

## Guidelines

# Recommendations from gynaecological (GYN) GEC-ESTRO working group – ACROP: Target concept for image guided adaptive brachytherapy in primary vaginal cancer



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## ABSTRACT

**Background and aim:** External beam radiotherapy (EBRT) combined with brachytherapy has an essential role in the curative treatment of primary vaginal cancer. EBRT is associated with significant tumour shrinkage, making primary vaginal cancer suitable for image guided adaptive brachytherapy (IGABT). The aim of these recommendations is to introduce an adaptive target volume concept for IGABT of primary vaginal cancer.

**Methods:** In December 2013, a task group was initiated within GYN GEC-ESTRO with the purpose to introduce an IGABT target concept for primary vaginal cancer. All participants have broad experience in IGABT and vaginal cancer brachytherapy. The target concept was elaborated as consensus agreement based on an iterative process including target delineation and dose planning comparison, retrospective analysis of clinical data and expert opinions.

**Results:** Gynaecological examination and MR imaging are the modalities of choice for local tumour assessment. A specific template for standardised documentation with clinical drawings for vaginal cancer was developed. The adaptive target volume concept comprises different response-related target volumes. For EBRT these are related to the primary tumour and the lymph nodes, while for IGABT these are related to the primary tumour and are consisting of the residual gross tumour volume (GTV-T<sub>res</sub>) and the high-, and intermediate risk clinical target volumes (CTV-T<sub>HR</sub>, CTV-T<sub>IR</sub>).

**Conclusion:** This target concept for IGABT of primary vaginal cancer defines adaptive target volumes for volumetric dose prescription and should improve comparability of different radiotherapy schedules of this rare disease. A prospective evaluation of the target volume concept within a multicentre study is planned.

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Primary vaginal cancer is a rare gynaecologic cancer, constituting approximately 3% of gynaecological malignancies [1]. Radiotherapy including brachytherapy is the treatment of choice for the majority of patients as organ-sparing surgery with negative resection margins is difficult to achieve [2]. Due to its rarity, the treatment strategy for primary vaginal cancer is based on experience from the treatment of locally advanced cervical cancer with

which it shares many similarities. Therefore, a combination of external beam radiotherapy (EBRT) (45–50 Gy with 1.8–2 Gy per fraction) and a brachytherapy-boost up to a total dose of 70–80 Gy in combination with concomitant weekly cisplatin-based chemotherapy is currently considered standard of care [3–5].

First conceptual ideas on a target volume concept for vaginal cancer brachytherapy date back from the era before the use of volumetric 3-dimensional imaging. These concepts were related to the application technique and dose prescription according to institutional experience. The concepts included: (1) in small well-defined superficial tumours: the gross tumour volume (GTV) with 1–2 cm margin; (2) in larger tumours after EBRT: either the initial

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tumour volume with a safety margin (mainly related to the tradition of prescribing to the cumulative 60 Gy reference isodose), or alternatively the GTV at time of brachytherapy with a safety margin to prescribe a higher dose (>60 Gy) [6]. Treatment planning and reporting was based on the clinical experience using mainly applicator related points, and systems (e.g. the Paris system) in case of interstitial techniques. Dose reporting followed the International Commission on Radiation Units and measurements (ICRU) reports 38 and 58 [7,8]. Several large institutional radiograph-based brachytherapy experiences report local/pelvic control rates ranging from 47–88% (~75%). Pelvic control was good for stage I–II (~80%) compared to 40–80% (~60%) for stage III and 0–69% (~45%) for stage IV, while severe morbidity was mainly described for the GU and GI tract [3–5,9–16].

Developments in the field of image-guided adaptive brachytherapy (IGABT) for cervical cancer also appear attractive for vaginal cancer. The principle of IGABT for cervical cancer is to apply three-dimensional (3D) volumetric imaging to visualise both the targets and organs at risk in relation to the applicator. During dose planning the dose is shaped according to the individual target volumes, taking tumour regression during or after radiochemotherapy into account [17–21]. Clinical studies of IGABT demonstrated improved local control with a simultaneous reduction of treatment related morbidity in comparison to conventional point-A based treatment planning [22–26]. Due to the similarities between cervical cancer and vaginal cancer, IGABT for vaginal cancer appears to be a logical step. Indeed, first clinical experiences in a limited number of patients showed the feasibility of IGABT for vaginal cancer with promising clinical results [27–30]. However, there are also distinct differences with cervical cancer, in particular in regard to anatomy and applicator systems, and a common concept for target

volume and dose reporting is lacking. Therefore, a task group within the Gynaecological Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GYN GEC-ESTRO) was established with the aim to introduce IGABT concepts for vaginal cancer. This report summarises the GYN GEC-ESTRO concepts and recommendations for target volume definition in IGABT for primary vaginal cancer.

## Background and methods

### Methods

In December 2013, a task group was initiated within GYN GEC-ESTRO with the purpose to introduce IGABT concepts for the vagina (primary and recurrent). All participants have wide experience using IGABT for gynaecologic malignancies and participate in the EMBRACE (An international study on MRI-guided brachytherapy in locally advanced cervical cancer) studies (Aarhus University Hospital (AUH), Amsterdam University Medical Center (Amsterdam UMC), Leiden University Medical Center (LUMC), Gustave Roussy Cancer Campus, Paris (GRCC) and Medical University of Vienna (MUV)).

