EMBRACE III – Promise

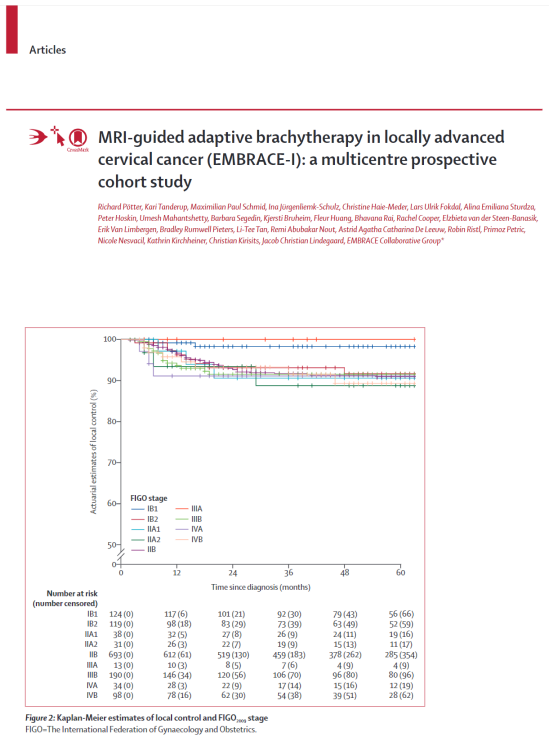
Prospective Real-wOrld MRI baSed treatmEnt

Background and Rationale

- Role of MR-IGABT
- Diversification of treatment
- Lack of knowledge
- ESGO-ESTRO-ESP guideline – update 2023

Role of MR-IGABT

PRO:



Articles

MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study

Richard Pötter, Kari Tanderup, Maximilian Paul Schmid, Ina Jürgenliemk-Schulz, Christine Haie-Meder, Lars Ulrik Fokdal, Alina Emiliana Sturdza, Peter Hoskin, Umesh Mahantshetty, Barbara Segedin, Kjersti Bruheim, Fleur Huang, Bhavana Rai, Rachel Cooper, Elzbieta van der Steen-Banasik, Erik Van Limbergen, Bradley Rumwell Peters, Li Tee Tan, Remi Abubakar Nout, Astrid Agatha Catharina De Leeuw, Robin Ristl, Primoz Petric, Nicole Nesvacil, Kathrin Kirchheiner, Christian Kirisits, Jacob Christian Lindegaard, EMBRACE Collaborative Group*

Figure 2: **Kaplan-Meier estimates of local control and FIGO$_{2018}$ stage**
FIGO=The International Federation of Gynaecology and Obstetrics.

CON:

