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Chapter

Ultrasound-Guided Brachytherapy for Cervical Cancer - A Tool for Quality Improvement in Brachytherapy?

Ekkasit Tharavichitkul and Razvan M. Galalae

Abstract

Nowadays, brachytherapy is one of the major components to treat inoperable cervical cancer. Brachytherapy yields a higher dose to the target (cervix) while sparing normal tissues. Developments of brachytherapy stepped forward in the previous decade by image-guided brachytherapy (IGBT) turning brachytherapy from point-based planning to volume-based planning and IGBT improves the treatment quality for cervical cancer. Magnetic resonance imaging (MRI) or computed tomography (CT) is utilized in brachytherapy and showed promising results internationally. However, in a limited-resource area, the implementation of IGABT is difficult due to many causes (manpower, equipment, or budgets). To improve the quality in limited resources, ultrasound is introduced. The utilization of ultrasound in brachytherapy practice is to prevent uterine perforation during application. With present data, measurement by ultrasound showed the correlation to MRI measurement in uterine dimensions. With these aspects, there are many researches using ultrasound to improve the quality of treatment in brachytherapy, for example, to guide contouring on CT or to support brachytherapy planning. The use of ultrasound improves the quality of brachytherapy in comparison to conventional planning and supports the improvement in brachytherapy for cervical cancer.

Keywords: brachytherapy, cervical cancer, ultrasound

1. Introduction

Cervical cancer is one of the most common cancers among the female population with the fourth most common after breast, colorectal, and lung cancer. In 2018, there were approximately 570,000 new cases of cervical cancer with 311,000 deaths [1]. Treatment of cervical cancer is composed of surgery, radiotherapy and systemic treatment. Concurrent chemoradiation is the standard treatment for locally advanced cervical cancer (LACC) and the combination of external beam radiotherapy (EBRT) and brachytherapy (BT) maximizes the local control while minimizing the risk of toxicity. Standard EBRT should deliver a dose of 45–50.4 Gy to the whole pelvis encompassing the uterus, adnexal structures, parametria, and pelvic lymph nodes. With BT, various dose fraction schedules are used, applying a dose of 5.5–8 Gy by 3–5 fractions and the total combined dose with EBRT and BT should be in the range of 80–90 Gy [2]. From the publications of Han et al. and

Gill et al. BT is one of the major components for curative radiotherapy for LACC [3–5]. Completion of the radiation program within a suitable time is an important goal as it has a direct correlation to the outcome. The current recommendation is to finish the entire protocol of EBRT and BT within 8 weeks [2].

2. Point-based brachytherapy for cervical cancer

Brachytherapy was used to increase the curative dose to cervical cancer from the year when Todd and Meredith et al. introduced the Manchester system with radium [6, 7]. The using of point A, bladder point, and rectum point (identified in orthogonal X-rays) were reported with ICRU 38 concepts [8, 9]. The intrauterine tandem and intravaginal applicators were used in many institutes to treat cervical cancer, with acceptable results. **Figure 1** shows orthogonal X-rays for conventional planning.

