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REVIEW

Effects of Image-Guided Adaptive Brachytherapy on Morbidity and Quality of Life in Cervical Cancer

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SUMMARY

Image-guided adaptive brachytherapy (IGABT) is a technique now applied in locally advanced cervical cancer. This technique, in which magnetic resonance imaging is used prior to and during brachytherapy application, has led to important advances in gynecological brachytherapy, in terms of both dosimetric and clinical results. The reasons for using IGABT in cervical cancer include capacity of external radiotherapy to significantly shrink tumor prior to brachytherapy, high internal organ motion of cervix due to factors such as filling of urinary bladder, etc., and low local control rate in large tumors using 2-dimensional brachytherapy. In the last 20 years, there has been an increase in the success of treatment of cervical cancer with concomitant chemoradiotherapy and widespread use of IGABT. According to the results of major series using IGABT in cervical cancer, incidence of serious side effects is lower than 10%, and local control is in the range of 79% to 95%. Clinical results of IGABT studies have recommended organ at risk (OAR) dose parameters and limitations, and offered specific OAR (rectum, sigmoid, urinary bladder, bowel, vagina, urethra) toxicity measures and predictive dose-volume parameters. Studies have also provided review of this modality's impact on quality of life. Cancer patients must be informed about conditions they may confront after therapy and be offered detailed consultation and support regarding how to arrange their business, family, and social lives.

Keywords: Adaptive brachytherapy; cervical cancer; image-guided; quality of life; toxicity.

Introduction

Image-guided adaptive brachytherapy (IGABT) is a technique which has begun to be applied for the last 10 years in locally advanced cervical cancer.[1] By the help of this technique in which MRI is used for imaging prior and during brachytherapy application, important advances have been obtained in gynecological brachytherapy in terms of both dosimetric and clinical results.[2,3]

There are important reasons for applying IGABT in cervix cancer: 1) Since cervix cancer is a sensitive tumor to radiotherapy and chemotherapy, it is capable of shrinking significantly during external radiotherapy prior to brachytherapy. The average magnitude of this shrinking of cervix cancer under 40–50 Gy external radiotherapy may reach 20–30% of the volume at diagnosis.[4] 2) Cervix is an organ with high internal organ motion with change in its position caused by some factors such as filling of urinary bladder, etc. 3) Local control is low in large tumors using 2-dimensional brachytherapy. 4) Local control rises above 90% when D90 is greater than 87 Gy in target volume with external radiotherapy + IGABT.

In the last 20 years, there has been an increase in the success of treatment of cervix cancer with the developments related to concomitant chemoradiotherapy

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Table 1 Radiotherapy related side effects in organs at risk (rectum, sigmoid, urinary bladder, bowel, urethra, and vagina) according to the nomenclature in CTCAE v 4.03

Organ at risk	Side effect
Rectum	Fecal incontinence, proctitis, rectal pain, rectal mucositis, rectal bleeding, rectal fistula, rectal ulcer, rectal necrosis, rectal stenosis, rectal perforation
Sigmoid	Gastrointestinal pain, lower gastrointestinal bleeding, colon fistula, colon ulcer, colon stenosis, colon perforation
Urinary bladder	Urinary bladder spasm, non-infective cystitis, urgency, frequency, hematuria, urinary tract pain, urinary fistula, urinary bladder perforation, urinary tract obstruction, urinary incontinence
Bowel	Gastrointestinal pain, lower gastrointestinal bleeding, colon fistula, colon ulcer, colon stenosis, colon perforation (large bowel)
	Gastrointestinal pain, lower gastrointestinal bleeding, diarrhea, ileus, small bowel ulcer, small bowel stenosis, small bowel obstruction, small bowel perforation, malabsorbtion (small bowel)
Urethra	Urgency, frequency, hematuria, urinary tract pain, urinary fistula, urinary tract obstruction, urinary incontinence
Vagina	Vaginal discharge, vaginal pain, vaginal inflammation, vaginal dryness, vaginal fistula, vaginal bleeding, dyspareunia, vaginal stricture, vaginal perforation

