. This is a moderate uptake compared to world uptake of 5 – 44%, Table 1. A vaginal spatula (rectal retractor) was used by 50% of respondents. The importance of using a retractor has been clearly demonstrated. Stitt *et al*. showed that use of retractor increased the distance to the rectum by 4-14 mm, reducing the dose by an average of 30%³³. Similarly, it has been shown that use of a retractor leads to lower rectal and sigmoid doses when compared with vaginal packing alone³⁴.

Planning

In the 2009 survey four departments (20%) based contouring, treatment volumes and dose prescriptions on GEC-ESTRO recommendations¹⁷. This survey has identified nine departments (64%) contouring the HRCTV and 43% optimising plans to this volume. Only seven

departments use MRI. This means two departments contour the HRCTV based on CT alone. There have been significant differences noted in the width of the cervix as identified on CT and MRI. Cervix width on CT has been shown to be wider than on MRI and resulted in statistically significant differences in the volume treated to the prescription dose³⁵. Of interest is that the two departments using CT alone do employ ultrasound to aid applicator insertion. Van Dyk *et al.* have measured cervix dimensions on ultrasound and MRI and shown good agreement between the two modalities³⁶. There is potential for departments using CT alone to extend the role for ultrasound to assist in more accurately identifying the cervix. There was high uptake of OAR contouring for rectum, bladder and sigmoid, less so for small bowel (29%) while the vagina was not contoured by any respondents. Reporting doses received by the vagina was not recommended in ICRU report 38³⁷. The latest report aimed at prescribing, recording, and reporting brachytherapy for cancer of the cervix, ICRU report 89, does recommend reporting vaginal doses and details methods based on the imaging used for planning³⁸.

Doses

The majority of departments deliver brachytherapy over four fractions prescribing 6 – 7 Gy per fraction. Combined with average EBRT doses of 45 Gy the mean total dose prescribed is 81.6 Gy₁₀ EQD2, (range 73.2 – 85.6 Gy₁₀). The range of doses are somewhat more conservative compared to the doses used by departments listed in Table 1, where the mean dose is 82.7 Gy₁₀ (range 73.1 - 96.5 Gy₁₀). It should be noted that the current survey asked for prescription doses and Table 1 records mean doses received by the target volumes. Smaller volumes of disease would receive higher doses. The greater use of combined interstitial/intracavitary applicators by departments listed in Table 1 also contributes to higher absorbed tumour doses. Dose reporting was not specifically queried although one respondent stated that dose was prescribed to the HRCTV and dose to Point A was documented. Interestingly, ICRU report 89 recommends reporting dose at Point A be continued even by departments employing 3D imaging to plan treatment³⁸. This enables comparison of doses over different eras and across different levels of planning complexity.

Workload

The burden of cervix cancer is not high in Australia and New Zealand, largely due to well subscribed screening programs and high standards of living. However, there is a small consistent caseload, particularly in areas of lower socioeconomic status and a higher immigrant population. Managing smaller numbers of patients presents unique problems. These include, maintaining skills, accessing resources and infrastructure, offering support services, and following recommendations. An American patterns of care study by Eifel *et al.* found that smaller departments treating few patients were more likely to treat with EBRT alone, prolong overall treatment time and deliver lower doses of radiation to Point A³⁹. Fortunately, the results of the current survey do not seem to mimic the American experience. All departments that did not offer brachytherapy do refer patients to another facility and all respondent brachytherapy facilities have treatment guidelines in place. For departments who do find their caseload diminishing it may be prudent and pragmatic to refer their patients to larger facilities for treatment⁴⁰.

Barriers to IGABT

The main barriers to implementation of IGABT were access to MRI, budgetary constraints, anaesthetics/ theatre access and insufficient patient numbers. The most common reason cited for not implementing IGABT was insufficient patient numbers. All the centres that had no inclination to implement IGABT, did not provide a cervix brachytherapy service. Given the capital costs, staff training, logistical difficulties and learning curve associated with this technique, it is understandable that these centres send their patients elsewhere for their brachytherapy. Of the centres that provide an intrauterine cervix brachytherapy service, 71% (10/14) reported already performing IGABT. The remaining 4 centres indicated that they would like to implement IGABT. Access to MRI remains the main barrier to implementing or improving 3D image based planning. Respondents already using MRI indicated that they would like to expand use of MRI but access to it remains difficult. In Australia, only one simulation and one dosimetry episode is funded per course of brachytherapy. Despite this lack of funding for replanning 57 % of respondents replan each fraction.