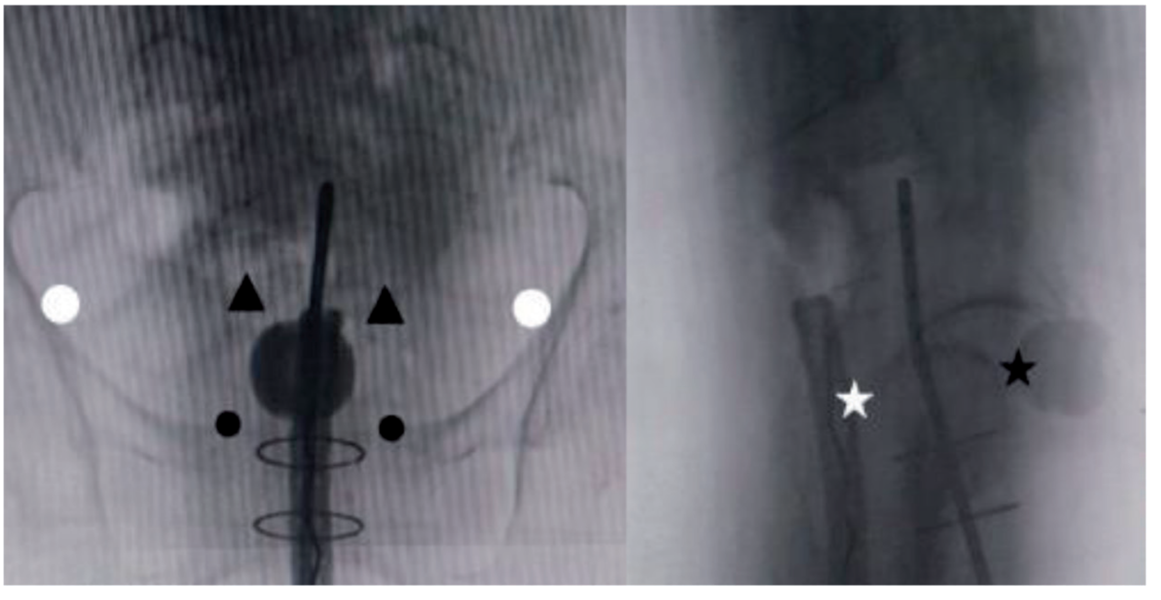

Figure 1.
Point A (black triangle), point B (white circle), ICRU bladder (black star), ICRU rectum (white star) and 5-mm vagina points (black circle) from The Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University.

3. Volume-based IGBT for cervical cancer

The concepts of volume-based brachytherapy in magnetic resonance imaging (MRI) started by the publications of the Groupe European de Curietherapie and the European Society for Radiotherapy and Oncology GEC-ESTRO in 2005–2006 to propose the definitions of targets (high-risk clinical target volume; HR-CTV and intermediate-risk clinical target volume; IR-CTV) and normal tissues (Organs at risk (OARs); bladder, rectum and sigmoid) with dose constraints for evaluation [10, 11]. Moreover, the additional concepts of HR-CTV were extrapolated to CT since 2007 and developed to many international publications [12–15]. **Figure 2** shows the HR-CTV and IR-CTV according to GEC-ESTRO recommendations.

In comparison to conventional brachytherapy (point A), IGBT keeps the cumulatively curative dose to the target (HR-CTV) while sparing the cumulative dose to normal tissues [16–19]. After the first clinical results of IGBT were reported by Pötter et al. in 2007, many institutes started to develop IGBT around the world [20]. The selected publications of IGBT are shown in **Table 1** and shown promising results in local control and toxicity.

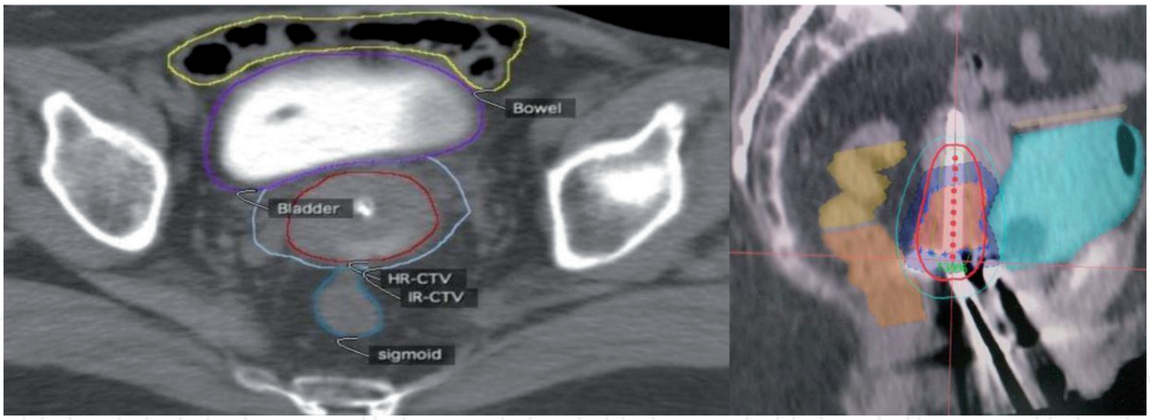

Figure 2.
HR-CTV and IR-CTV on MRI and CT related to GEC-ESTRO recommendations from the division of radiation oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University.