Table 2 Clinical results obtained in cervical cancer patients receiving external radiotherapy ± concomitant chemotherapy + IGABT

Reference	No. of patients	Dose rate	Image guidance	Local control (%)	Cancer specific survival (%)	Overall survival (%)	> Grade 3 side effects (%)
Pötter R et al, 2011[5]	156	HDR	MRI	95	74	68	7
Lindegaard JC et al, 2013[6]	140	PDR / MDR	MRI	91	87	79	7
Mazeron R et al, 2013[7]	163	PDR	MRI (%88) CT (12%)	92	78	76	7.4
Nomden CN et al, 2013[8]	46	PDR / HDR	MRI	93	74	65	9.5
Rijkmans EC et al, 2014[9]	83	HDR / LDR	MRI (87%) CT (13%)	93	NR	86	8.4
Charra-Brunaud C, et al, 2012[13]	117	PDR	MRI CT	79	60	74	2.6
Lakosi F et al, 2015[10]	85	PDR	MRI	94	85	81	8[a]
Castelnau-Marchand P et al, 2015[11]	225	PDR	MRI	86	72	76	6.8
Gill BS et al, 2015[12]	128	HDR	MRI	92	85	77	0.9[b]

a: Total percentage of side effects not stated, however serious organ-specific side effects given separately <8%; b: Total percentage of side effects not stated, however serious organ-specific side effects given separately <0.9%; NR: Not reported; HDR: High dose rate; PDR: Pulsed dose rate; MDR: Medium dose rate; MRI: Magnetic resonance imaging; CT: Computerized tomography.

and beginning of the application and widespread use of IGABT. Since survival gets longer due to this increase, the late side effects of radiotherapy have been gaining more importance in time.

Table 1 shows the list of radiotherapy related side effects for organs at risk (OAR) (rectum, sigmoid, urinary bladder, bowel, vagina, and urethra) according to the classification in CTCAE v 4.03.

Clinical results of IGABT studies

The clinical results of the studies including more than 30 patients on IGABT in cervix cancer are seen in Table 2. According to the results of these series, the incidence of serious side effects is lower than 10% while local control is in the range of 79%–95%.[5–13] In the study of Pötter et al., from the Medical University of Vienna presenting clinical results of 3-D conformal radiotherapy ± concomitant chemotherapy + IGABT in cervix cancer, favorable results have been reached for both local control and morbidity with IGABT in which MRI is used systematically.[5] In this series of 156 patients with stage IB–IVA cervix cancer, 3-year local control is 85–90% in locally advanced stage while it is 95–100% for early stage. Besides, the frequency of serious (LENT-SOMA grade 3 and 4) side effects is 7%. Compared to the results of historical 2-dimensional brachytherapy

Table 3 Organ at risk dose parameters recommended for reporting routinely (excluding research) in ICRU 89[14]

Organ at risk	Level 1 (minimum standard)	Level 2 (advanced standard)
Rectum	Recto-vaginal reference point dose, D0.1cc, D2cc	Recto-vaginal reference point dose, D0.1cc, D2cc V15Gy, V25Gy, V35Gy, V45Gy or D98%, D50%, D2%
Sigmoid	–	D0.1cc, D2cc V15Gy, V25Gy, V35Gy, V45Gy or D98%, D50%, D2%
Urinary bladder	D0.1cc, D2cc	D0.1cc, D2cc, urinary bladder reference point dose V15Gy, V25Gy, V35Gy, V45Gy or D98%, D50%, D2%
Bowel	–	Dcc V15Gy, V25Gy, V35Gy, V45Gy or D98%, D50%, D2%
Vagina	–	Vaginal point doses at 5 mm lateral to the vaginal mucosa at the level of radioactive sources Inferior and middle vagina doses (PIBS, PIBS + 2cm)