Limitations

Not every centre in Australia & New Zealand is represented in this survey and due to the voluntary nature of the survey questionnaire, response bias is unavoidable. Another limitation of this survey was that patient outcomes were not explored. This is of particular

interest in light of the toxicity, local control and survival outcomes that are now being reported by the EMBRACE and Retro-EMBRACE collaborations⁴¹. Details regarding the imaging protocols used for those centres which incorporated MRI into their brachytherapy workflow were also not explored.

Patterns of care surveys are an important way of monitoring progress in the treatment of cervix cancer with brachytherapy. They can act as a means to benchmark treatment protocols and also draw attention to emerging research, updated guidelines and recommendations, and implementation of clinical trial outcomes. By necessity the questions asked by the survey must change to reflect changes in these entities. It is hoped that such surveys continue to be conducted and embraced within the Australian and New Zealand brachytherapy community.

Conclusions

Brachytherapy remains an integral component of definitive treatment for cervix cancer in Australia and New Zealand. None of the survey respondents were willing to substitute it with IMRT or SBRT if brachytherapy was still technically possible.

Most of the survey respondents who offer brachytherapy to their cervix cancer patients demonstrate a substantial shift toward 3D IGABT techniques and volume based planning.

There appears to be some heterogeneity in how brachytherapy dose is prescribed, reflecting the shift in approach from a purely geometrical applicator based prescription to one which takes into account individual anatomy.

Uptake of soft tissue imaging has increased significantly since 2009, with an emphasis on guiding applicator insertion and verifying applicator placement. Despite the high uptake of soft tissue imaging and volume based planning there are still perceived barriers to implementation of image guided brachytherapy.

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Figure Legends

Figure 1. Average number of patients with cervix cancer treated per department

Figure 2. Percentage of departments offering brachytherapy for metastatic disease

479 Figure 3. Percentage of departments using imaging

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Table 1. Literature review of clinical outcomes from image based brachytherapy

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Table 2. Comparison of imaging modalities used throughout Australia and New Zealand over three survey periods

Australia and New Zealand	2005 ¹⁷	2009 ¹⁸	2013
Departments treating cervix cancer with BT	21	20	14 [†]
Use of X-ray	81%	30%	14%
Use of CT	19%	65%	79%
Use of MRI	5%	15%	50%
Use of Ultrasound	5%	15%	86% (aid insertion) 29% (aid planning)

[†]14 respondents practice brachytherapy

Table 3. Comparison of imaging modalities used for brachytherapy planning throughout the world

Reference, Region			Imaging modality used for planning				
	Survey period		Ultrasound used for insertion	x-ray	CT	MRI	US
van Dyk <i>et al.</i> ¹⁷							
Australia & New Zealand	2010	2009	15%	30%	65%	15%	5%
Lim <i>et al.</i>							
Australia & New Zealand	2016	2013	86%	14%	79%	50%	29%
Viswanathan <i>et al.</i> ²¹							
2010	2007		56%		56%		
ABS USA			42% routinely				
Guedea <i>et al.</i> ²²							
2010	2007		48% available	71%	54%	15%	
Pavamani <i>et al.</i> ²³							
2011	2008		59%				
Canada			24% routinely	50%	45%		
Phan <i>et al.</i> ²⁴							
2015	2012			21%	75%	38%	
Canada							
Tan <i>et al.</i> ²⁵							
2011	2010				51%	20%	
United Kingdom							ABS American
Guedea <i>et al.</i> ²⁶							Brachytherapy
2011	2007		24% available	97%	22%	2%	Society; USA
Latin America							United States of
Viswanathan <i>et al.</i> ²⁷							America; GCIG
2012	2008		62% available	57%	25%		Gynecological
GCIG International			18% routinely				Cancer
							Intergroup.

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