Studies	*N*	Imaging	FU time	LC	Gr 3-4 Toxicities
Pötter et al. [21]	156	MRI	42 months	95%	11 events
Lindegaard et al. [22]	140	MRI	36 months	91%	1%(GU), 3%(GI)
Sturdza et al. [23]	731	MRI > > CT	43 months	91%	5% GU, 7% GI, 5% vagina
Tinkle et al. [24]	111	MRI with IPSA	42 months	94%	8%
Castelnau-Marchand et al. [25]	225	MRI	38.8 months	86.4%	6.6%
Mahanshetty et al. [26]	94	MRI	39 months	90.1%	3% (GU), 9%(GI)
Murakami et al. [27]	51	CT	39 months	91.7%	2% (GI)
Ohno et al. [28]	80	CT	60 months	94%	1% (GU)
Tharavichitkul et al. [29]	47	CT	26 months	97%	2.1%(GU) 2.1% (GI)
Pötter et al. [30]	1341	MRI	51 months	92%	6.8% (GU), 8.5% (GI)

BT, brachytherapy, CT, computed tomography, GI, gastrointestinal toxicity, GU, genitourinary toxicity, MRI, magnetic resonance imaging, IPSA, inverse planning simulated annealing.

Table 1.
Selected studies of IGBT.

4. Clinical results of ultrasound in brachytherapy for cervical cancer

Ultrasound in medicine was firstly developed by the military (as "sonar") and was firstly investigated in the 1940s by the method of echo-reflection to detect tumors, exudates, or abscesses [31]. Ultrasound developed very much in obstetrics and gynecology to evaluate the growing fetus and examinations in gynecological conditions [32]. Using ultrasound in clinical practice of brachytherapy divides into three aspects a) applicator guidance, b) CT-based contouring, and c) planning process. The most common use of ultrasound in brachytherapy for cervical cancer is to guide insertion of intrauterine tandem to prevent uterine perforation. Although, in this era, the incidence of uterine perforation was 3% from Segedin et al. [33]. The use of ultrasound can support accurate and safe application in brachytherapy procedures in cervical cancer. Moreover, ultrasound can help the practitioner to adjust the applicator to be a suitable position before patient transportation to the next steps. **Figure 3** shows uterine perforation by TAUS.

Figure 3.
Uterine perforation during insertion by TAUS from The Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University.

Studies	N	Modality	Findings
Van Dyk et al. [40]	2	TAUS	TAUS is portable, nonexpensive, and simple to use and allows for accurate, conformal, re-producible, and adaptive treatments.
Van Dyk et al. [34]	71	TAUS	TAUS plan in comparison to two-dimensional MRI image was comparable for target volume (p = 0.11), rectal point (p = 0.8), and vaginal mucosa (p = 0.19). Local control was 90%. Late GI toxicity was less than 2%.
Mahanshetty et al. [43]	20	TAUS	TAUS correlated with MR in evaluating uterus, cervix, and central disease for IGBT.
Van Dyk et al. [35]	192	TAUS	The mean differences between TAUS and two-dimensional MRI images were less than 3 mm in the cervix. The mean differences were less than 1.5 mm at all measurement points on the posterior surface.
Narayan et al. [42]	292	TAUS	At median FU time of 41 months, 5-yr overall survival rate was 65%.
Schmid et al. [44]	19	TRUS	TRUS is better than CT as it produces systematically smaller deviations from MRI, with good to excellent image quality.
Van Dyk et al. [41]	191	TAUS	At median FU time of 5.3 years, 5-yr overall survival rate was 63%. Late toxicities were 3% for GI, 1.6% for GU, and 2% for vagina.
Mahanshetty et al. [37]	25	TRUS	CT-based delineation using MRI at diagnosis and TRUS during BT seems comparable with MRI-based approach in IGBT for cervical cancer.
Tharavichitkul et al. [45]	92	TAUS	At median FU time of 41 months, pelvic control rate was 84.8%.

BT, brachytherapy; CT, computed tomography; FU, follow up; GI, gastrointestinal; GU, genitourinary; IGBT, image-guided brachytherapy; MRI, magnetic resonance imaging; TAUS, transabdominal ultrasound; TRUS, transrectal ultrasound.

Table 2.
Selected studies showed progression of US guidance in brachytherapy.