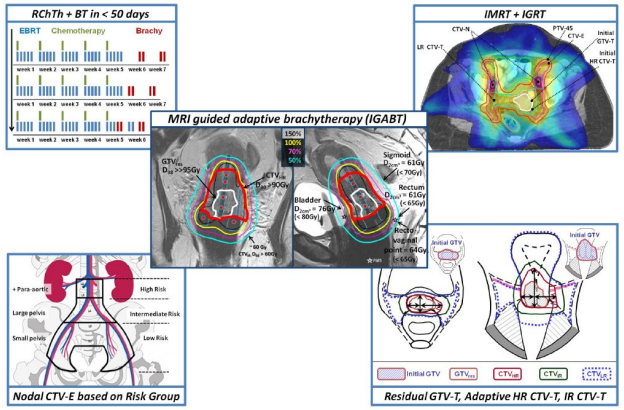
MR-IGABT is…

- too complex
- only possible in selected expert centers
- not reproducible

NEED: Strengthen the role of MR-IGABT

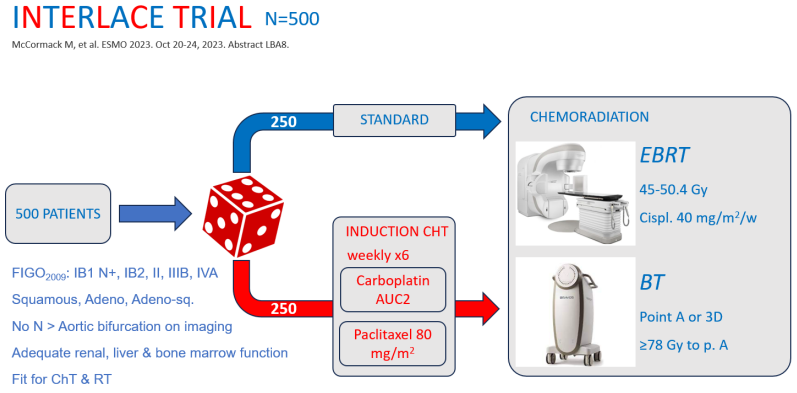
Diversification of treatment

EMBRACE II



Publication planned for 2025

INTERLACE



Published

KEYNOTE A18

Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial

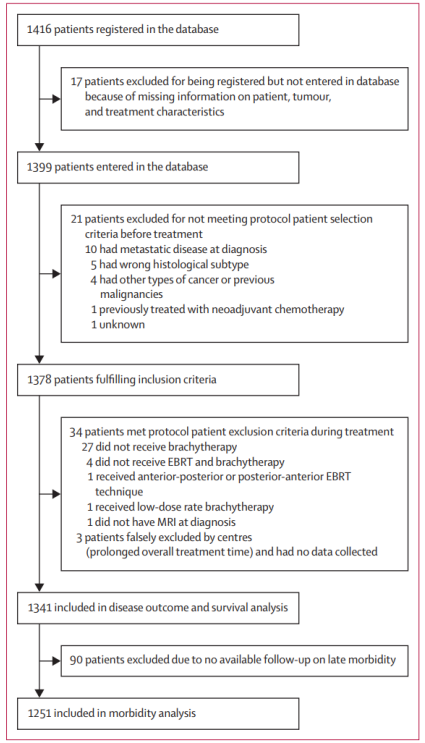
Domenica Lorusso, Yang Xiang, Kosei Hasegawa, Giovanni Scambia, Manuel Leiva, Pier Ramos-Elias, Alejandro Acevedo, Vladyslav Sukhin, Noelle Cloven, Andrea J Pereira de Santana Gomes, Fernando Contreras Mejía, Ari Reiss, Ali Ayhan, Jung-Yun Lee, Valeriya Saevets, Flora Zagouri, Lucy Gilbert, Jalid Sehouli, Ekkasit Tharavichitkul, Kristina Lindemann, Roberta Lazzari, Chih-Long Chang, Rudolf Lampé, Hong Zhu, Ana Oaknin, Melissa Christiaens, Stephan Polterauer, Tomoka Usami, Kan Li, Karin Yamada, Sarper Toker, Stephen M Keefe, Sandro Pignata, Linda R Duska*, on behalf of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 investigators†*

Published

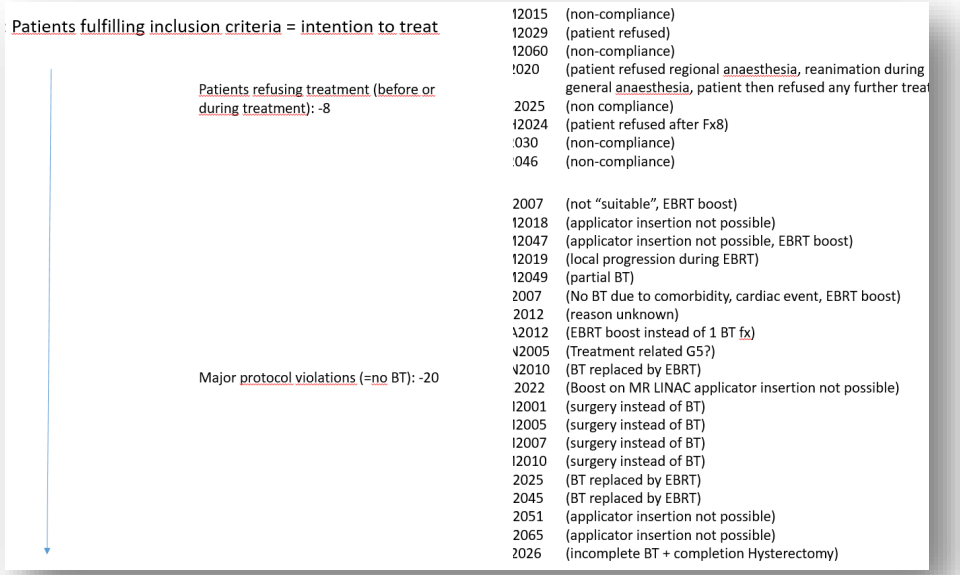
NEED: systematic data assessment for comparability and risk factor analysis

