Improving therapeutic outcomes with radiotherapy in cancer cervix – Embrace and beyond

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EMBRACE

- The GEC ESTRO gyn network - designed and initiated the EMBRACE studies - develop, perform and evaluate image guided radiotherapy in cervix cancer with a special focus on improving clinical outcome

EMBRACE I - The original focus was on MRI based adaptive brachytherapy

RetroEMBRACE study - initiated in parallel to the EMBRACE I study. It was carried out to built up clinical experience before the EMBRACE I study, applying the Gyn GEC ESTRO Recommendations for target delineation and dose volume reporting

EMBRACE II- The scope was then widened to include also image guided radiotherapy and systemic treatment, at present in the form of concomitant radiochemotherapy

MAX Healthcare

RETROEMBRACE

RetroEMBRACE

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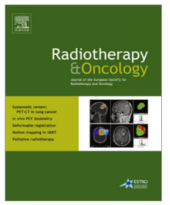

Original article

Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

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A. Sturdza et al. / Radiotherapy and Oncology xxx (2016)

Retro EMBRACE

1. Retrospective observational Study
2. 1998 - 2012 - study period
3. n= 814 pts
4. EBRT ± concurrent chemotherapy followed by IGBT, were analysed (IGBT was based on MRI guidance in at least one application in 80.9% and on CT alone in19.1%)

Retro EMBRACE

FIGO Stage	
IA/IB/IIA	22.8%
IIB	50.4%
IIIA–IVB	26.8%

84.8% had squamous cell carcinomas

77.4% received concurrent chemotherapy

40.5% lymph node involvement

In 23.0%, a combined intracavitary and interstitial approach was used in at least 1 BT fraction

RESULTS

Table 2
Crude number of local failure, pelvic failure, and any failure based on FIGO stage. Mean D90 HRCTV, actuarial local and pelvic control, cancer specific survival and overall survival at 3 and 5 years.

FIGO stage	Number of patients	Total number of local failures	Total number of pelvic failures	Number of patients with any failure	Number of patients with no evidence of disease	Mean D90 HRCTV in Gy (±SD)	Actuarial local control at 3/5 years	Actuarial pelvic control at 3/5 years	Actuarial overall survival at 3/5 years	Actuarial cancer specific survival at 3/5 years
1A	2	0	0	0	2	–	100%	100%	100%	100%
1B	123	2	4	19	104	93 ± 17	98%/98%	96%/96%	88%/83%	93%/90%
2A	42	3	4	9	33	89 ± 16	97%/94%	95%/92%	83%/80%	87%/84%
2B	368	28	42	97	271	88 ± 14	93%/91%	89%/87%	78%/70%	83%/77%
3A	23	5	6	13	10	83 ± 12	71%/71%	66%/66%	54%/42%	54%/48%
3B	145	28	36	68	77	83 ± 13	79%/75%	73%/67%	56%/42%	65%/53%
4A	23	3	3	13	10	78 ± 13	76%/76%	76%/76%	43%/32%	53%/ 40%
4B	5	0	1	3	2	78 ± 2	–	–	–	
Total	731	69	96	222	509	87 ± 15	91%/89%	87%/84%	74%/65%	79%/73%

- the dose to the HRCTV (EQD210) decreased significantly with advancing stage, which leaves room for further improvement through dose escalation
- In CTV-HR volumes of 30 cm3, use of ICIS BT has improved 3-year local control by 10% without additional treatment-related late morbidity through conformal dose escalation

