Potential role of TRAns Cervical Endosonography (TRACE) in brachytherapy of cervical cancer: proof of concept

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Abstract

Purpose: Magnetic resonance imaging (MRI) is the gold standard for image guided adaptive brachytherapy (BT) of cervical cancer. Ultrasound is an attractive alternative with reasonable costs and high soft tissue depiction quality. This technical note aims to demonstrate the proof of principle for use of TRAns Cervical Endosonography with rotating transducer in the context of brachytherapy (TRACE BT).

Material and methods: TRACE BT presentation is based on a single stage IIB cervical cancer patient. Prior to second BT implant, rotating US transducer (6.9 mm diameter) was inserted in cervical canal and axial images obtained at 10 MHz, focal range of 30 mm, and axial resolution of 0.4 mm. Size and topography of hypo-echoic areas were assessed and optimal positions of interstitial needles were determined. Finally, intracavitary applicator was placed and needles inserted through vaginal ring-template according to TRACE pre-plan. MRI-based high risk clinical target volume (CTVHR) dimensions were compared with hypoechoic areas on TRACE. Topography of parametrical needles on post-insertion MRI was compared with TRACE pre-plan.

Results: Insertion of rotating mechanism into cervico-uterine cavity was safe, feasible and fast. The 360° imaging in axial plane enabled real-time assessment of cervix, uterus, and adjacent parametria. Qualitative comparison of TRACE with post-insertion MRI revealed favorable agreement of findings. In-plane size of CTVHR on MRI was comparable to hypoechoic areas on TRACE. Needle positions on post-insertion MRI corresponded to TRACE-based pre-plan. Main limitation of TRACE was gradual deterioration of image quality due to coupling gel removal.

Conclusions: Present proof of concept demonstrates potential role of TRACE-BT for cervical cancer as an attractive high-tech approach with reasonable costs. Prior to investigation of its clinical role, further development of TRACE methodology is needed. This includes reliable transducer-tissue coupling, applicator reconstruction, imaging range, limitations in extensive tumors, US-based contouring concepts, registration with other imaging methods, organ dose-assessment, real-time dosimetry, etc.

Key words: brachytherapy, cervical cancer, image guidance, ultrasound.
published recently [12]. However, CT is characterized by inherent limitations when compared with MRI, especially for the delineation of the target volume. Even the often cited notion that CT is adequate for the organs at risk (OAR) delineation can be considered as an oversimplification. This notion is based on a single small published series [13], and is not generally supported by our clinical experience. In addition, the results of inter-observer studies indicate inferior results of CT-based organ contouring [14,15,16]. Hybrid approach with MRI at first BT, followed by CT at subsequent fraction(s) has been suggested as a solution to reduce costs of IGABT while maintaining treatment accuracy [17]. While reliable and reproducible for selected patients, this method fails to eliminate MRI from the treatment planning process.

Ultrasound (US) has several advantages over MRI and CT. It is widely available, enables real-time image guidance during the procedure, and offers good depiction of soft tissues. Clinicopathological studies demonstrate comparable accuracy of ultrasound and MRI for assessment of primary tumor in early disease [18] as well as residual tumor in locally advanced cases treated with preoperative chemoradiation [19,20]. Recent comparison of trans-rectal ultrasound (TRUS) and MRI in inoperable cases treated with definitive chemoradiation demonstrated high correlation between the two methods, indicating potential of TRUS for target definition in IGABT [21]. Ultrasound has long tradition in BT with numerous publications on its use in the assessment of the intrauterine tandem position and real-time interstitial needle placement [22,23,24,25,26,27,28]. Recently, the use of US for treatment planning has been reported but the proposed approach did not eliminate MRI from the workflow [29,30,31,32,33]. In summary, the literature review demonstrates that the major potential of US for IGABT of cervical cancer extends beyond its conventional applications and may play a role in treatment planning. However, further research and development is required before it can be systematically implemented as a more widely available alternative to the current gold-standard [34].

In the present technical note, we propose an innovative and promising concept of real-time US imaging for cervical cancer BT - TRAns Cervical Endosonography (TRACE BT). Trans-cervical endosonography is a recognized medical procedure for diagnostic assessment and therapeutic interventions in the cervix and uterus [35,36]. In IGABT of anal cancer, the use of endo-anal rotating US probe has been reported as safe and feasible technique that enables real-time guidance of insertion and offers better information for dose planning when compared with CT [37,38,39]. To our knowledge, the potential of trans-cervical US with rotating transducer has never been explored in gynecological BT. At the author’s institution, we have experience with using TRACE prior to BT procedure in selected patients with locally advanced tumors to aid tumor visualization and implant technique. This technical note summarizes our initial experience, demonstrated on a single patient case report and should be regarded as a proof of concept that warrants further research.

Material and methods

The theoretical design of TRACE BT system is presented on an example of endosonographic imaging findings in a patient with stage IIB cervical cancer with bilateral parametrial extension. The patient underwent whole pelvis external beam irradiation (50.4 Gy in 1.8 Gy daily fractions) with concomitant chemotherapy (40 mg/m² of cisplatin weekly), followed by two fractions of MRI pulsed dose rate IGABT, delivered in 25 hourly pulses. Details of our BT schedule, planning aims, and dose-optimization strategy are presented in [5]. Directly prior to the second BT implant, TRACE was performed under sterile conditions with the patient in lithotomy position and under spinal anesthesia.