Lack of knowledge in „real-world setting“

EMBRACE I

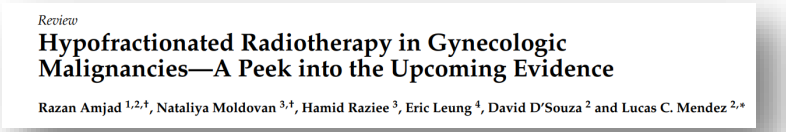


EMBRACE II



Patients not recruited for EMBRACE

- Rare histologies
- Alternative radiotherapy schedules
- Elderly/frail patients

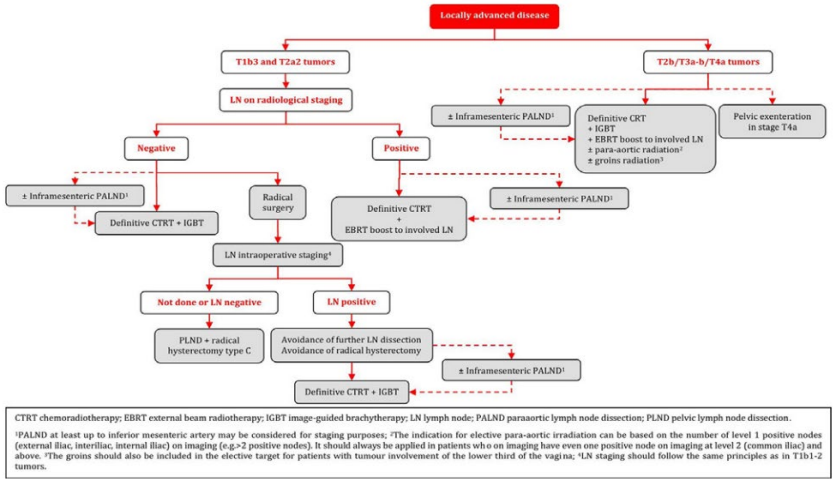

Review

Hypofractionated Radiotherapy in Gynecologic Malignancies—A Peek into the Upcoming Evidence

Razan Amjad [1,2,†], Nataliya Moldovan [3,†], Hamid Raziee [3], Eric Leung [4], David D'Souza [2] and Lucas C. Mendez [2,*]

NEED: for data collection to increase evidence

ESTRO-ESGO-ESP guideline – update 2023



Cibula D et al. Int J Gynecol Cancer 2023

PRINCIPLES OF RADIOTHERAPY

Definitive CTRT and BT - General Aspects

Definitive management (ie, without tumor related surgery) consists of EBRT with concomitant platinum-based chemotherapy and BT. Delay of treatment and/or treatment interruptions have to be prevented to avoid tumor progression and accelerated repopulation. The overall treatment time including both EBRT and BT should therefore not exceed 7 weeks.