Retro EMBRACE

- Median follow up - 43 months

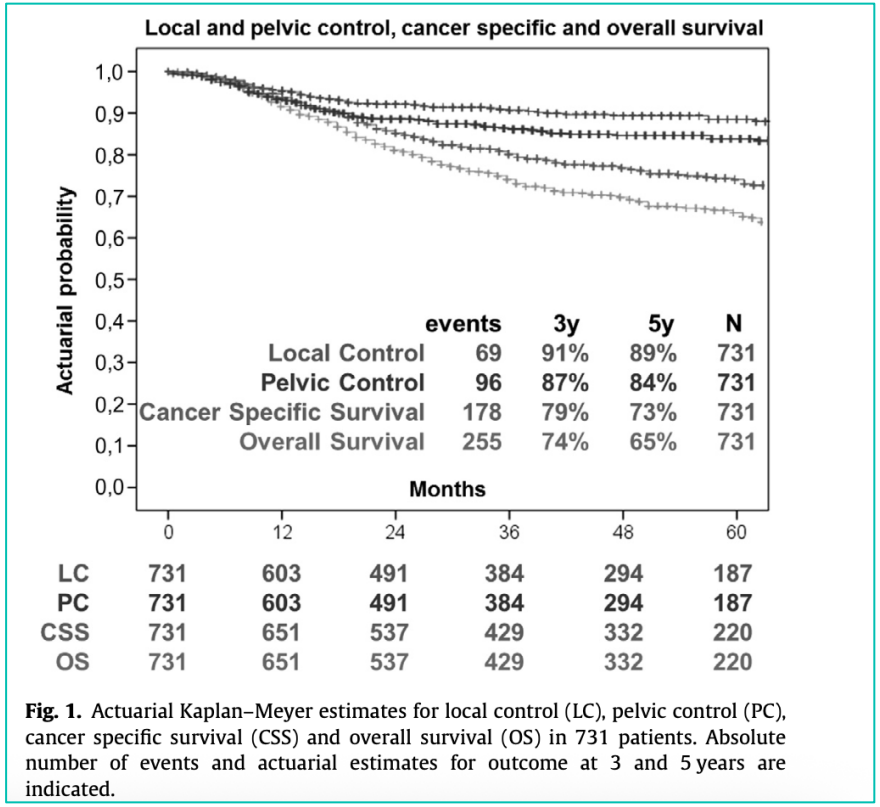

Fig. 1. Actuarial Kaplan–Meyer estimates for local control (LC), pelvic control (PC), cancer specific survival (CSS) and overall survival (OS) in 731 patients. Absolute number of events and actuarial estimates for outcome at 3 and 5 years are indicated.

Conclusions

- Actuarial 5-year G3–G5 morbidity was 5%, 7%, 5% for bladder, gastrointestinal tract, vagina
- IGBT improved pelvic control by approximately 10% compared to conventional 2D BT. This effect - larger (>10%) in advanced stages
- The improvement in OS and CSS by 10% and 14%, respectively, for the RetroEMBRACE cohort compared to the UK cohort is seen across all stages.
- The absolute difference in 3-year CSS was 17% for IB disease (93% vs. 76%), 7% for IIB disease (83% vs. 76%) and 11% for IIIB disease (65% vs. 54%).

Key Takeaway

Further improvements in survival could be achieved through the use

- of better IGBT techniques to further reduce local and pelvic recurrences in advanced stage disease
- of paraaortic EBRT and the use of adjuvant chemotherapy and/or targeted drugs for patients at high risk for distant failure

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Clinical Investigation

Change in Patterns of Failure After Image-Guided Brachytherapy for Cervical Cancer: Analysis From the RetroEMBRACE Study

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Curves for local, regional, para aortic and systemic failure