Basic US-scanner settings were prepared in advance. The probe, transducer cable, and scanner keyboard were covered with sterile foil before patient transport to procedure room. Following the usual dilatation of cervical canal, a rotating US transducer with 6.9 mm diameter and sector angle of 360° (BK Medical, type 1850 with 6005 transducer head, B&K Medical, Herlev, Denmark) was covered with sterile coupling gel and manually inserted into the cervical canal. At a frequency of 10 MHz, US images were obtained with a focal range of 30 mm and axial resolution of 0.4 mm (measured at 25 mm), using the Flex Focus 400 scanner (BK Medical). Images were obtained in axial plane at the levels of the cervix and uterus that were considered representative by the operator. Size and topography of the hypo-echoic areas, corresponding to the residual pathological tissues in the parametria were assessed. Based on this assessment, the target volume regions where interstitial needles would improve dose conformity were determined. After completion of the TRACE examination, the rotating probe was removed and intra-cavitary tandem and ring placed in the uterus and vagina. Finally, the interstitial needles were inserted through the vaginal ring template [3,4] according to the TRACE pre-plan. Vaginal packing was performed, followed by MRI-based IGABT treatment planning. TRACE images were not used for dose planning or co-registration with MRI. They were qualitatively compared with post-insertion para-transverse T2 weighted fast spin echo MRI. Quantitative assessment was limited to comparison of maximal latero-lateral and antero-posterior dimensions of the MRI-based high risk clinical target volume (CTV_11B) with corresponding dimensions of hypoechoic areas on TRACE. The positions of parametrial needles on post-insertion MRI were compared with the TRACE pre-plan.

Results

Ultrasound scanner setup and probe preparation prior to the procedure enabled fast and feasible TRACE imaging, resulting in 10 minutes prolongation of the BT procedure. Small diameter of the transducer (6.9 mm), which is comparable to the intrauterine applicator diameter (6 mm), resulted in feasible and safe insertion of the rotating mechanism into the cervico-uterine cavity. Mechanical rotating probe enabled 360° axial imaging with refreshment rate that enabled clinically useful real-time
assessment of pathoanatomy. Main relative limitation of
the approach was gradual deterioration of image quality
due to removal of the coupling gel, which was challeng-
ing in parts with tumor-related irregularities of the cer-
vical canal.

The interval between TRACE and post-insertion MRI
was 57 minutes. Results of the qualitative comparison of
findings between both modalities were favorable (Figure 1).
TRACE imaging enabled accurate depiction of the cervix,
uterus, and adjacent parametrial tissues. Direct qualita-
tive comparison of intraoperative TRACE with post-in-
sertion MRI revealed favorable spatial agreement be-
tween sonographically suspicious bilateral hypoechoic
areas and the grey zones, visible on the MRI (Figure 1).
In-plane size of the CTVHR on MRI was comparable to
hypoechoic areas on TRACE with maximum latero-lat-
eral and anteroposterior dimensions differing for up to
2 and 3 mm, respectively. While nearby OAR (rectum,
bladder, sigmoid), were more clearly depicted on MRI
(Figure 1).

TrAns Cervical Endosonography
in brachytherapy

Fig. 1. Free-hand TRAns Cervical Endosonography (TRACE – left) compared to the T2 weighted fast spin echo magnetic reso-
nance imaging (MRI) with the applicator in place (right) in the same patient at two different levels (A and B). The MRI slices are
cropped and oriented to show the area of interest, which corresponds to the TRACE field of view; due to the manual acquisition
of the TRACE images, slight rotational post-processing in axial plane was required to enable comparisons. TRACE and MRI
were obtained with 57 minutes interval. (A) Representative slice at the level of the target volume. The cervix and suspicious
extra-cervical hypoechoic areas on TRACE correspond in size and topography to the high risk clinical target volume depicted
on the MRI (thin white dotted lines). Thick dotted lines on the TRACE image (left) represent areas where interstitial needles
would be beneficial. Actual needle positions on MRI (right) are depicted by arrowheads and correspond to the pre-planned ar-
ear on TRACE. Note the difference in OAR topography between TRACE and MRI. Sigmoid colon loop (magenta) that is visible
on TRACE, is not present in the same position on MRI. Bladder filling and topography of posterior bladder wall also differ
between modalities. (B) Representative slice through the uterine corpus (above the target volume). P – rotating endosonographic
probe, inserted in the cervical canal, T – tandem applicator.
Acoustic shadow and frame of reference