Definitive CTRT and BT

CTRT

Target contouring for EBRT should be based on 3D imaging (preferably fused MRI and PET-CT) performed in the supine treatment position. Controlled bladder filling is recommended to minimize uterus movements and to push the intestines away. The result of the gynecological examination (ie, clinical drawing and description) as well as diagnostic imaging should be available during the contouring phase. A contouring protocol including a margin strategy for handling of internal movement (ITV) should be used to minimize irradiation of organs at risk. The EMBRACE II protocol may serve as a template. The tumor related target volume for EBRT (CTV-T-LR) includes the primary cervical tumor (GTV-T), the uterus, parametria and upper vagina (or minimal 2 cm tumour-free margin below any vaginal infiltration respectively) and is optimally defined on MRI with assistance of the clinical findings.

The elective target (CTV-E) includes the obturator, internal, external and common iliac and presacral regions. The inguinal nodes should be included if the primary tumor involves the distal third of the vagina. A reduced elective target volume for EBRT without the common

...

Cibula D et al. Radiother Oncol 2023

Brachytherapy

IGABT is recommended, preferably using MRI with applicator in place. Repeated gynaecologic examination is mandatory, and alternative imaging modalities such as CT scan and ultrasound may be used. The tumour-related targets for BT include: 1) the residual gross tumor volume (GTV-T_{res}) after CTRT; 2) the adaptive high-risk clinical target volume (CTV-T_{HR}) including the whole cervix and residual adjacent pathologic tissue; and 3) the intermediate-risk clinical target volume (CTV-T_{IR}) taking the initial tumor extent into consideration. The BT applicator should consist of a uterine tandem and a vaginal component (ovoids/ring/mold/combined ring/ovoid). A combined intracavitary/interstitial implant is recommended in advanced cases to achieve the dose planning aim (see below), in particular in case of residual disease in the parametrium.

Ultrasound (transabdominal and/or transrectal) maybe used to intraoperatively support applicator insertion (avoidance of uterine perforation by the tandem, guidance of interstitial needles). In IGABT, the planning aim should be to deliver a BT dose of 40 to 45 Gy EQD2 to reach a total EBRT+BT dose of 85 to 95 Gy EQD2 (D90) (assuming 45 Gy through EBRT) to the CTV-T_{HR}, equal to or greater than 60 Gy (D98) to the CTV-T_{IR}, and equal to or greater than 90 Gy (D98) to the GTV-T_{res}. The use of three dimensional and 2D dose volume and point constraints for rectum, bladder, vagina, sigmoid, and bowel are recommended, and they have to be based on the published

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Cibula D et al. Virchows Arch 2023

Overall aim

To comprehensively collect and analyze patterns of care, treatment data, and outcome for patients with malignances of the uterine cervix receiving definitive chemo-radiation and MR-IGABT in real-world setting

Standard cohort

= Definitive chemo-radiation and MR-IGABT according to the ESGO-ESTRO-ESP guidelines (update 2023) for primary SQ, Adeno- and Adenosquamous carcinoma of the uterine cervix in curative intention

optional

Evi Guide

Standard cohort + additional systemic treatment

= Definitive chemo-radiation and MR-IGABT + additional systemic treatment (e.g. INTERLACE, KEYNOTE A18) for primary SQ, Adeno- and Adenosquamous carcinoma of the uterine cervix in curative intention

Non-standard cohort

= Definitive treatment in terms of combination of external beam radiotherapy (+/- chemotherapy) and MR-IGABT for all patients outside the standard arm (= e.g elderly or frail patients treated with deviating radiotherapy schedules (e.g. hypofractionation) or patients with rare histologies)

Study design

prospective non-interventional observational multi-arm cohort study

- Standard cohort (chemoradiation + MR-IGABT): Phase IV study
- Standard cohort + additional systemic treatment: explorative observational hypothesis-generating study
- Non standard cohort: explorative observational hypothesis-generating study

Endpoints

- **Progression-free survival**
- Overall survival
- Local control
- Nodal control
- Systemic control
- **Second malignancy**

- Late side effects ≥ **G3**
  - gastrointestinal
  - genito-urinary
  - vaginal
  - muscolo-skeletal
  - **hematologic/immunotherapy-related**
- Quality of life (optional)