During the first meeting in Vienna in 2014, primary vaginal cancer was prioritised. Based on 10 cases (two cases from each centre) various institutional treatment concepts were documented, and discussed. All relevant aspects for IGABT in primary vaginal cancer were recorded and similarities and differences in regard to target volume definition, dose prescription and reporting between the centres were observed. In particular, the need for common terminology was outlined. After this discussion, the methodology for consensus-based recommendations was agreed upon. In brief, four

**Table 1**

Local tumour staging.

	Clinical aspects	MRI signs for T2-weighted sequences
“Normal” vagina	The vagina extends from the vulva to the cervix. The hymen or hymenal remnants at the level of the ostium urethrae mark the transition from the vagina to the introitus. At the level of the cervix the fornices mark the transition to the cervix. The paravaginal space contains connective tissue, the (lymph) vascular and nerve supply and is limited by the pelvic floor musculature caudally and laterally, the bladder ventrally, the mesorectum fascia dorsally and the parametria cranially. Lymph drainage of the upper vagina follows that of the cervix through the vaginal and uterine arteries towards the obturator and iliac regions. While the drainage of the lower third is towards the inguino-femoral nodal regions. In case of dorsal extension, drainage toward the para-rectal nodes has been described	MRI allows for the differentiation of the three layers of the vaginal wall (mucosa, submucosa/tunica muscularis and tunica adventitia): The mucosa is depicted as hyperintense layer, followed by the submucosa and tunica muscularis with hypointense signal intensity. The tunica adventitia is – due to the lymphatic and venous plexus – again hyperintense. Note, that if gel is applied to improve the visualisation of the vagina, the mucosal layer can not be identified (gel and mucosa have a similar signal intensity)
Vaginal cancer	The vagina should be the primary tumour site, and other genital and non-genital sites of origin should be excluded. Tumours extending to the portio and involving the ostium should be classified as cervical cancer; and as vulvar cancer in case of involvement of the vulva. The upper dorsal third is most frequently affected, followed by the lower anterior third. Multifocal disease has been reported in up to 50% of patients. In addition to routine gynaecological examination, colposcopy using combined acetic and Lugol iodine staining allows for detection of smaller or superficial lesions. All suspicious lesions should be histologically confirmed and their topographic outline (location, size, thickness) systematically documented	Vaginal cancer presents as a rather homogeneous mass with intermediate to high signal intensity in comparison to the hypointense submucosal layer. An irregular and diffuse shape indicates a rather infiltrative and ulcerating pattern of disease in contrast to well-defined exophytic tumours
FIGO Stage I/T1	The tumour is limited to the vagina	The hypointense ring of the submucosal and muscularis layer is intact
FIGO Stage II/T2	The tumour invades the paravaginal tissue but does not extend to the pelvic wall	The hypointense ring of the submucosal and muscularis layer is disrupted and the tumour extends into the paravaginal/parametrial fat
FIGO Stage III/T3	The tumour extends to the pelvic wall	The tumour reaches the pelvic wall in terms of the piriformis, levator ani or internal obturator muscle
FIGO Stage IVa/T4	Invasion of the mucosa of rectum and bladder	A loss of the fat planes between the vagina and the urinary bladder/rectum and a loss of the hypointense bladder/rectal wall are signs for tumour invasion

projects were initiated, involving the description of the target concept, target delineation, treatment planning and dose reporting, and the assembly of a retrospective cohort of patients treated with IGBT. Results of treatment planning, dose reporting and of the retrospective dataset have contributed in the process of reaching consensus but will be described elsewhere. The task group has had regular meetings and telephone conferences with discussions of specific aspects in depth to reach consensus in an iterative process. Interim results of all projects were reported and feedback was provided during GYN GEC ESTRO meetings.