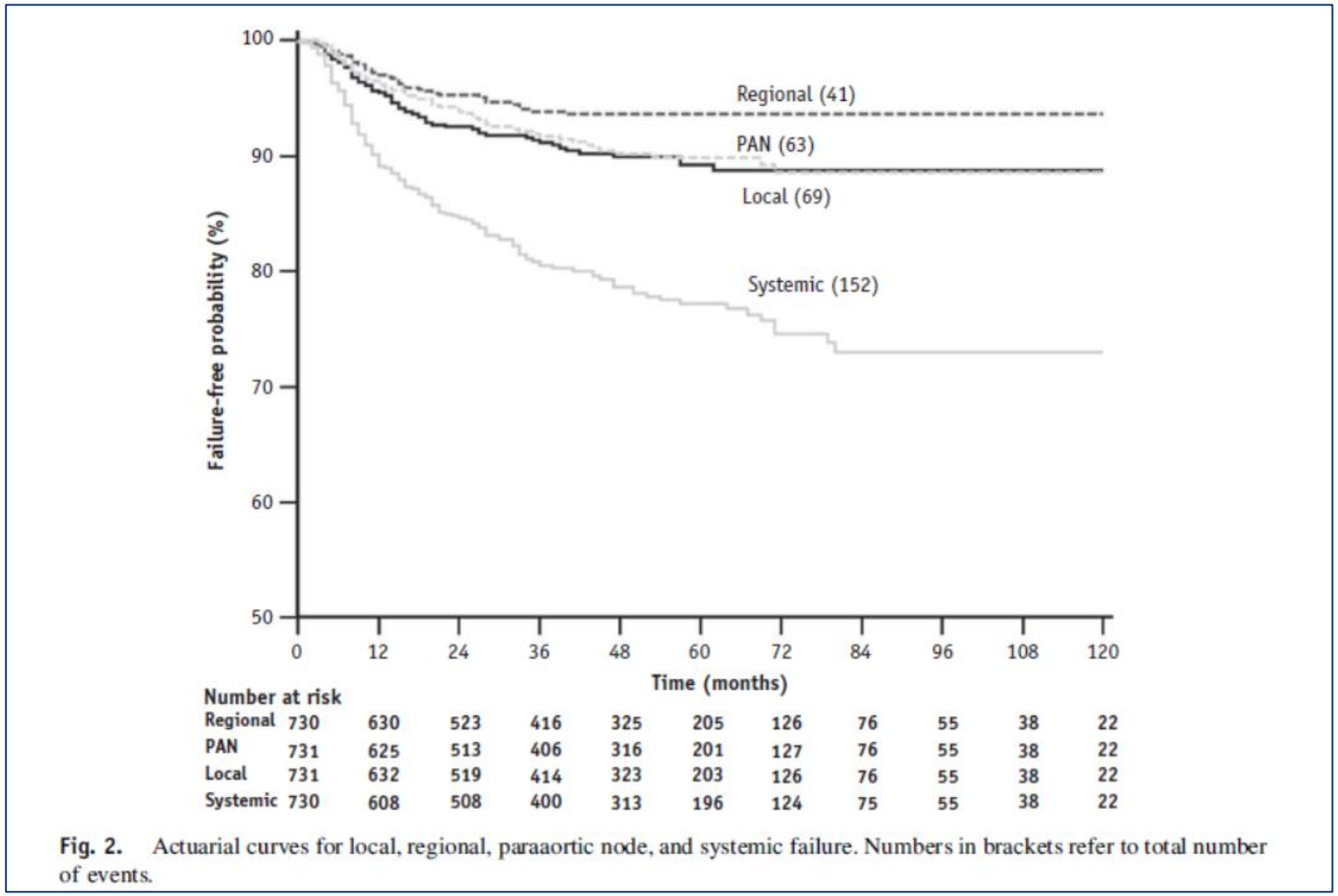


Fig. 2. Actuarial curves for local, regional, paraaortic node, and systemic failure. Numbers in brackets refer to total number of events.

Tan et al, Int J Radiation Oncol Biol Phys, 2019

Conclusion

- The implementation of IGABT - changed the patterns of relapse after definitive CT-RT
- The predominant failure after IGABT is systemic, whereas the predominant failure with conventional brachytherapy is pelvic.
- 6% pts - pelvic failure without distant failure, and 17% had distant failure without pelvic failure.

Tan et al, Int J Radiation Oncol Biol Phys, 2019

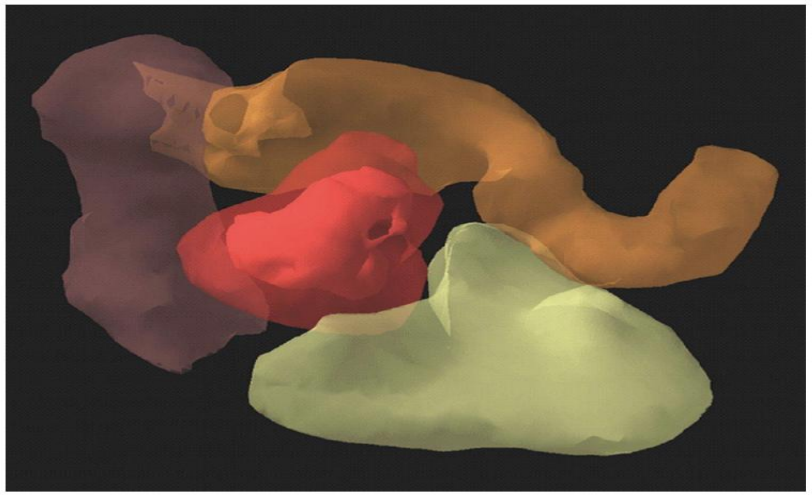
EMBRACE - I

EMBRACE-1

A European study on MRI-guided brachytherapy in locally advanced cervical cancer

EMBRACE

(ENDORSED BY GEC ESTRO)