To guide CT-based contouring is very new for using ultrasound. This comes from the pain point of CT-based contouring is an overestimation in comparison to MRI-based contouring [12]. To find the support equipment, some researchers found that the US in transabdominal (TAUS) or transrectal (TRUS) approaches showed a correlation in measurement with MRI [34–37]. Moreover, the publication from Schmid et al. showed TRUS is superior to CT as it yields systematically smaller deviations from MRI, with good to excellent image quality [38] and Mahanshetty et al. published the correlation of MRI-based contouring versus CT-based contouring supported by TRUS [37]. In recently, the latest publication from IBS-GEC ESTRO-ABS recommended TRUS to support CT-based contouring in IGBT for cervical cancer [39].

The use of TAUS in the planning process was firstly developed by Peter MacCallum Cancer Center, Melbourne, Australia [40]. This process developed from the measurement by TAUS showed a correlation to MRI [35]. In Peter MacCallum Cancer Center, the cooperation of TAUS and MRI (in first application) supported the high-end treatment in brachytherapy for cervical cancer. With this implementation, international publications were reported to support TAUS in brachytherapy [34, 35, 40, 41]. In 2014, they published a survival outcome that showed a 5-year overall survival rate of 65% [42].

The developments of US guidance for brachytherapy are concluded in **Table 2**.

5. Experiences of TAUS-guided brachytherapy in the division of radiation oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University

In the Faculty of Medicine, Chiang Mai University, TAUS-guided was implemented 10 years ago to support the conventional brachytherapy during the transformation process from 2D to 3D brachytherapy since 2011. The concepts of TAUS-guided brachytherapy were adapted from Van Dyk et al. [34, 40]. From our process, we performed brachytherapy as an outpatient basis. The workflow of our procedure is shown in **Figure 4**.

After walk-in, patients were adjusted to lithotomy position and skin preparation was performed. Then, Foley's application was performed and at least 200 ml of NSS were filled into the bladder to improve the image quality of TAUS. TAUS was performed during uterine sound and intrauterine tandem applications to prevent uterine perforation. After the application finished, TAUS was performed to measure the dimension of the cervix. Eight measurements (L1-L4 and A1-A4) of cervix dimensions (from intrauterine tandem to the uterine wall) were performed (sagittal

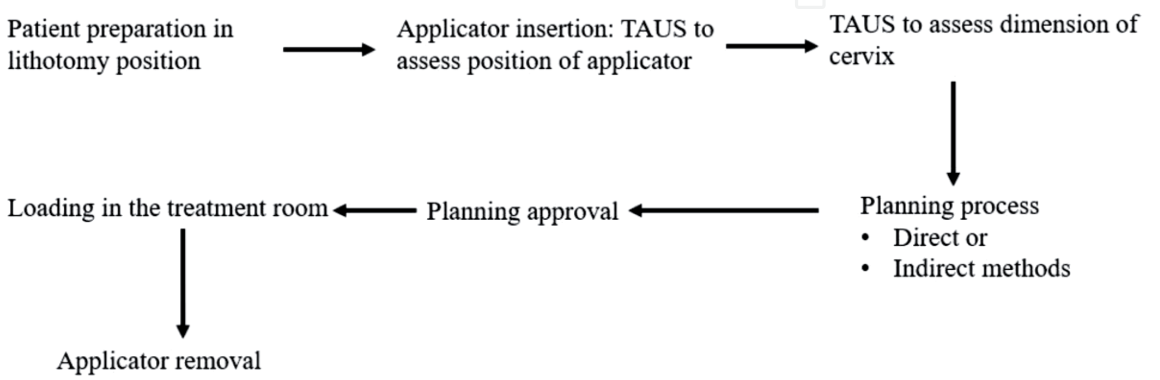

Figure 4.
Workflow of TAUS-based brachytherapy.