## Results

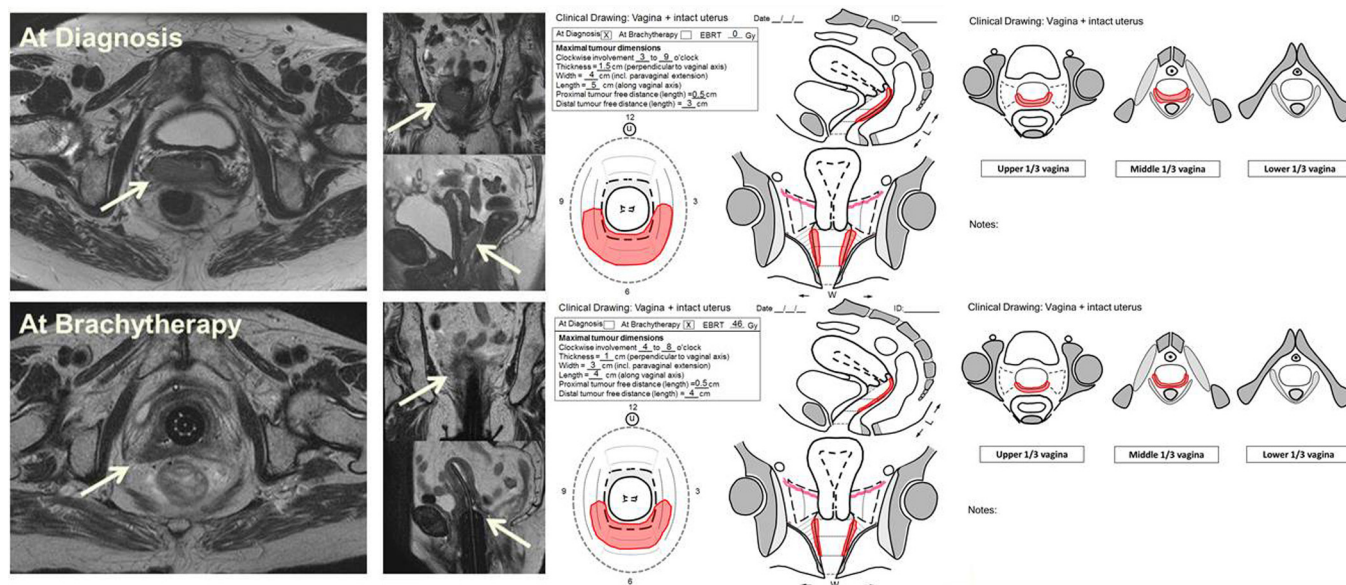
### Clinical background

The International Federation of Gynaecology and Obstetrics (FIGO) and/or TNM classification systems are used for staging purposes [31,32] in primary vaginal cancer. In Table 1 relevant aspects of the vaginal anatomy and local tumour extension are summarised in regard to the clinical examination and MR imaging. Clinical examination, preferably under general anaesthesia, is the most important part for local staging. Colposcopy and staining with acetic acid or Lugol's solution can aid in assessing superficial spread, detection of premalignant disease and guide biopsies. A vaginal impression may be performed to provide an accurate description of the tumour dimensions and topography at diagnosis, as well as to show residual disease at time of brachytherapy [43]. Different imaging modalities play a role in the diagnostic work-up and in response assessment. MRI combines the advantages of superior soft tissue contrast, the ability to image both primary tumour and regional nodes, and allows for different functional imaging sequences [33]. One study specifically addressed the role of MRI in primary vaginal cancer. This study included 25 consecutive patients and showed that MRI identified 95% of the primary

vaginal tumours and enabled radiological staging, which correlated with outcome. It was concluded that T2-weighted images are the preferred sequence for evaluating the vagina and visualising vaginal cancer [34]. Due to poor soft tissue image quality in the lower pelvis CT is less suitable to assess the primary tumour. CT has been used to assess nodal and/or metastatic involvement, but current data from cervical cancer points out that Fluorine-18 fluorodeoxyglucose positron emission tomography – computed tomography (FDG-PET-CT) has a higher sensitivity and specificity to detect (lymph node) metastasis [35]. Like CT alone, the role of FDG-PET-CT in evaluation of the primary tumour site is limited by the low resolution and the presence of FDG signal in the bladder. Ultrasound (US) has been used to document the extension of vaginal cancer and evaluate response to treatment. The advantages of US include the availability, good resolution, and dynamic aspects; but limitations are operator dependency and reproducibility of volumetric recording.

Limited data exists on the risk and prevalence of lymph node metastases. Pathologic lymph nodes are reported in at least 30% of the patients with locally advanced disease [36]. Lymph drainage and subsequently nodal spread is determined by the location of the tumour. Tumours in the upper and middle third of the vagina show a similar pattern as in cervical cancer with the highest risk assumed for the internal, external iliac and obturator region, whereas tumours in the lower third of the vagina also drain to the inguino-femoral nodes. A tumour location involving the posterior vaginal wall/rectovaginal septum indicates an increased risk for nodal spread towards the presacral and mesorectal nodes.

FIGO stage, histological type and grade, lymph node metastases, tumour size, tumour site (upper third better), age, prior hysterectomy are reported as prognostic factors [37,38]. In addition, a radiotherapy dose >70 Gy, and the use of concurrent chemotherapy (most frequently weekly cisplatin) have been associated to improve outcomes [37,38]. Recent data from the Surveillance,



**Fig. 1.** Case Amsterdam UMC: advanced disease. (a) T2-weighted MRI and clinical drawings at the time of diagnosis (upper row) and at the time of brachytherapy (lower row) of a 83 year old patient (WHO grade 0) with primary vaginal cancer in the upper third posteriorly, FIGO stage II. Beside previous history of coloncarcinoma (treated by laparoscopic hemicolectomy) and hypertension no further co-morbidities. The patient was treated with 46 Gy intensity modulated radiotherapy with 2 Gy per fraction without concomitant chemotherapy, however with concomitant deep hyperthermia because of limited kidney function. The tumour showed good response, but still significant residual disease was detected at the time of brachytherapy. Due to the tumour size and the excentric spread the patient received combined intracavitary interstitial brachytherapy. The white arrow indicates the tumour on the MR images. The tumour is outlined in red on the clinical drawings. (b) Target delineation and OAR based on the recommended structures: GTV-T<sub>res</sub> (white), CTV-T<sub>HR</sub> (red), CTV-T<sub>IR</sub> (blue), vagina outside CTV-T<sub>HR</sub> (light blue), urinary bladder (yellow), rectum (light brown), sigmoid (green), bowel (olive), anal canal (dark brown), urethra (grey, partly depicted). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