ICRU: International Commission on Radiation Units and Measurements; PIBS: Posterior-inferior limit of symphisis pubis.

series of Vienna, these results display a statistically significant increase in overall survival and pelvic control rates and a statistically significant decrease in distant metastasis rate. Additionally, using IGABT has caused a threefold decrease in the rate of serious side effects (21% vs. 7%) and the rate of 3-year actuarial serious toxicity has declined from 15% to 8% (p=0.06).[5]

In a French multicentric non-randomized prospective study including 235 patients with cervix cancer treated with concomitant chemotherapy and external radiotherapy + brachytherapy, while the incidence of grade 3–4 toxicity is 22.7% in 2-dimensional brachytherapy, it decreases to 2.6% in 3-dimensional brachytherapy.[13] In a retrospective study from Leiden University including a total of 126 patients with cervix cancer, compared to 2-dimensional brachytherapy, IGABT has provided a statistically significant increase in both complete response (99% vs. 84%) and overall survival (86% vs. 51%), together with a decrease in the frequency of grade 3–4 side effects from 15% to 8% (p=0.06).[9] In a retrospective study from Aarhus University performed in a total of 239 patients with cervix cancer, the cohort of patients applied 2-dimensional brachytherapy was compared with the cohort of patients applied IGABT.[6] In this study, overall survival has increased (79% vs. 63%; p=0.005) and also grade 3–4 combined urological and gastrointestinal morbidity has decreased (3% vs. 10%; p=0.01) with IGABT compared to 2-dimensional brachytherapy.[6]

The positive results obtained with IGABT are aimed to be confirmed repetitively through multicentric prospective studies in which this modality is applied systematically in the light of GEC-ESTRO recommendations. In 2008, an international study on MRI-guided brachytherapy in locally advanced stage cervix cancer (EMBRACE) has been designed with this aim. It is thought that the correlation between local control and target dose-volume parameters and late morbidity and OAR dose-volume parameters can be demonstrated in the perspective of EMBRACE data.

Recommended OAR dose parameters to be reported and OAR dose limitations

Table 3 shows the OAR dose parameters recommended for reporting routinely (excluding research) in the recent report of ICRU (No: 89) related with cervix cancer brachytherapy.[14] OAR dose limitations in IGABT advised by cooperative study groups in the USA and Europe are given in Table 4.[15]

Rectal side effects

The frequency of serious rectal side effects for IGABT is declared as 1–5%.[5,8,16–18] In the study of Georg et al., from the Medical University of Vienna, the frequency of grade 1–4 late side effects in rectum is13.8% and the most frequent one is bleeding (10.7%).[17] Five-year actuarial incidence of late rectal side effects has been calculated as19% in that study and all late side effects have emerged in the first 3 years following radiotherapy. Mean time for occurrence of late side effects was 14 (3–34) months, whereas their mean duration period was 19 (1–75) months.[17]

In the study performed by Mazeron et al., from Gustave Roussy Cancer Center, it has been shown that grade 1–4 and grade 2–4 morbidities of rectum have a relation with D2cc parameter of rectum.[16] In a study made in Leuven Cancer Institute, a correlation has been determined between rectal D2cc >65 Gy and occurrence of > grade 3 late rectal morbidity.[18]

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Table 4 Dose limitations for organs at risk in IGABT recommended by the cooperative study groups in the USA and Europe[15]

Volume/Point	ABS	Embrace
Point A	Variable	No recommendation
HR-CTV D90	>80–90 Gy EQD2	Depends on the institutional routine
IR-CTV D90	No recommendation	Depends on the institutional routine
D2cc bladder	<90 Gy EQD2	<90 Gy EQD2
D2cc rectum	<75 Gy EQD2	<70–75 Gy EQD2
D2cc sigmoid	<75 Gy EQD2	<75 Gy EQD2

ABS: American Brachytherapy Society; HR-CTV: High-risk clinical target volume; IR-CTV: Intermediate-risk clinical target volume; EQD2: Equivalent total dose in 2 Gy fractions (calculations performed accepting α/β: 10 for target volume doses, and accepting α/β: 3 for doses in organs at risk).

