

**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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11

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

26 radiation (EBRT) (22/23; 96%). Fourteen responses were from departments that also use
27 intracavitary brachytherapy (14/22; 64%). The remaining eight departments who do not offer
28 intracavitary brachytherapy referred their patients on to other centres for brachytherapy.
29 Ultrasound was used by 86% for applicator guidance. CT and MRI were used by 79%, and 50%
30 respectively for planning. Optimisation was based on organs at risk (93%) and target volumes
31 (64%).

32 **Conclusions**

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

38 **Five key words:**

39 Brachytherapy
40 Cervix cancer
41 Image guidance
42 Patterns of practice

44 **Introduction**

45
46 Brachytherapy plays an integral role in the curative treatment of inoperable cervix cancer,
47 enabling tumouricidal doses of radiation to be delivered directly to the primary site of
48 disease¹. Recent SEER data suggests that brachytherapy utilisation in cervix cancer has
49 declined in the USA from 83% in 1988, to 58% in 2009, with a sharp decline in 2003 (43%)².
50 This decline in brachytherapy usage has been shown to impact adversely on cause-specific
51 and overall survival².

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

58 Previous reports have demonstrated that centres in Australia are adopting image guided
59 protocols with an increase in the use of 3D imaging in brachytherapy planning from 27% in
60 2005 to 65% in 2009^{17,18}. The purpose of this survey was to explore the current patterns of
61 practice for brachytherapy in cervix cancer in Australia and New Zealand. The survey was also
62 intended to explore clinician attitudes toward IGABT and identify barriers to the
63 implementation of IGABT.

64

65 **Methods**

66

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

72

73 **Results**

74

75 *Overview*

76 Responses were received from all states and territories of Australia and New Zealand except
77 for the Northern Territory. There are 75 radiotherapy centres in Australia and New Zealand,
78 23 of which treat cervix cancer with brachytherapy. Overall, 23 departments replied to the
79 survey (23/75 = 31% response rate). Twenty two responding departments treat cervix cancer
80 with external beam radiation (EBRT) (22/23=96%). Fourteen responses were from
81 departments that also treat intracavitary brachytherapy (14/22=64% response rate). The
82 remaining eight departments who do not offer intracavitary brachytherapy all referred their
83 patients on to other centres who do provide brachytherapy services.

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

88

89 *External beam radiotherapy (EBRT)*

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

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

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

99

100 *Brachytherapy*

101 *Overview*

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

110 One department also treats twice daily occasionally. The majority of applicator insertions
111 occur in an operating theatre, (64%), with the remainder (36%) occurring in a dedicated
112 brachytherapy suite. All respondents reported using general anaesthetic for applicator
113 insertion. Spinal anaesthesia was also widely used (57%) and epidural anaesthesia less so
114 (7%). The prescription dose range from 3.5 – 8.5 Gy per fraction. The most common dosages
115 are 6 and 7 Gy per fraction.

116

117 *Workload*

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

120

121 The number of radiation oncologists performing procedures per department, varies from one
122 (14%), two (57%), three (21%) or four (7%).

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

130

131 *Use of Imaging*

132 All respondents use some form of imaging at the time of brachytherapy to aid in treatment
133 planning, although not all considered this image guided brachytherapy. The majority of
134 centres offering brachytherapy use 3D imaging, Figure 3. Image guided brachytherapy is
135 performed by 71% of respondents, with the remaining 29% of respondents indicating they
136 would like to implement image guided brachytherapy in the future. Computed tomography
137 (CT) is the most commonly used form of 3D imaging (79%) with 50% of the respondents using
138 magnetic resonance imaging (MRI) and 29% using ultrasound. Many of the respondents use
139 multi-modality imaging. Most planning imaging takes place in the radiotherapy department
140 (79%). Ultrasound is used to guide applicator insertion by 86% of respondents. It is also used
141 to aid planning by 29%. Twenty nine percent of respondents take intrafraction verification
142 images after patient transfers and prior to brachytherapy treatment. Ultrasound is used by
143 21% and x-ray by 14% for intrafraction verification. CT and MRI are not used for intrafraction
144 verification. Of the 71% of respondents who do not take intrafraction verification images,
145 there is considerable reliance on skin markings to indicate applicator position. Twenty one
146 percent of respondents who take intrafraction verification images adjust the applicator
147 position if it is unsatisfactory, 7% replan based on the updated applicator position and 7%
148 reimage and replan with CT. Use of 3D imaging is employed by 50% of respondents for every
149 fraction of brachytherapy. Interfraction imaging is used for replanning by 57% respondents,
150 while 29% back project the original plan onto the new image set. The purpose of interfraction
151 imaging for those not replanning is to verify the applicator position, 36%; verify the target
152 volume, 21%; and verify the organs at risk (OAR), 29%.