- Prospective
- Observational
- multicenter cohort study

- Launched in 2008 – 2015

- n = 1416

AIMS

1. To introduce MRI- based IGABT in locally advanced cervical cancer
2. To present reference material for treatment parameters
3. To investigate the effects of CT RT f/b MRI-based IGABT on disease and late morbidity, allowing for variations in techniques and dose.
4. To provide a benchmark for clinical outcome with MRI-based IGABT in a large patient population.

Primary endpoints

1. Local control
2. Late morbidity

Secondary endpoints

1. Pelvic control
2. nodal control
3. Disease free Survival
4. Over all Survival
5. Quality of Life

Methods

1. Permitted EBRT techniques – 3 DCRT, IMRT/ VMAT
2. EBRT dose was 45–50 Gy in 1·8–2 Gy/ frs. (boosts to pathological lymph nodes)
3. Concurrent cisplatin 40 mg/m², 5–6 cycles
4. There were no dose prescription constraints, neither for the residual tumor and the adaptive target volume, nor for organs at risk.
5. Dose prescription for MRI based BT had to follow institutional guidelines.
6. Overall treatment time was restricted to 50 days.

Treatment

- Brachytherapy: Target volume definition and reporting were according to Gynaecological (GYN) GEC-ESTRO recommendations.

TARGET
HRCTV: EQD2: 85-90Gy IRCTV: EQD2: 60Gy

OARs
1. Rectum :D2cc- 70-75Gy EQD2 2. Sigmoid : D2cc- 70-75Gy EQD2 3. Bladder: D2cc- 90-95Gy EQD2

EMBRACE I

Baseline patient and Tumor Characteristics

	Patient cohort (n=1341)
Demographics	
Age, years	49 (41–60)
Missing	0
Histology	
Squamous cell carcinoma	1097 (81·8%)
Adenocarcinoma	192 (14·3%)
Adenosquamous carcinoma	50 (3·7%)
Missing	2 (0·1%)
FIGO stage	
IB1	124 (9·2%)
IB2	119 (8·9%)
IIA1	38 (2·8%)
IIA2	31 (2·3%)
IIB	693 (51·7%)
IIIA	13 (1·0%)
IIIB	190 (14·2%)
IVA	34 (2·5%)
IVB	98 (7·3%)
Missing	1 (0·1%)
Nodal status	
N0	641 (47·8%)
N1	699 (52·1%)
Missing	1 (0·1%)

23%

Treatment characteristics

3 DCRT- 58·8%, IMRT/ VMAT - 41·0%

- Intracavitary - 56·6%
- Combined intracavitary and interstitial - 43·0%

Cumulative CTV HR D 90 %- 90 Gy (IQR 85–94) EQD2(10).

Median HR CTV BT - 28 cm³ (IQR 20–40)

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

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Summary

Background The concept of the use of MRI for image-guided adaptive brachytherapy (IGABT) in locally advanced cervical cancer was introduced 20 years ago. Here, we report on EMBRACE-I, which aimed to evaluate local tumour control and morbidity after chemoradiotherapy and MRI-based IGABT.

Methods EMBRACE-I was a prospective, observational, multicentre cohort study. Data from patients from 24 centres in Europe, Asia, and North America were prospectively collected. The inclusion criteria were patients older than 18 years, with biopsy-proven squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, The International Federation of Gynecology and Obstetrics (FIGO) stage IB–IVA disease or FIGO stage IVB disease restricted to paraaortic lymph metastasis below the L1–L2 interspace, suitable for curative treatment. Treatment consisted of chemoradiotherapy (weekly intravenous cisplatin 40 mg/m², 5–6 cycles, 1 day per cycle, plus 45–50 Gy external-beam radiotherapy delivered in 1·8–2 Gy fractions) followed by MRI-based IGABT. The MRI-based IGABT target volume definition and dose reporting was according to Groupe Européen de Curiethérapie European Society for Radiation Oncology recommendations. IGABT dose prescription was open according to institutional practice. Local control and late morbidity were selected as primary endpoints in all patients available for analysis. The study was registered with ClinicalTrials.gov, NCT00920920.