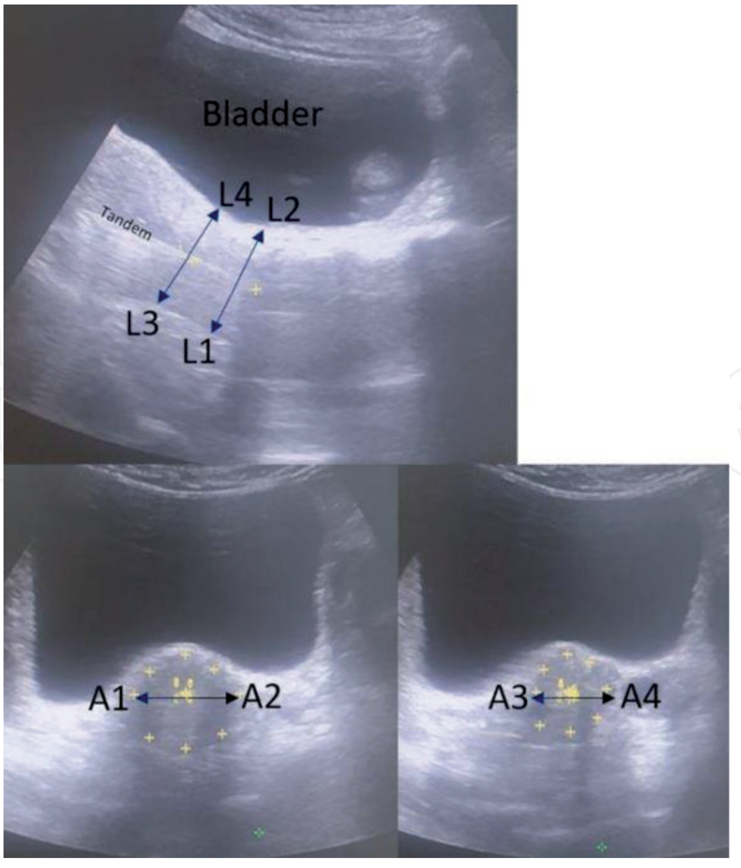

Figure 5.
Measurements in sagittal and axial views by TAUS from The Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University.

and transverse approaches) at the level of the cervical OS, and 2 cm cranially to the cervical OS, adapted from previous work by Van Dyk et al. [40]. **Figure 5** shows the measurement of the cervix by TAUS.

The planning processes of TAUS-guided brachytherapy in our institute were defined as the two methods for delivering TAUS measurements into treatment planning software. When we started TAUS-guided brachytherapy in 2011, conventional brachytherapy by orthogonal X-rays was utilized by the PLATO workstation. At that time, an indirect process (to transfer the measurements from TAUS to the orthogonal X-ray) was performed. After we installed the new Oncentra workstation in 2014, a direct process (to import the DICOM images of TAUS in sagittal view to the workstation) adapted from Peter MacCallum Cancer center [34, 42] was developed to use in our patients. After applicator reconstruction by manual process or applicator library, the eight dimensions were generated to be eight cervix reference points correlated to intrauterine tandem in lateral and anteroposterior view. **Figure 6** shows the cervix reference points in the sagittal view of ultrasound sound.

After generation of eight cervix reference points, dwell weight or time was optimized to achieve a sufficiently minimal dose to the cervix reference points of at least prescribed dose (6–7 Gy per fraction). **Figure 7** shows dose distribution by TAUS.

From our experiences, TAUS-guided brachytherapy improved the dose to the normal tissues. It reduced the cumulative overdose to the bladder (>80 Gy) and rectum (>75 Gy) in comparison to standard point A treatment and our intermediate-term results showed the 2-year local control of 88% [45]. From 2012 to 2018, more than 100 patients were treated with this technique. Nowadays, after CT was installed in our brachytherapy unit in 2019, we totally transformed to 3D (volume-based) brachytherapy. We still use TAUS to evaluate proper placement and support our CT contouring.