Sigmoid side effects

Generally, the documentation of sigmoid side effects is insufficient for brachytherapy applied patients. In a limited number of studies offering data on this subject for IGABT applied patients, the frequency of sigmoid serious side effects is reported as 0–2%.[5,18,19] Sigmoid D0.1cc and D2cc parameters have not been shown to play any role to predict radiotherapy related sigmoid side effects. The reasons of not being able to determine any dose-volume parameters related with sigmoid morbidity are as follows: 1) Sigmoid is a mobile organ. 2) The frequency of side effects is low for sigmoid. 3) There is a clinical misunderstanding that the side effects originate from r rectum instead of sigmoid. 4) It is necessary to perform sigmoidoscopy, which is not a routine procedure, in order to determine sigmoid side effects.[19]

At present, D2cc, D1cc, and D0.1cc are evaluated for sigmoid, similar to the situation for rectum. Besides, in case of any sigmoid loop being adjacent to the applicator, this situation certainly must be paid attention during dose optimization in computerized treatment planning.

Urinary bladder side effects

The incidence of serious urinary bladder side effects has been reported as 3–6% for IGABT.[5,16–18,20] The incidence of grade 1–4 urinary bladder late side effects is 21.8%, urinary incontinence (13.8%) being the most frequent one, in the study of Georg et al., from the Medical University of Vienna.[17] In Georg et al.'s study, in which the 5-year actuarial incidence of late urinary bladder side effects has been measured as 28%, all side effects have occurred within the first 3 years following radiotherapy. The mean time period for the occurrence of late side effects was 27 (3–94) months while the mean duration period was 20 (1–62) months. [17] In this study, it has been demonstrated that urinary bladder side effects emerge later and heal more slowly than rectal side effects in patients receiving external radiotherapy + IGABT.[17]

In the study of Mazeron et al., from Gustave Roussy Cancer Center, it has been shown that grade 2–4 and grade 3–4 morbidities of urinary bladder are in relation with urinary bladder parameters D0.1cc and D2cc.[16] In another study by the same author, it has been displayed that the mean position of urinary bladder D2cc differs from the position of ICRU urinary bladder point, being located at 1.7 cm. cranial and 0.6 cm. posterior of the urinary bladder ICRU point.[21] According to the study, if D2cc/DICRU is >1.1, D2cc volume will be located at the cranial of ICRU urinary bladder point, and if the ratio is <1.1, it will be located at the caudal of ICRU urinary bladder point. For the patients with the ratio D2cc/DICRU is <1.1, it has been determined that urinary bladder D2cc correlates with the risk of grade 2–4 incontinence (p=0.017).[21]

Bowel side effects

The incidence of serious bowel side effects for IGABT has been reported as 0–4.8%.[5,8,22] There are problems in comparison of studies with respect to bowel side effects related to radiotherapy. One of the most important reasons for that is the variability in bowel contouring. The group of patients who are not allowed oral intake for being under anesthesia cannot be given contrast agent orally during imaging in CT-simulation for IGABT. Such a situation makes it difficult to view bowel loops during contouring on CT sectional images and also prevents the distinction between small and large bowel loops being made easily. In cases of being unable to make such a distinction, the whole of small and large bowels above sigmoid are contoured as bowel. Besides, in some centers, it may be preferred to contour not only bowel segments, but also the bowel including peritoneal cavity in order to reduce uncertainty due to bowel motility.