153

154 *Applicators and fixation*

155 The majority of respondents used intracavitary applicators, tandem and ovoids, 93%; tandem
156 and ring, 29%; and tandem and cylinder, 86%. Use of combined interstitial and intracavitary
157 applicators is 29%. A vaginal spatula (to move the rectum away) is used by 50% of
158 respondents. Applicators are fixed in position by use of intravaginal packing by 93% of
159 respondents. Perineal sutures are used by 43%, a perineal bar by 7%, and mesh underpants by
160 14%. Two departments also use fabric tape around the applicator to secure it in position.

161

162 *Planning methods*

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

172

173 *Prescription and dosimetry*

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

179 Planning constraints for the bladder range from 68 – 90 Gy in equivalent doses to 2 Gy
180 fractionation (EQD2). Constraints for the rectum and sigmoid range from 64 – 75 Gy and 54 –
181 75 Gy respectively. Only one respondent indicated a vaginal mucosal constraint of 85 Gy.

182 Only one respondent reported using a rectal probe to measure the rectal dose during
183 treatment and commented that treatment is corrected if the dose is hotter than expected.

184

185 *Moving toward and improving image guided brachytherapy*

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

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

194

195 **Discussion**

196

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

209

210 *Imaging*

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

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

223

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

239

240 *Applicators*

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

249

250 *Planning*

251 In the 2009 survey four departments (20%) based contouring, treatment volumes and dose
252 prescriptions on GEC-ESTRO recommendations¹⁷. This survey has identified nine departments
253 (64%) contouring the HRCTV and 43% optimising plans to this volume. Only seven

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

268

269

270 *Doses*

271 The majority of departments deliver brachytherapy over four fractions prescribing 6 – 7 Gy
272 per fraction. Combined with average EBRT doses of 45 Gy the mean total dose prescribed is
273 81.6 Gy₁₀ EQD2, (range 73.2 – 85.6 Gy₁₀). The range of doses are somewhat more
274 conservative compared to the doses used by departments listed in Table 1, where the mean
275 dose is 82.7 Gy₁₀ (range 73.1 - 96.5 Gy₁₀). It should be noted that the current survey asked for
276 prescription doses and Table 1 records mean doses received by the target volumes. Smaller
277 volumes of disease would receive higher doses. The greater use of combined
278 interstitial/intracavitary applicators by departments listed in Table 1 also contributes to higher
279 absorbed tumour doses. Dose reporting was not specifically queried although one
280 respondent stated that dose was prescribed to the HRCTV and dose to Point A was
281 documented. Interestingly, ICRU report 89 recommends reporting dose at Point A be
282 continued even by departments employing 3D imaging to plan treatment³⁸. This enables
283 comparison of doses over different eras and across different levels of planning complexity.