Findings Patient accrual began on July 30, 2008, and closed on Dec 29, 2015. A total of 1416 patients were registered in the database. After exclusion for not meeting patient selection criteria before treatment, being registered but not entered in the database, meeting the exclusion criteria, and being falsely excluded, data from 1341 patients were available for analysis of disease and data from 1251 patients were available for assessment of morbidity outcome. MRI-based IGABT including dose optimisation was done in 1317 (98·2%) of 1341 patients. Median high-risk clinical target volume was 28 cm³ (IQR 20–40) and median minimal dose to 90% of the clinical target volume (D_{90}) was 90 Gy (IQR 85–94) equi-effective dose in 2 Gy per fraction. At a median follow-up of 51 months (IQR 20–64), actuarial overall 5-year local control was 92% (95% CI 90–93). Actuarial cumulative 5-year incidence of grade 3–5 morbidity was 6·8% (95% CI 5·4–8·6) for genitourinary events, 8·5% (6·9–10·6) for gastrointestinal events, 5·7% (4·3–7·6) for vaginal events, and 3·2% (2·2–4·5) for fistulae.

Interpretation Chemoradiotherapy and MRI-based IGABT result in effective and stable long-term local control across all stages of locally advanced cervical cancer, with a limited severe morbidity per organ. These results represent a positive breakthrough in the treatment of locally advanced cervical cancer, which might be used as a benchmark for clinical practice and all future studies.

At median F/U – 51 mths

Clinical outcomes according to the stage

	Number of patients	CTV_{HR} volume, cm^{3*}	CTV_{HR} $D_{90\%}$ $EQD2_{10}$ Gy	Local failure (n)	Pelvic failure (n)	Any failure (n)	Patients dead (n)	5-year local control (95% CI)	5-year pelvic control (95% CI)	5-year disease-free survival (95% CI)	5-year overall survival (95% CI)
IB1	124	22 (17–27)	91 (87–95)	2	6	20	24	98% (94–100)	95% (87–98)	76% (67–83)	83% (75–89)
IB2	119	26 (20–38)	89 (84–93)	9	18	36	35	92% (84–96)	84% (75–90)	65% (56–73)	73% (64–81)
IIA1	38	23 (14–31)	91 (85–96)	3	4	6	7	91% (73–97)	88% (71–95)	75% (58–86)	80% (63–90)
IIA2	31	34 (24–42)	87 (80–91)	3	6	10	8	89% (68–96)	77% (55–89)	65% (44–79)	74% (53–87)
IIB	693	27 (19–36)	90 (86–95)	55	78	146	152	91% (88–93)	88% (85–90)	73% (69–76)	78% (75–82)
IIIA	13	30 (24–35)	84 (82–88)	0	0	2	3	100%	100%	76% (43–92)	76% (42–91)
IIIB	190	40 (30–56)	88 (83–91)	15	24	61	78	92% (86–95)	86% (79–90)	59% (52–66)	64% (57–71)
IVA	34	57 (39–89)	86 (78–89)	3	6	10	17	91% (75–97)	81% (62–91)	47% (28–63)	52% (33–68)
IVB	98	34 (22–47)	89 (85–92)	8	16	40	38	89% (79–95)	81% (70–88)	48% (37–58)	61% (49–70)
Total	1341†	28 (20–40)	90 (85–94)	98	158	331	363†	92% (90–93)	87% (85–89)	68% (65–70)	74% (72–77)

Data are n, median (IQR), or Kaplan-Meier estimates (95% CI). *Mean dose delivered over all fractions. †One patient with unknown FIGO stage. FIGO=The International Federation of Gynaecology and Obstetrics. CTV_{HR}= high-risk clinical target volume. $D_{90\%}$=minimal dose to 90% of the clinical target volume. $EQD2_{10}$=equi-effective dose in 2 Gy per fraction of 10 Gy.