In the study of Petit et al., from Gustave Roussy Cancer Center performed in patients with locally advanced stage cervix center receiving concomitant chemoradiotherapy + IGABT, it has been found that the incidence of > grade 3 late small bowel side effects was 2.6% and parameters of D2cc and D0.1cc did not influence late small bowel toxicity.[22] In recent years, small bowel is claimed to be a complex model formed by organization of mucosal, mesenchymal, vascular, immune and inflammatory components, in addition to being a serial organ.[23] For this reason, it is thought that the parameters like D2cc and D0.1cc which are more valid for serial organs may have not been significantly correlated with small bowel morbidity of radiotherapy.[22] It has been suggested by some authors that "moderate doses to large volumes" stemming from external radiotherapy could play a greater role than "high doses to small volumes" originating from brachytherapy for the occurrence of radiotherapy related late small bowel toxicity.[22,24] However, bowel D2cc and D0.1cc may still be important especially for side effects like fistula, stricture and obstruction, gaining more importance in the presence of a small bowel segment adjacent to the applicator. This must be absolutely paid attention during dose optimization in computerized treatment planning of IGABT.

Vaginal side effects

The incidence of serious vaginal side effects with IGABT has been reported as 3–5.7%.[5,8,18,20,25,26] In EMBRACE study, vaginal stenosis, vaginal dryness and vaginal bleeding/mucositis, respectively, were the most frequent ones among vaginal morbidity types encountered in external radiotherapy + IGABT.[25] In general, the incidence of vaginal morbidity due to radiotherapy reaches its peak in the 2nd year starting from the end of the radiotherapy. Compared to the other vaginal side effects, vaginal stenosis (shortening and/or narrowing) and vaginal dryness tend more to be permanent.[25]

According to some studies, vagina D2cc does not have a role to predict radiotherapy related vaginal morbidity.[26,27] In a series of 34 patients with cervix cancer from the Medical University of Vienna, mean vagina D2cc was 95.2 Gy with only IGABT and 141 Gy totally with the combination of external radiotherapy and IGABT.[27] Rai et al., from Chandigargh Research Institute, India have not observed any relation between vagina D0.1cc, D2cc, D5cc, D10cc and vaginal toxicity (telangiectasia, shortening of vagina, dyspareunia) within the 1st year after the end of the external radiotherapy + IGABT.[26] The reasons of being unable to show such a relation are as follows: 1) There is inherent difficulty in contouring vagina (alteration of organ thickness due to personal anatomical differences, probability of getting too much thin at some parts depending on the diameter of the applicator used). 2) Different approaches exist in contouring of vagina (inclusion of distal surface of cervix also into vagina by some researchers, etc.). 3) Vagina is both a target volume and OAR totally or partially. 4) There is an increase in uncertainty with regard to high doses formed in vaginal mucosa due to closeness of especially vaginal surface to the radioactive sources during brachytherapy. 5) It is difficult to determine the total dose (external radiotherapy + IGABT) received by the portion of vagina included within the external radiotherapy fields. On the other hand, in a study held at Duke Cancer Center in the USA, which is the biggest cohort investigating vaginal morbidity with IGABT, both vagina D2cc and vagina D1cc have been displayed as independent prognostic factors affecting ≥ grade 2 vaginal morbidity.[28] In this study, where vagina is contoured without including the mucosa covering distal part of cervix, it is recommended that vagina D2cc should not exceed 108 Gy totally with external radiotherapy + IGABT.[28] In a recent study from the Medical University of Vienna, rectovaginal reference point total dose >65 Gy, external radiotherapy dose >45 Gy/25 fx and extension of tumor to vagina have been determined as risk factors for vaginal stenosis.[29]

Also it is known that the radiotherapy tolerance of distal vagina is lower than that of proximal vagina. With the help of prospective IGABT studies, it will be possible to determine dose-volume limitations differing according to the upper-middle-lower anatomical parts of vagina.

Urethral side effects

The reporting of urethral side effects related to radiotherapy is very limited in IGABT applied patients with gynecological tumors. As a result of this, organ tolerance information that is present for prostatic urethra is not available for female urethra. Currently, D2cc is reported for urethra as being similar for urinary bladder. The reasons of being unable to show dose-volume parameters predictive of urethral morbidity are as follows: 1) There is difficulty in the contouring of urethra. 2) Female urethra usually is not exposed to a significant dose level due to its relatively more distal location while only the 1/3 upper part of vagina is included into the target volume for the majority of gynecological tu-

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mors. 3) There is scarcity of series of patients with vaginal tumors in which urethra receives significant dose.