284 *Workload*

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

298 *Barriers to IGABT*

299 The main barriers to implementation of IGABT were access to MRI, budgetary constraints,
300 anaesthetics/ theatre access and insufficient patient numbers. The most common reason
301 cited for not implementing IGABT was insufficient patient numbers. All the centres that had
302 no inclination to implement IGABT, did not provide a cervix brachytherapy service. Given the
303 capital costs, staff training, logistical difficulties and learning curve associated with this
304 technique, it is understandable that these centres send their patients elsewhere for their
305 brachytherapy. Of the centres that provide an intrauterine cervix brachytherapy service, 71%
306 (10/14) reported already performing IGABT. The remaining 4 centres indicated that they
307 would like to implement IGABT. Access to MRI remains the main barrier to implementing or
308 improving 3D image based planning. Respondents already using MRI indicated that they
309 would like to expand use of MRI but access to it remains difficult. In Australia, only one
310 simulation and one dosimetry episode is funded per course of brachytherapy. Despite this lack
311 of funding for replanning 57 % of respondents replan each fraction.

312

313 *Limitations*

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

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

321

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

328

329

330 **Conclusions**

331

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

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

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

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

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476 **Figure Legends**

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

478 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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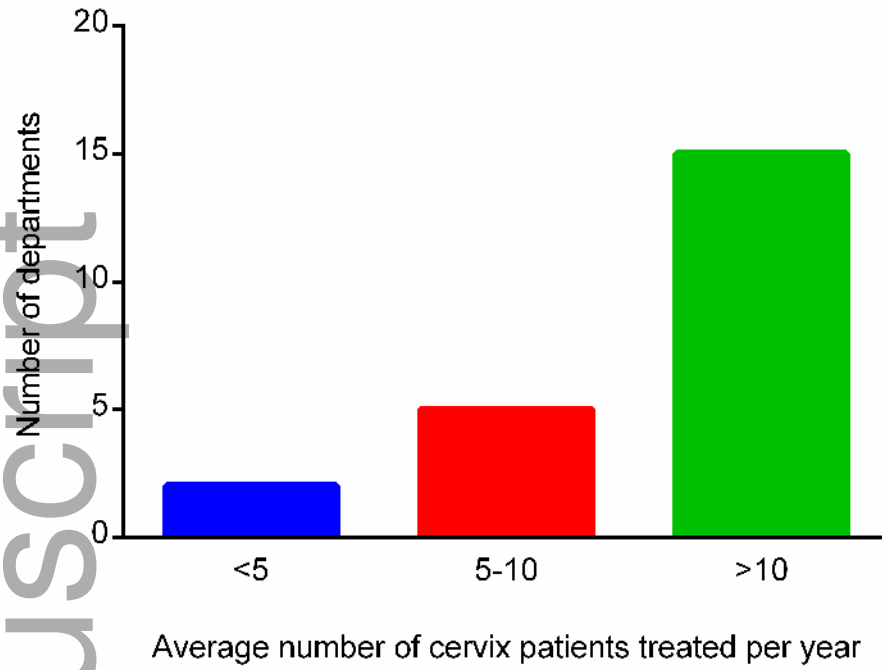
Table 2. Comparison of imaging modalities used throughout Australia and New Zealand over three survey periods

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)