Table 3: CTV_{HR} volume, and dose and clinical outcomes according to $FIGO_{2009}$ stage

the patterns of local failure in the EMBRACE I study - found that 98% of local failures were located within the CTVHR and the CTVIR

RESULTS

- In the post-hoc analysis of outcomes by nodal status at diagnosis, 5-year nodal control was 93% in N0 and 81% in N1 patients
- Superior local control rates for stage IB–IIB disease compared to historical series using 2 D point A-based BT
- An absolute improvement of 14-17% in local/ pelvic control in stage IIIB compared with values previously reported with 2 D BT
- The overall local control achieved across all stages-92%, (with a small 95% CI of 90–93) was unprecedented

MORBIDITY

	Gastrointestinal	Genitourinary	Vaginal	Fistula*	Overall (gastrointestinal, genitourinary, vaginal, and fistula)
Grade 3 adverse events					
Number of events	83	93	54	18	248
Number of patients	54 (4·3%)	59 (4·7%)	50 (4·0%)	13 (1·0%)	128 (10·2%)
Actuarial 5-year cumulative incidence of grade 3 or higher morbidity (95% CI)	8·5% (6·9–10·6)	6·8% (5·4–8·6)	5·7% (4·3–7·6)	3·2% (2·2–4·5)	18·4% (16·0–21·2)
Grade 4 adverse events					
Number of events	34	19	5	24	82
Number of patients	27 (2·2%)	16 (1·3%)	5 (0·4%)	21 (1·7%)	55 (4·4%)
Actuarial 5-year cumulative incidence of grade 4 or higher morbidity (95% CI)	3·0% (2·0–4·3)	1·0% (0·6–1·9)	0·5% (0·2–1·2)	2·1% (1·5–3·2)	5·2% (4·0–6·9)

Data are n, n (%), or actuarial cumulative incidence (95% CI). Adverse events were classified according to the Common Terminology Criteria for Adverse Events, version 3.0. Data were available for 1251 patients. Grade 5 events are not listed because they were not always allocated to a single organ system. Eight gastrointestinal events, four genitourinary events, four fistulas, and five septic infections contributed to treatment-related death in 12 patients.
*15 vesico-vaginal, 10 recto-vaginal, 4 sigmoid-vagina, 13 other fistulas.

Table 4: **Grade 3–4 morbidity**

- for EMBRACE I for organ-related morbidity, with 2% or less for genitourinary and 2% or less for gastrointestinal during follow-up which was 3–4 times lower than the actuarial incidence.

MORBIDITY

- Analysis of rectal morbidity demonstrated that G3 and G4 rectal morbidity is uncommon with IGABT
- Dose effect relationships have been demonstrated for rectal morbidity
- Limiting the rectal D2cc to 65 Gy reduces the incidence of bleeding and proctitis to 5.2% and 4.6%, respectively
- Limiting the rectal D2 cc to 75 Gy reduces the incidence of fistulae to 2.7%

CONCLUSION

- CT RT and MRI-based IGABT result in effective and stable long-term local control across all stages of locally advanced cervical cancer, with a limited severe morbidity per organ.

- **At a median follow-up of 51 months (IQR 20–64), actuarial overall 5-year local control was 92% (95% CI 90–93)**.

- Compared with previous results of IGABT with a similar stage distribution, the overall survival at 5 years has improved in EMBRACE study from 67% to 74%.

Potter R et al; ***Lancet Oncol*** **2021; 22: 538–47**

Implication of EMBRACE 1

- It provides clinical evidence for MRI-guided IGABT as being the new gold-standard IGABT for LACC , to be implemented across the world, replacing the traditional 2 D point A concept.

- It entails a comprehensive system for collecting information on patient, tumour, and treatment parameters, associating these with disease outcome and morbidity, and quality of life.

original reports

Risk Factors for Local Failure Following Chemoradiation and Magnetic Resonance Image–Guided Brachytherapy in Locally Advanced Cervical Cancer: Results From the EMBRACE-I Study

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abstract

PURPOSE To report clinical and treatment characteristics, remission and failure patterns, and risk factors for local failure (LF) from the EMBRACE-I study.

MATERIALS AND METHODS EMBRACE-I was a prospective, observational, multicenter cohort study on magnetic resonance imaging–based image-guided adaptive brachytherapy (MR-IGABT) in locally advanced cervical cancer. Treatment consisted of external beam radiotherapy, concurrent chemotherapy, and MR-IGABT. LF was defined as progressive or recurrent disease in the cervix, uterus, parametria, pelvic wall, or vagina. Competing risk analysis was used to estimate local tumor control (LC) and Cox proportional regression models for multivariable analysis and dose-response analysis.