In a series by Dimopoulos et al., from the Medical University of Vienna including 13 patients with locally advanced stage vagina cancer who received IGABT after concomitant external radiotherapy and chemotherapy, urethral necrosis has been detected following radiotherapy in 1 patient who had extensive tumor invasion into urethra. Mean urethra D2cc was 76 Gy in this study, in which no urethral morbidity has been reported except for that case.[30]

Quality of life

Therapy related late morbidity is an important problem for cancer patients receiving curative therapy. As late morbidity may create problems which need to be solved clinically, it also affects patients' quality of life negatively. The studies on IGABT have to guide to develop quality of life by evaluating it prospectively in addition to evaluating treatment success and morbidity.

Fifty sequential patients with locally advanced stage cervix carcinoma have been evaluated prospectively and longitudinally in terms of quality of life in the study of Kirchheiner et al., from the Medical University of Vienna.[31] In this study, EORTC QLQ C30 general quality of life questionnaire and EORTC CX24 quality of life questionnaire for patients with cervix cancer have been applied to the patients prior to, and during radiotherapy and also 1 week and 3 months after IGABT. A comparison has been made in terms of quality of life with the reference group taken from general population and matched according to age. In the study, it has been determined that the state of global health and physical and role functioning of patients with cervix cancer are apparently reduced ($p<0.001$), returning to its base value in the 3rd month after therapy. Besides, the state of global health and emotional and role functioning of patients with cervix cancer have been found lower compared to the reference group. The symptoms expressed to have been experienced by patients "at an important level" have been stated as fatigue (78%), diarrhea (68%), urinary frequency (60%), and nausea (54%) in the study. It has been expressed that these symptoms recovered partially 3 months after the end of radiotherapy, although fatigue (50%) continued and hot flush (44%), sexual anxiety (38%), and leg edema (22%) emerged.[31]

In one of the recent EMBRACE studies, quality of life of the 744 patients with locally advanced stage cervix cancer applied concomitant chemoradiotherapy + IGABT has been evaluated prospectively and longitudinally.[32] Similar to the study mentioned in the paragraph above, same questionnaires have been used for the measurement of quality of life, this time, for a longer period after IGABT (every 3 months in the 1st year, every 6 months in the 2nd and 3rd years, then once in a year for people who became disease-free). In EMBRACE study, it is stated that while general quality of life and emotional and social functioning of patients with cervix cancer were insufficient prior to therapy, they recovered in the first 6 months following therapy and reached to the level of the reference group, although cognitive functioning kept to be insufficient. On the other hand, it has been detected that while social and role functioning were at the lowest level prior to therapy, they recovered after therapy (forming a plateau at 6th month) and deteriorated slightly in the 3rd and 4th years. It has been observed that while symptoms of tumor (pain, loss of appetite, constipation) were severe prior to therapy, they reduced apparently at the first control after therapy. Also it has been detected that therapy related symptoms appeared suddenly after therapy and kept their level (diarrhea, menopausal symptoms, peripheral neuropathy, sexual dysfunction) or initiated slowly and increased gradually (lymph edema, dyspnea).[32]

Conclusion

As a conclusion, the patients with gynecological cancers must be informed about the conditions they may confront after therapy and be offered detailed consultation and more support about how to arrange their business, family and social lives.

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Disclosure Statement

The authors declare no conflicts of interest.

References

1. Haie-Meder C, Pötter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al; Gynaecological (GYN) GEC-ESTRO Working Group. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005;74(3):235–45.