US-guided insertion techniques that are reported in the literature and summarized above [21,22,23,24,25,26, 27,28,29,30,31,32,33,34] are based on placement of the US probes outside the target volume. These techniques are characterized by inherent limitations, which include different frames of reference of the transducer and the BT applicator as well as distortion of image quality by inserted applicators. The main difference between these methods and our concept is that the rotating TRACE probe and BT tandem are located inside the cervical canal and thus related to the same frame of reference during endosonography and treatment, respectively. Consequently, the problem of tandem-induced acoustic shadow during US imaging is eliminated. In addition, movement of the probe (or tandem) results in the corresponding movement of the target volume, and vice versa. This setup enables the “tandem-eye-view” of the target volume by the TRACE probe, which is independent of patient’s setup. In present report, TRACE imaging and applicator placement were performed in lithotomy position, while MRI for treatment planning was obtained in supine position. In spite of this difference in setup, the relative topography between the target volume and the tandem on MRI corresponded to topography between the target volume and the probe on TRACE (Figure 1). However, this paradigm is only valid for the target volume and cannot be extrapolated to the OAR. Sectional imaging with the patient in treatment position, followed by co-registration [17] with TRACE imaging is needed for adequate assessment of spatial inter-relations between the OAR and the applicator.

Intraoperative pre-planning of implant geometry

Keeping the limitations of a single-patient report in mind, our results, experience, and mere intuition indicate that TRACE deserves further attention as promising tool for intraoperative pre-planning of implant geometry. We have used the information obtained from TRACE to plan the optimal position of interstitial needles, resulting in excellent topography of the final implant (Figure 1). Recently, MRI-based pre-planning has been shown to achieve excellent implant geometry and dosimetric results but implementation of these sophisticated methods remained limited to a few specialized centers [5,41]. Adaptations of TRACE system to the specific needs of gynecological BT, followed by its validation in clinical studies could result in a widely available and cost-effective alternative to MRI-based pre-planning in near future.

Real time insertion guidance and treatment planning

There is a longstanding experience with endosonography in the field of uro-oncology, including prostate BT and systems for trans-rectal and trans-urethral US-guided interventional diagnostic procedures. Endosonography-guided needle insertion has been employed in BT of anal cancer with excellent local control rates and minimal treatment-related morbidity [37,38]. In this tumor site, the use of endoscopic rotating probes has been proven feasible and efficient in optimizing the implant procedure and treatment planning [39]. Trans-cervical endosonography has been used for diagnostic exploration of the cervix and uterus [35], and image guided radiofrequency ablation of uterine fibroids [36]. Existing technologies, developed in the above listed fields, include adjustable arms and steppers for ultrasound probes, template-based su-
TRAns Cervical Endosonography in brachytherapy

perimposition of needle path on the real-time images, and real-time dosimetry during BT implant. Our theoretical design of real-time TRACE BT system for target volume delineation and insertion guidance is currently under development. It is based on rigid connection between vaginal template for needle insertion and stepper-mount
ed rotating endosonic transducer. Due to the location of the probe inside the target volume, the artifacts during real-time TRACE-guided needle insertion are expected to be less pronounced when compared with conventional US setups (trans-abdominal, trans-rectal, and trans-vaginal). Assuming adequate vaginal packing for applicator immobilization, the relative position between the target and the applicator is not expected to change by altering the patient’s position from lithotomy to supine. However, as discussed above, registration of TRACE images containing target volume with post-implant sectional imaging (i.e. CT) would be mandatory for delineation of the OAR and treatment planning, in order to account for positional changes of the OAR.

Limitations

In our experience, the main limitations of the presented prototype TRACE system were related to positional uncertainties due to free-hand probe handling and deterioration of image quality due to suboptimal coupling between the probe and the tissue at certain levels of the target volume (Figure 1). The probe that was employed in our report is not a part of a dedicated gynecological BT system. Therefore, several preconditions should be met prior to eventual clinical studies on TRACE BT for cervical cancer IGABT treatment planning. Technical adaptations of TRACE system, improved coupling, definition of the US-based target volume concepts, and their benchmarking against current gold-standard (MRI) are some of the issues, which need attention before clinical studies of TRACE-guided BT can be considered. It needs to be admitted that this technical note is based on our limited experience with a single patient case report, which has its major inherent limitations. Conclusions regarding feasibility, safety, and clinical utility of the procedure will require further studies, which we are planning as the next step. In spite of the above listed limitations, TRACE deserves further investigation as a promising and cost effective potential tool for cervical cancer IGABT.

Conclusions

This technical note is a proof of concept, demonstrating the potential role of TRACE in pre-planning, real-time guidance, and treatment planning of cervical cancer IGABT. Main limitations of currently available technology were identified and limitations of single patient based report acknowledged. Our favorable initial experience warrants further multidisciplinary research and development of a dedicated TRACE system for gynecological IGABT. The areas of investigation include effective transducer-tissue coupling, applicator reconstruction, imaging range, US contouring concepts and their validation, OAR dose assessment, registration with other imaging methods, and real-time dosimetry. These basic developments should be conducted before any clinical studies on feasibility, safety, and effectiveness of TRACE BT can be considered. Hypothetically, TRACE BT could be an interesting addition to complement existing imaging technologies in the future (MRI, CT, trans-abdominal US, trans-rectal US), to improve the image quality in the center of the target volume. When combined with CT, TRACE BT could be a cost-effective alternative to the gold-standard MRI-based IGABT once the pre-conditions listed above are met.

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Disclosure

Authors report no conflict of interest.

References