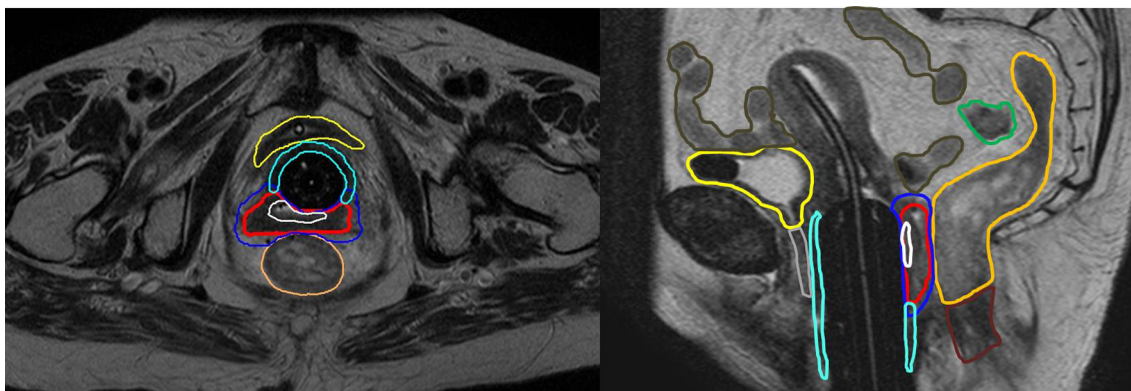


Fig. 1 (continued)

Epidemiology, and End Result (SEER) database also suggested that overall survival was higher among patients receiving brachytherapy as part of their treatment for a primary vaginal cancer, with the greatest benefit from brachytherapy observed among patients with tumours larger than 5 cm [38].

#### Delineations

One representative case per centre was selected for delineation. Inclusion criteria were (a) diagnosis of primary vaginal cancer, (b) use of intracavitary or combined intracavitary/interstitial applicators and (c) performance of MRI-based treatment planning. The cases were selected to cover the spectrum from limited to advanced disease in different locations of the vagina. All participants were asked to delineate a residual gross tumour volume, a high risk clinical target volume and an intermediate risk clinical target volume based on institutional traditions. To support the contouring additional information was provided: clinical case description, clinical drawings from the gynaecological examinations (at that time using the existing template for cervical cancer) and imaging at diagnosis and at brachytherapy. One case is described in detail to illustrate the target concept (Fig. 1a and b), the other 4 cases are summarised in Fig. 2.

Overall a high agreement between the different centres was observed. Differences were mainly found in the cranio-caudal direction along the vaginal axis. Further discussions during the review process pointed out that the differences were mainly related to discrepancies in the interpretation of the clinical case descriptions and the clinical drawings. Therefore, the need for more vagina-specific templates for clinical drawings was recognised.

#### Clinical drawings

Local extent of vaginal cancer is most often easily accessible during a gynaecological examination. Clinical examination including documentation of clinical findings at diagnosis and at brachytherapy is regarded of utmost value to support target delineation for IGABT.

A template to allow for precise and reproducible clinical drawings of vaginal cancer was developed and modified through clinical use into a final version that allows for a complete three-dimensional description (supplementary Figs. S1 and S2). This implies a clockwise definition of the tumour spread at upper, middle and lower third, the length of the tumour along the vaginal axis, the thickness perpendicular to the vaginal axis and the width of the tumour including any paravaginal extension. Due to the potential deformation of the vagina by the tumour, the expected

tumour regression during radiochemotherapy and the possibility that the vagina is stretched during the examination, tumour-free distances from the apex to the cranial border of the tumour (proximal) and from the caudal border of the tumour to the level of the introitus should be reported. The external urethral ostium, the posterior commissura, the cervix, the fornices (if present) and the anus represent important anatomical landmark reference structures.