2. Lindegaard JC, Tanderup K, Nielsen SK, Haack S, Gelineck J. MRI-guided 3D optimization significantly improves DVH parameters of pulsed-dose-rate brachytherapy in locally advanced cervical cancer. Int J Radiat Oncol Biol Phys 2008;71(3):756–64.
3. Pötter R, Dimopoulos J, Georg P, Lang S, Waldhäusl C, Wachter-Gerstner N, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiother Oncol 2007;83(2):148–55.
4. Potter R, Kirisits C, Fidarova EF, Dimopoulos JC, Berger D, Tanderup K, et al. Present status and future of high-precision image guided adaptive brachytherapy for cervix carcinoma. Acta Oncol 2008;47(7):1325–36.
5. Pötter R, Georg P, Dimopoulos JC, Grimm M, Berger D, Nesvacil N, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol 2011;100(1):116–23.
6. Lindegaard JC, Fokdal LU, Nielsen SK, Juul-Christensen J, Tanderup K. MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. Acta Oncol 2013;52(7):1510–9.
7. Mazeron R, Gilmore J, Dumas I, Champoudry J, Goulart J, Vanneste B, et al. Adaptive 3D image-guided brachytherapy: a strong argument in the debate on systematic radical hysterectomy for locally advanced cervical cancer. Oncologist 2013;18(4):415–22.
8. Nomden CN, de Leeuw AA, Roesink JM, Tersteeg RJ, Moerland MA, Witteveen PO, et al. Clinical outcome and dosimetric parameters of chemo-radiation including MRI guided adaptive brachytherapy with tandem-ovoid applicators for cervical cancer patients: a single institution experience. Radiother Oncol 2013;107(1):69–74.
9. Rijkmans EC, Nout RA, Rutten IH, Ketelaars M, Neelis KJ, Laman MS, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. Gynecol Oncol 2014;135(2):231–8.
10. Lakosi F, de Cuypere M, Viet Nguyen P, Jansen N, Warlimont B, Gulyban A, et al. Clinical efficacy and toxicity of radio-chemotherapy and magnetic resonance imaging-guided brachytherapy for locally advanced cervical cancer patients: A mono-institutional experience. Acta Oncol 2015;54(9):1558–66.
11. Castelnau-Marchand P, Chargari C, Maroun P, Dumas I, Del Campo ER, Cao K, et al. Clinical outcomes of definitive chemoradiation followed by intracavitary pulsed-dose rate image-guided adaptive brachytherapy in locally advanced cervical cancer. Gynecol Oncol 2015;139(2):288–94.
12. Gill BS, Kim H, Houser CJ, Kelley JL, Sukumvanich P, Edwards RP, et al. MRI-guided high-dose-rate intracavitary brachytherapy for treatment of cervical cancer: the University of Pittsburgh experience. Int J Radiat Oncol Biol Phys 2015;91(3):540–7.
13. Charra-Brunaud C, Harter V, Delannes M, Haie-Meder C, Quetin P, Kerr C, et al. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. Radiother Oncol 2012;103(3):305–13.
14. ICRU Report 89. Journal of ICRU 2013;13(1-2). Available at: https://academic.oup.com/jicru/article-abstract/13/1-2/NP/2379433/Report-89?redirectedFrom=fulltext. Accessed Jun 14, 2017.
15. Harkenrider MM, Alite F, Silva SR, Small W Jr. Image-Based Brachytherapy for the Treatment of Cervical Cancer. Int J Radiat Oncol Biol Phys 2015;92(4):921–34.
16. Mazeron R, Maroun P, Castelnau-Marchand P, Dumas I, del Campo ER, Cao K, et al. Pulsed-dose rate image-guided adaptive brachytherapy in cervical cancer: Dose-volume effect relationships for the rectum and bladder. Radiother Oncol 2015;116(2):226–32.
17. Georg P, Boni A, Ghabuous A, Goldner G, Schmid MP, Georg D, et al. Time course of late rectal- and urinary bladder side effects after MRI-guided adaptive brachytherapy for cervical cancer. Strahlenther Onkol 2013;189(7):535–40.
18. Ribeiro I, Janssen H, De Brabandere M, Nulens A, De Bal D, Vergote I, et al. Long term experience with 3D image guided brachytherapy and clinical outcome in cervical cancer patients. Radiother Oncol 2016;120(3):447–54.
19. Georg P, Lang S, Dimopoulos JC, Dörr W, Sturdza AE, Berger D, et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. Int J Radiat Oncol Biol Phys 2011;79(2):356–62.
20. Sturdza A, Pötter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol 2016;120(3):428–33.
21. Mazeron R, Dumas I, Rivin E, Martin V, Benhabib-Boukhelif W, Tailleur A, et al. D2cm^3/DICRU ratio as a surrogate of bladder hotspots localizations during image-guided adaptive brachytherapy for cervical cancer: assessment and implications in late urinary morbidity analysis. Brachytherapy 2015;14(2):300–7.