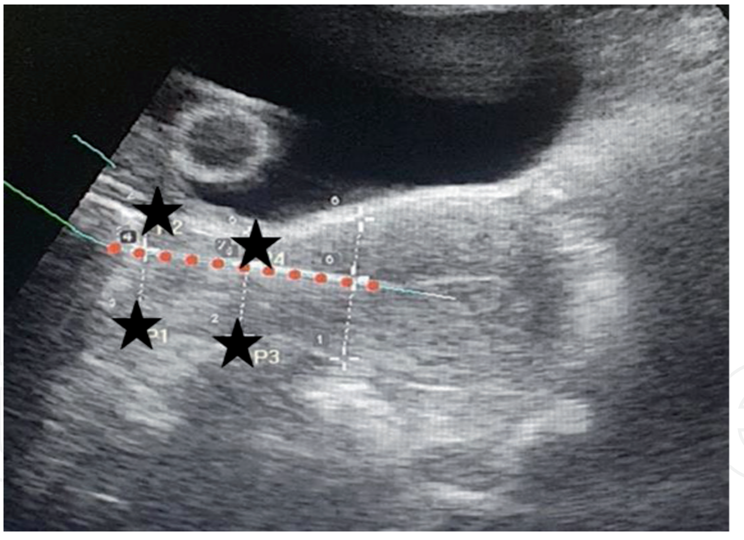

Figure 6.
TAUS images showed cervix reference points (black star) in sagittal view from The Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University.

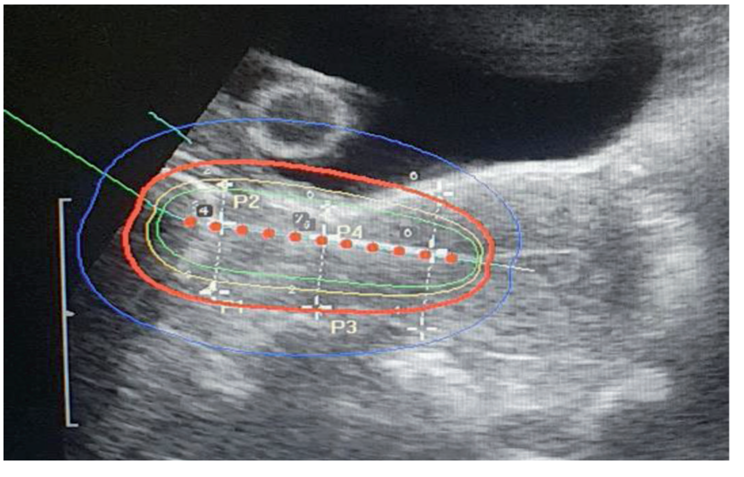

Figure 7.
Isodose distribution for TAUS-guided brachytherapy for cervical cancer (red line is 100% of prescribed dose that focus on the first 2 centimeter of uterus) from The Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University.

However, TAUS still has some limitations in patients who cannot have a full bladder (cystostomy or vesicovaginal fistula), and the concept of TAUS in adaptive treatment is still on point-based planning (e.g., cervix reference points). The concept of volume-based approaches via 3D ultrasound is pending [31]. However, TAUS is inexpensive, portable, non-ionizing, and real-time equipment. TAUS supports application safely, CT contouring, and planning itself. TAUS encourages treatment quality in low-resource and high-workload centers to propose improvement in conventional brachytherapy (point A) to adaptive point-based planning (adaptive plan to cervix reference points; 2.5D). Further studies in ultrasound in CT-based contouring and planning should be performed to support the alternatives for brachytherapy in place in which MRI or CT are inaccessible.

6. Conclusion

Although trends of brachytherapy turned from point-based to volume-based plans via MRI or CT, not all cancer centers can access this equipment. To improve the quality of the point-based plan, ultrasound supports the whole process of brachytherapy, for example, applicator insertion, CT-based contouring, and planning process. TAUS-guided brachytherapy shows promising results by international publications and the cost of TAUS is cheap, and portable. Ultrasound can be applied to all levels of the cancer center to improve the quality of brachytherapy.

Acknowledgements

The author offers many thanks to all staff of the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, and Chiang Mai University for supporting all works.

Conflict of interest

The authors declare no conflict of interest.

Author details

Ekkasit Tharavichitkul[1,2]* and Razvan M. Galalae[3,4]

1 Faculty of Medicine, The Division of Radiation Oncology, Department of Radiology, Chiang Mai University, Chiang Mai, Thailand

2 Faculty of Medicine, Northern Thailand Radiation Oncology Group, Department of Radiology, Chiang Mai University, Chiang Mai, Thailand

3 MedAustron Ion Therapy Center, Wiener Neustadt, Austria

4 Faculty of Medicine, Christian-Albrechts-University, Kiel, Germany

*Address all correspondence to: ekkasit.t@cmu.ac.th

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