Selected examplary specific aims

- to collect “real-world data” on MR-IGABT
- to analyze clinical outcome and safety of MR-IGABT under “real-world conditions”
- to assess patterns of care in locally advanced cervical cancer undergoing definitive chemoradiation and monitor the introduction of new systemic treatment modalities
- to compare and analyze outcome of new systemic treatment modalities

Hypotheses – Performance of treatment

derived from E-I, E-II, Interlace, Keynote A-18, Aarhus RW data

Standard cohort / Standard cohort + additional systemic treatment

- EBRT completed as planned in >95%
- BT performed in >90%
- Concomitant chemotherapy initiated in >75% and >= 4 cycles in >70%
- All EMBRACE II hard constraints for CTV and OARs fulfilled in 80%

Hypotheses – outcome

derived from E-I, E-II, Interlace, Keynote A-18, Aarhus RW data

Standard cohort

- 3-year local control >90%
- Rate of ≥G4 late side effects: <3%
- No difference between E-II centers and non-E-II centers
- No difference between predicted outcome based on TCP/NTCP models and actual outcome

- 3-year PFS >70% for a cohort comparable to the EMBRACE II study
- 3-year OS >75% for a cohort comparable to the EMBRACE II study

Hypotheses – outcome

derived from E-I, E-II, Interlace, Keynote A-18, Aarhus RW data

Standard cohort plus additional systemic treatment (Interlace-like)

- 3-year PFS >80% for a cohort comparable to the Interlace study
- 3-year OS > 85% for a cohort comparable to the Interlace study

Standard cohort plus additional systemic treatment (Keynote-like)

- 3-year PFS >70% for a cohort comparable to the Keynote study
- 3-year OS >75% for a cohort comparable to the Keynote study

Hypotheses – non standard cohort

No specific hypothesis - > observational registry

Sample size calculation

No concrete sample size calculation due to observational study design

- aim for ~1500 patients in standard cohorts for comparability to E-I, E-II
- ~340 patients treated with neoadjuvant chemotherapy (Interlace-like)
- ~560 patients treated with additional immunotherapy (Keynote-like)

- no aims for non-standard cohort

Inclusion criteria

Inclusion criteria for standard cohort = EMBRACE II

Inclusion criteria for all other patients

- Biopsy showing any primary malignant tumor of the uterine cervix
- Treatment in curative intent with combination of external beam radiotherapy (+/- chemotherapy) and MR-IGABT
- MRI of pelvis at diagnosis is performed
- MRI, CT or PET-CT of the retroperitoneal space and abdomen at diagnosis is performed
- MRI with the applicator in place at the time of (first) BT will be performed
- Para-aortic metastatic nodes below L1-L2 are allowed
- Patient informed consent

- Performance of EBRT, CHT and MR-IGABT does not need to be in the same institution
- Patient inclusion can be also at MR-IGABT, if baseline parameters are available
- Patient inclusion should be as consecutive as possible

Treatment

Basis for EBRT + MR-IGABT = ESGO-ESTRO-ESP guideline + EMBRACE II protocol

Considerations/clarifications (optional):

1. Risk adapted target volume selection for EBRT
2. Lymph node boost
3. Chemotherapy including NACT
4. Brachytherapy target volume definition (NACT)
5. Risk adapted brachytherapy dose prescription
6. Intraoperative TRUS guidance
7. Dwell time optimization
8. Vaginal dose de-escalation
9. Morbidity management and supportive measures in Follow-up

Conclusion

New Study Protocol and Tools

- **Addressing Hot Topics & Unmet Needs**
  - Protocol circulated to interested centers
  - Open for feedback and adaptation
- **No Dummy Run or Prior Training Required**
- **Enhanced Software & Website**
  - Reduces workload and streamlines documentation
  - Provides current evidence for MR-IGABT
  - Includes QA and data monitoring tools
- **Access to Structured Data**
  - Centers can access their own data anytime
    - For clinical quality assurance
    - For research purposes

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Thank you