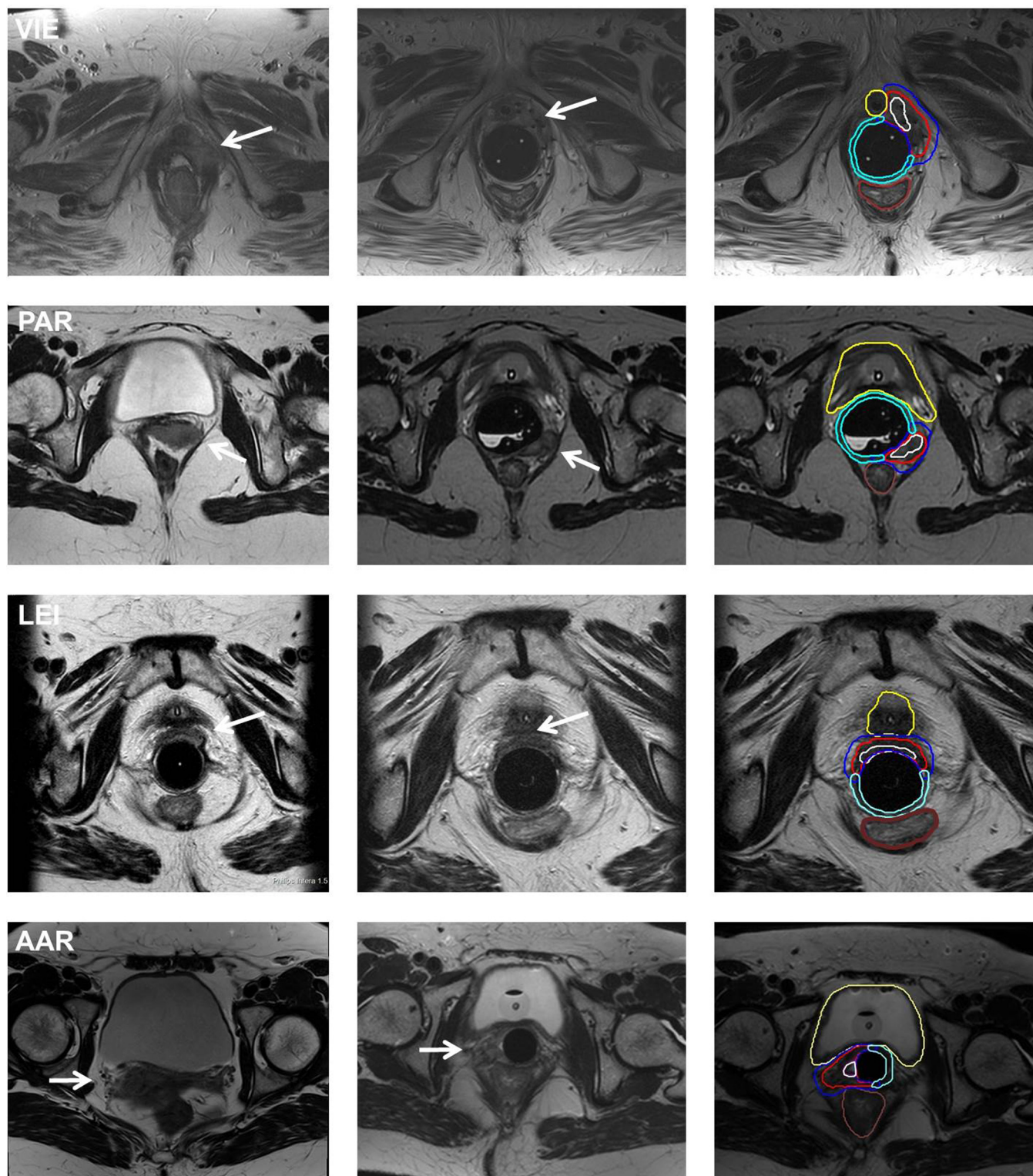
#### Target concept

Vaginal cancer is associated with substantial shrinkage during radio(chemo)therapy in the majority of patients, which needs to be taken into account for brachytherapy boost treatment planning. This implies the definition of different response-related brachytherapy target volumes according to the expected different cancer cell densities. Based on the expected cancer cell densities (decreasing with distance from the GTV) and routes of microscopic tumour extension, different target volumes can be defined and adapted according to the tumour regression during the course of treatment (Fig. 3). For EBRT, target volumes are related both to the primary tumour and to lymphatic spread and further details can be found in Table 2. For IGABT the target volumes are related to the vaginal tumour and are detailed in Table 3. Classical organs at risk for pelvic radiotherapy and brachytherapy include the bladder, rectum, sigmoid and bowel. In addition, given the anatomic considerations for vaginal cancer the urethra and anal canal are organs at risk as well as the non-involved vagina (see also discussion). Recent studies indicate that anatomical organ subvolumes (e.g. the bladder trigone, external and internal sphincter of anal canal, urethra) deserve consideration [39]. In particular in tumours involving the lower third of the vagina, additional anatomical structures such as vulva and clitoris should be considered. For all these organs the outer wall or boundary should be contoured.

#### Specific situations

##### Complete remission

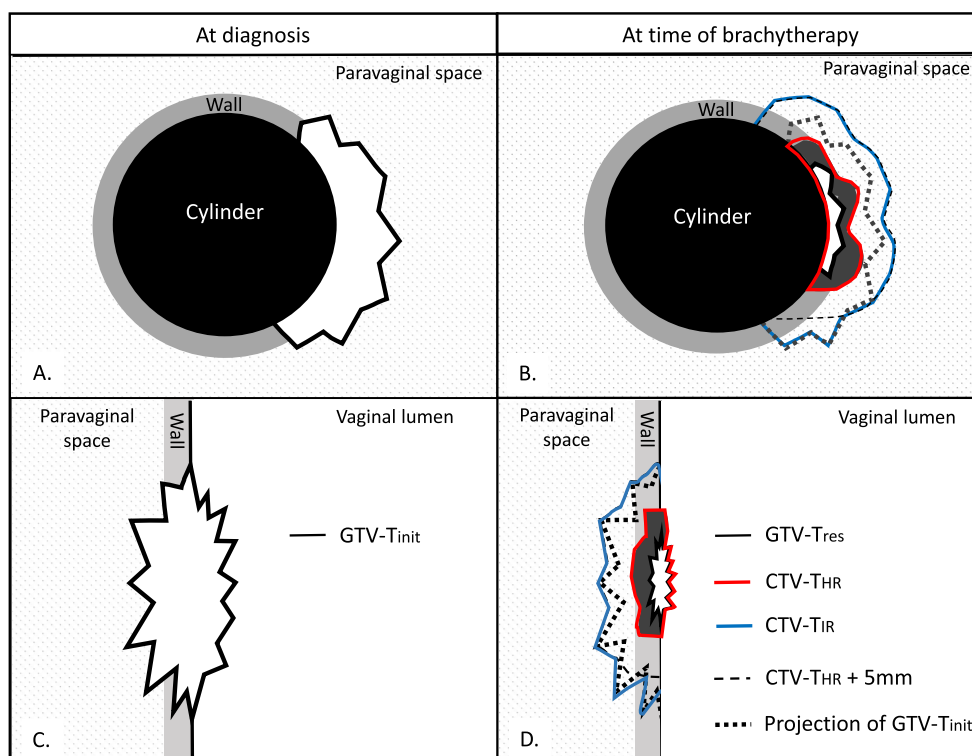
Most patients with a clinical complete remission after EBRT still have residual radiologic abnormalities in the vaginal wall, necessitating a CTV-T<sub>HR</sub> and CTV-T<sub>IR</sub>. Especially residual abnormalities associated with fibrosis, which typically appear hypointense on T2 weighted MRI, are often visible. Patients achieving both a complete clinical and radiological remission of areas suspicious of macroscopic disease after EBRT are rare, and pose a specific challenge for target delineation in IGABT. Following the outlined target concept for IGABT, with the currently available clinical imaging modalities, there is at present no distinct substrate to contour a CTV-T<sub>HR</sub> volume in this situation. The CTV-T<sub>IR</sub>, however, which