Turk J Oncol 2017;32(2):81–88
doi: 10.5505/tjo.2017.1585

22. Petit C, Dumas I, Chargari C, Martinetti F, Maroun P, Doyeux K, et al. MRI-guided brachytherapy in locally advanced cervical cancer: Small bowel D0.1cc and D2cc are not predictive of late morbidity. Brachytherapy 2016;15(4):463–70.
23. Hauer-Jensen M, Denham JW, Andreyev HJ. Radiation enteropathy-pathogenesis, treatment and prevention. Nat Rev Gastroenterol Hepatol 2014;11(8):470–9.
24. Mouttet-Audouard R, Lacornerie T, Tresch E, Kramar A, Le Tinier F, Reynaert N, et al. What is the normal tissues morbidity following Helical Intensity Modulated Radiation Treatment for cervical cancer? Radiother Oncol 2015;115(3):386–91.
25. Kirchheiner K, Nout RA, Tanderup K, Lindegaard JC, Westerveld H, Haie-Meder C, et al. Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys 2014;89(1):88–95.
26. Rai B, Dhanireddy B, Patel FD, Kumari R, Oinam AS, Simha V, et al. Vaginal dose, toxicity and sexual outcomes in patients of cervical cancer undergoing image based brachytherapy. Asian Pac J Cancer Prev 2014;15(8):3619–23.
27. Fidarova EF, Berger D, Schüssler S, Dimopoulos J, Kirisits C, Georg P, et al. Dose volume parameter D2cc does not correlate with vaginal side effects in individual patients with cervical cancer treated within a defined treatment protocol with very high brachytherapy doses. Radiother Oncol 2010;97(1):76–9.
28. Susko M, Craciunescu O, Meltsner S, Yang Y, Steffey B, Cai J, et al. Vaginal Dose Is Associated With Toxicity in Image Guided Tandem Ring or Ovoid-Based Brachytherapy. Int J Radiat Oncol Biol Phys 2016;94(5):1099–105.
29. Kirchheiner K, Nout RA, Lindegaard JC, Haie-Meder C, Mahantshetty U, Segedin B, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. Radiother Oncol 2016;118(1):160–6.
30. Dimopoulos JC, Schmid MP, Fidarova E, Berger D, Kirisits C, Pötter R. Treatment of locally advanced vaginal cancer with radiochemotherapy and magnetic resonance image-guided adaptive brachytherapy: dose-volume parameters and first clinical results. Int J Radiat Oncol Biol Phys 2012;82(5):1880–8.
31. Kirchheiner K, Nout RA, Czajka-Pepl A, Ponocny-Seliger E, Sturdza AE, Dimopoulos JC, et al. Health related quality of life and patient reported symptoms before and during definitive radio(chemo)therapy using image-guided adaptive brachytherapy for locally advanced cervical cancer and early recovery - a mono-institutional prospective study. Gynecol Oncol 2015;136(3):415–23.
32. Kirchheiner K, Pötter R, Tanderup K, Lindegaard JC, Haie-Meder C, Petrič P, et al. Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study. Int J Radiat Oncol Biol Phys 2016;94(5):1088–98.