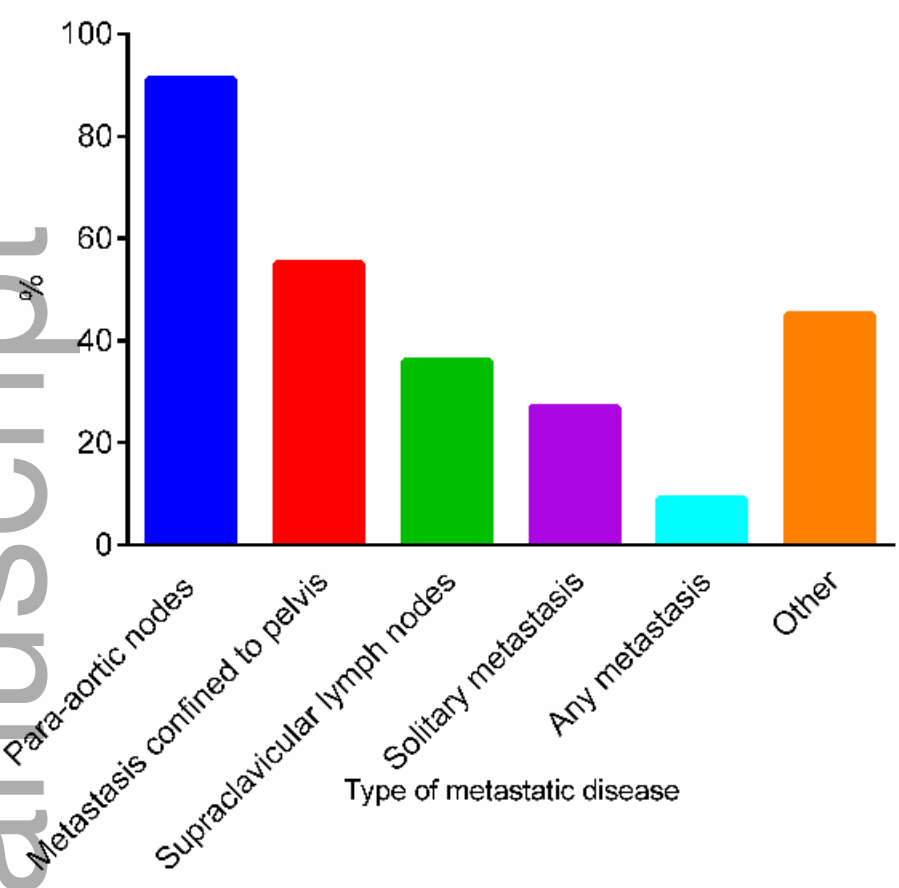
†14 respondents practice brachytherapy

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

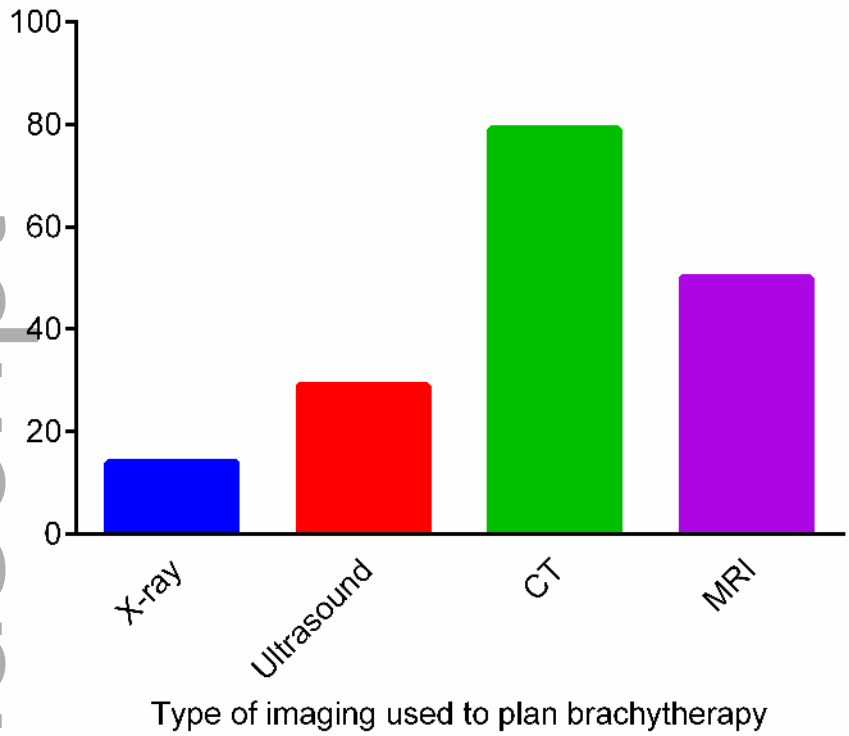
Reference, Region	Survey period	Imaging modality used for planning					
		Ultrasound used for insertion	x-ray	CT	MRI	US	
van Dyk <i>et al.</i> ¹⁷							
Australia & New Zealand	2010-2009	15%	30%	65%	15%	5%	
Lim <i>et al.</i>							
Australia & New Zealand	2016-2013	86%	14%	79%	50%	29%	
Viswanathan <i>et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



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