**Fig. 2.** Axial T2-weighted MR images of patients with primary vaginal cancer at the time of diagnosis (left column), at the time of brachytherapy without contours (middle column) and at the time of brachytherapy with contours according to the recommended target concept from Aarhus (AAR), Leiden (LEI), Paris (PAR), Vienna (VIE): GTV- $T_{res}$  (white), CTV- $T_{HR}$  (red), CTV- $T_{IR}$  (blue), vagina outside CTV- $T_{HR}$  (light blue); AAR: advanced disease, upper third laterally, FIGO stage II; LEI: limited disease, middle third anteriorly, FIGO stage II; PAR: advanced disease, middle third posteriorly, FIGO stage III; VIE: advanced disease, lower third anteriorly, FIGO stage III; The white arrow indicates the tumour on the MR images. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

should reflect the initial tumour extension, is unaffected by complete remission at brachytherapy and should be used for dose prescription in this situation. Historically, in these cases the dose has been prescribed to applicator-related dose points typically at the

applicator surface and/or at 0.5 cm radial distance from the surface. Taking the brachytherapy dose gradient into account, the dose at the applicator surface is typically at least 150% higher compared to the dose at 0.5 cm. Since the vaginal wall is on average



**Fig. 3.** Schematic representation of IGABT target concept. Upper row shows transverse view, lower row coronal view; left column at time of diagnosis and right at time of brachytherapy; white GTV-T<sub>init</sub>, red CTV-T<sub>HR</sub>, blue CTV-T<sub>IR</sub>, dotted line projection of GTV-T<sub>init</sub>. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 2**

Target volume concept for external beam radiotherapy in primary vaginal cancer.

GTV-T <sub>init</sub>	The initial macroscopic gross tumour volume at time of diagnosis as described by clinical examination and/or imaging	Characterised by a hyperintense signal intensity on T2 weighted MRI. Due to the limited soft tissue contrast of CT in the lower pelvis, the GTV-T <sub>init</sub> can only be adequately delineated using MRI and clinical information
CTV-T <sub>LR</sub>	The low risk clinical target volume consists of the GTV-T <sub>init</sub> , vagina, paravaginal space, paracolpia, parametria, cervix	It is generally recommended to include the whole vagina in the CTV-T <sub>LR</sub> . For small (<2 cm) stage I tumours located in the upper third, it may be questioned if the whole vagina is at risk for microscopic spread, since surgery alone has acceptable outcomes when the upper third is removed
CTV-N	The elective clinical target volume contains lymph node regions according to the anatomical extension of the primary tumour and the presence of lymph node metastasis	In patients with tumours in the upper two thirds of the vagina, delineation of nodal areas includes internal, external and common iliac, obturator and pre-sacral regions. In case of involvement of the lower third of the vagina in the inguino-femoral nodes should be included in addition (as is done in vulvar cancer), however then omission of the common iliac area can be considered in node negative patients. In patients with multiple lymph node metastases including the common iliac region, the paraaortic lymph nodes (up to the renal vein) should be considered as part of the CTV-N. In case of paraaortic lymph node metastasis the paraaortic region with an additional margin above the most cranial pathologic lymph node should be included in the CTV-N
GTV-N <sub>x</sub> /CTV-N <sub>x</sub>		Additional sub volumes for EBRT boost to pathological lymph nodes if applicable.
ITV/PTV		Further margins for ITV and PTV based on available treatment planning imaging (e.g. planning-CT with full and empty bladder) and possibilities for image-guidance during EBRT (IGRT, e.g. daily cone beam CT)

0.3–0.5 cm thick (depending on the individual patient and the diameter of the applicator due to stretching effect), prescribing the dose to CTV-T<sub>IR</sub> in these situations should result in a dose to the vaginal mucosal surface that is in the range of the dose that would be prescribed to the CTV-T<sub>HR</sub>.

#### Involvement of cervix

Vaginal malignancies with partial involvement of the cervix but without involvement of the cervical ostium are classified as vaginal cancers. However, target delineation for IGABT should be based in addition on the recommendations for cervical cancer [17]. This



**Table 3**

Target volume concept for image-guided adaptive brachytherapy in primary vaginal cancer.

GTV-T <sub>res</sub>	The macroscopic gross residual tumour volume at the time of brachytherapy as described by clinical examination and/or imaging	Clinically this is the remaining visible and palpable residual macroscopic tumour during gynaecological examination. On T2-weighted MRI this is visualised as a remaining mass with hyperintense to isointense signal intensity, within the initial tumour extension at diagnosis, GTV-T <sub>init</sub> . There is usually considerable shrinkage of GTV-T <sub>init</sub> , resulting in small GTV-T <sub>res</sub> . This underlines the importance of proper documentation using clinical drawings of GTV-T <sub>init</sub> at time of diagnosis and at time of BT
CTV-T <sub>HR</sub>	The high risk clinical target volume includes the GTV-T <sub>res</sub> and areas of pathologic tissue	This includes the GTV-T <sub>res</sub> and any abnormal thickened or irregular vaginal wall within the initial tumour extension before EBRT (GTV-T <sub>init</sub> ). On T2-weighted MRI the thickened or deformed wall typically has a more hypointense appearance. In case of tumours infiltrating the paravaginal or parametrial space at diagnosis, so called "grey zones" can be observed, and are included in the CTV-T <sub>HR</sub> . In accordance to cervical cancer grey zones are considered as signs of tumour regression in terms of conversion of tumour cells into fibrotic tissue and are defined as areas with hypo-isointense signal intensity on T2-weighted MRI occurring within the initial tumour extension in the paravaginal or parametrial space
CTV-T <sub>IR</sub>	The intermediate risk clinical target volume should include all significant microscopic disease adjacent to the CTV-T <sub>HR</sub>	Therefore the CTV-T <sub>IR</sub> should minimally encompass the initial tumour extension at diagnosis (GTV-T <sub>init</sub> ), adapted to the anatomical situation at brachytherapy. At present, a safety margin of minimal 0.5 cm in tissue around the CTV-T <sub>HR</sub> should be applied, limited by previously unaffected anatomical borders/compartments: e.g. pubic bone, pelvic wall, pelvic floor musculature, bladder, urethra, mesorectal fascia, rectum, anal sphincter

implies that the CTV-T<sub>HR</sub> should always include the whole cervix in addition to the GTV-T<sub>res</sub> and areas at high risk for significant residual disease in the parametrial and paracolpic space.

#### *Involvement of urinary bladder, rectum, urethra, anus*

Macroscopic residual tumour at time of brachytherapy inside the urinary bladder, rectum, urethra or anal canal should be contoured as GTV-T<sub>res</sub> and included into the CTV-T<sub>HR</sub>. In case of infiltration of these organs before EBRT and no residual infiltration at brachytherapy, only the initially involved organ wall should be included in the CTV-T<sub>IR</sub>. Initially expansive tumour parts inside the lumen which resolved at the time of brachytherapy should not be included.

#### *Involvement of vulva*

Vaginal tumours with vulvar involvement should be considered as vulvar cancers, according to FIGO classification, and are not addressed here.

#### *Practical aspects*

There are various possibilities to improve the imaging and delineation process. For MR-imaging, transverse images perpendicular to the orientation of the vagina or applicator are recommended for optimal tumour/target volume depiction. The application of intravaginal gel should be considered for any MRI before or during EBRT if no applicator is in place [40]. An additional pre-planning MRI before brachytherapy with a provisional applicator (e.g. vaginal cylinder only) can help to plan the type of application (combined intravaginal and interstitial vs intravaginal alone) and facilitate later contouring in the case of an extensive interstitial component. These images can also be used to generate a full pre-plan, where the required needle positions in relation to the target volumes can be defined upfront [41]. The intraoperative use of transrectal or transvaginal ultrasound can help to identify the target volume, correlate it with clinical findings and support the application and delineation [42]. Overall, the integration of clinical findings into the delineation process can be challenging and also prone to errors caused by the deformation and stretching of the vagina by the applicator. The upper and lower border of the target volume appear to be the areas of highest uncertainty. Therefore

MRI compatible markers might be used for the identification of the maximum tumour dimensions.

## **Discussion**

A target concept for MRI-based IGABT for vaginal cancer was elaborated by a dedicated international task group as part of the GYN GEC ESTRO working group. This is a consensus based work which is based on [1] the preliminary work by the GYN GEC ESTRO working group for cervical cancer IGABT, now incorporated in ICRU report 89 [2] a delineation exercise with five cases with primary vaginal cancer, [3] a treatment planning and dose reporting study in these cases, [4] retrospective clinical results from 148 patients with primary vaginal cancer treated with IGABT in AUH, AMC, LUMC, IGR and MUV, [5] the institutional practises at these reference centres and [6] expert opinions. The recommendations follow the terminology established in the ICRU 89 report for cervical cancer [21]. Volumes related to brachytherapy are discussed in the following:

**GTV-T<sub>res</sub>:** The GTV-T<sub>res</sub> showed the highest variability in the delineation exercise which is in agreement with findings from interobserver studies in cervix cancer [44]. The GTV-T<sub>res</sub> can be difficult to distinguish on MRI at time of brachytherapy due to the rather inhomogeneous intermediate signal intensity and good response after EBRT in particular in patients with small residual tumours, which is frequently the case in primary vaginal cancer. Therefore, the definition of GTV-T<sub>res</sub> should also be guided by clinical examination which underlines the importance of drawings.

**CTV-T<sub>HR</sub>:** The CTV-T<sub>HR</sub> showed most concordance between the observers in the delineation exercise and the main areas of uncertainty were the upper and lower border of the target volume which is comparable to the findings from cervix cancer brachytherapy [44]. This illustrated the value of proper documentation designed for vaginal anatomy with clinical drawings, including measurements and the role for markers. Overall, the CTV-T<sub>HR</sub> appears rather hypointense on the MRI of the examined cases. Grey zones seem to be less common than in cervical cancer IGABT. Currently, dose prescription is performed on the CTV-T<sub>HR</sub> in the majority of the participating centres.

**CTV-T<sub>IR</sub>:** The CTV-T<sub>IR</sub> reflects the initial tumour extension and in addition should minimally have a 0.5 cm safety margin to the CTV-

T<sub>HR</sub> (limited by anatomical boundaries). This implies that in patients with minimal to no regression after EBRT the CTV-T<sub>IR</sub> can be larger than the GTV at diagnosis (GTV-T<sub>init</sub>). The CTV-T<sub>IR</sub> had moderate concordance among observers. While for cervical cancer a margin of up to 1.0 cm has been recommended in the direction of anatomical spread (parametria, vagina, uterine corpus), a minimum margin of 0.5 cm is recommended for vaginal cancer. This was motivated by the more narrow anatomy in the lower pelvis and reflected by observations from the delineation exercise and institutional practises. The definitive margin to apply should however take into account the availability of an exhaustive pre-treatment staging, including clinical examination and MRI, and larger margins may be justified in case of uncertainty (e.g. especially in the cranio-caudal direction up to 1.0 cm may be applied).

**Vagina:** The vagina is both target volume and OAR at the same time. Due to the possibility for microscopic multifocal and submucosal tumour spread, the whole vagina is typically part of CTV-T<sub>IR</sub>, which is usually treated with EBRT up to 45–50 Gy. Whether an intended additional (brachytherapy) boost dose to the whole vagina is necessary, is currently unclear. However, independent of the performance of an intended boost to the whole vagina, our treatment planning studies showed that there is always a (significant) dose contribution from brachytherapy to the entire vagina, which may contribute both to local tumour control and to morbidity. Furthermore, the extent of the primary tumour itself, the destruction of the vaginal wall and response to radiotherapy will add to the overall vaginal morbidity. The current recommendation is to delineate the vagina outside the CTV-T<sub>HR</sub> for brachytherapy dose reporting.

**PTV:** A PTV concept for cervical cancer brachytherapy was critically discussed in ICRU report 89 and is currently mainly used in intraluminal brachytherapy such as oesophageal or bronchus brachytherapy along the longitudinal axis. Applicator movements may be observed in intravaginal brachytherapy, in particular if the uterus has been removed, and in combined intravaginal/interstitial (perineal) brachytherapy. Techniques using only an intravaginal component (e.g. vaginal cylinder) may show rotations and cranio-caudal shifts. In combined intravaginal/interstitial techniques the applicator is fixed to the target volume and rotations are less likely but there may be significant cranio-caudal shifts due to insufficient applicator fixation and/or swelling due to oedema/haemorrhage [45,46]. Therefore, strategies to reduce or outweigh applicator movements are essential and clinical monitoring and/or repetitive imaging is recommended. This is especially the case for patients undergoing multi-fractionated treatments within one application. Use of markers, re-imaging, re-positioning, re-planning and optimization of fixation should be prioritised, but uncertainties remain especially for pulsed dose rate (PDR) and fractionated high dose rate (HDR) schedules lasting for a longer time period. A caudal shift of the applicator appears to be the most critical movement leading potentially to a dramatic unplanned dose reduction in the respective cranial parts of the target volume (and to a significant dose increase in the adjacent caudal region). Therefore, individual safety margins, only in the direction of the expected shift, can be considered depending on the applicator and technique, but no specific recommendations can be made. Careful evaluation of the increase in the treated volume by the introduction of a PTV is needed.

Recommendations on dose prescription and reporting are planned to be presented separately. In short, in accordance with cervical cancer brachytherapy, target volume related dose parameters (e.g. D90, D98), organ-related dose parameters (e.g. D2 cm<sup>3</sup>, D0.1 cm<sup>3</sup>) as well as anatomy and applicator related dose points (e.g. applicator surface, 0.5 cm tissue depth for intracavitary-only applications, ICRU bladder point) should be applied. The use of applicator related dose points should serve as a safety measure

for contouring uncertainties in particular for limited disease or complete remission at the time of brachytherapy and should link image-guided practise to non-image-guided practise and historic data. Furthermore, this target volume concept could also be used as template for adaptive non-image guided brachytherapy based on additional individual dose points. These dose points could be derived from tumour and target volume dimensions (especially thickness) assessed at the clinical examination including the documentation with clinical drawings and supported by e.g. intra-operative transvaginal or transrectal ultrasound or any available pre-brachytherapy imaging.

Few studies report on clinical results with IGABT showing excellent results in small patient cohorts and limited follow-up, with >90% local tumour control. A retrospective multicentre study with 148 patients is currently under preparation and seems to confirm these results [36]. A prospective multicentre evaluation of the proposed target concept, analogue to the EMBRACE studies in cervix cancer is planned, and especially valuable for this rare cancer. In conclusion, a target concept for IGABT of primary vaginal cancer was developed. It defines adaptive target volumes for volumetric dose prescription and should improve comparability of different radiotherapy schedules of this rare disease. A prospective evaluation of the target volume concept within a multicentre study is planned.

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## Conflict of interest

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## Appendix A. Supplementary data

Supplementary data (template for clinical drawings S1) with uterus S2) without uterus) to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.11.005>.

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