RESULTS One thousand three hundred eighteen patients with a median follow-up of 52 months were available for this analysis. Eighty-one patients had persistent disease 3 months after end of treatment. Of those, 60 patients achieved LC at 6-9 months without further treatment, whereas 21 patients had progressive disease. In addition, 77 patients developed a local recurrence after complete remission comprising a total number of 98 LFs. LFs were located inside the MR-IGABT target volumes in 90% of patients with LF. In multivariable analysis, histology, minimal dose to 90% of high-risk clinical target volume (CTV_{HR}), maximum tumor dimension, $CTV_{HR} > 45\ cm^3$, overall treatment time, tumor necrosis on magnetic resonance imaging at diagnosis, uterine corpus infiltration at diagnosis and at MR-IGABT, and mesorectal infiltration at MR-IGABT had significant impact on LF. Dose-response analysis showed that a minimal dose to 90% of 85 Gy to the CTV_{HR} led to 95% (95% CI, 94 to 97) LC 3 years postintervention for squamous cell in comparison to 86% (95% CI, 81 to 90) for adeno/adenosquamous carcinoma histology.

CONCLUSION The present study demonstrates the safety and validity of the GYN GEC-ESTRO/ICRU-89 target concept and provides large-scale evidence for dose prescription and new risk factors for LF in MR-IGABT in locally advanced cervical cancer.

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ASSOCIATED CONTENT
Appendix
Data Sharing Statement
Data Supplement
Protocol
Author affiliations and support

Schmid et al, J Clin Oncol 41:1933-1942. © 2023 by American Society of Clinical Oncology

Results from Multivariable Risk Factor Ananlysis

Variable	Category	No.	HR	95% CI	P
Maximum tumor dimension at diagnosis (MRI)	Continuous	1,291	1.03	1.01 to 1.04	**< .01**
Tumor necrosis on MRI at diagnosis	Absent	1,036	Ref	1.03 to 2.59	**.037**
	Present	255	1.63		
Histology	Squamous cell carcinoma	1,058	Ref	2.37 to 5.7	**< .01**
	Adeno- or adenosquamous carcinoma	233	3.67		
Uterine corpus infiltration at diagnosis (MRI)	Not involved	824	Ref		
	Lower infiltration	335	1.70	1.05 to 2.74	**.03**
	Middle infiltration	100	1.80	0.91 to 3.55	.089
	Upper infiltration	32	2.02	0.81 to 5.05	.132
Uterine corpus infiltration at brachytherapy (MRI)	Not involved	1,067	Ref		
	Lower infiltration	154	1.76	1.01 to 3.06	**.045**
	Middle infiltration	30	1.55	0.61 to 3.98	.36
	Upper infiltration	24	1.51	0.55 to 4.15	.42
Rectal involvement at brachytherapy (MRI)	Not involved	1,264	Ref		
	Mesorectal infiltration	10	4.28	1.31 to 14.02	**.016**
	Rectal wall infiltration	1			
Overall treatment time in days	Continuous	1,291	1.03	1.01 to 1.06	**.024**
D90 for CTV_{HR}	Continuous	1,291	0.97	0.94 to 0.99	**< .01**

NOTE. Bold entries indicate statistically significant results.

Abbreviations: CTV_{HR}, high-risk clinical target volume; D90, minimal dose to 90% of the respective target volume; HR, hazard ratio; MRI, magnetic resonance imaging; Ref, reference.

Schmid et al, J Clin Oncol 41:1933-1942. © 2023 by American Society of Clinical Oncology

Patterns of Local Remission and Failure

- At 3 yrs the LC rates are 95% for SCC in comparison to 86% for adeno/ adenosquamous ca.
- At 3-mths, 81 pts had persistent disease. Of those, 21 patients had true persistent disease evolving into progressive disease, whereas 60 patients achieved CR at 6- to 9-month follow-ups without intervening treatment
- 48 % of the patients with LF presented with synchronous nodal or systemic recurrence.
- LFs were located inside the BT target volumes in 90% of the patients with LF

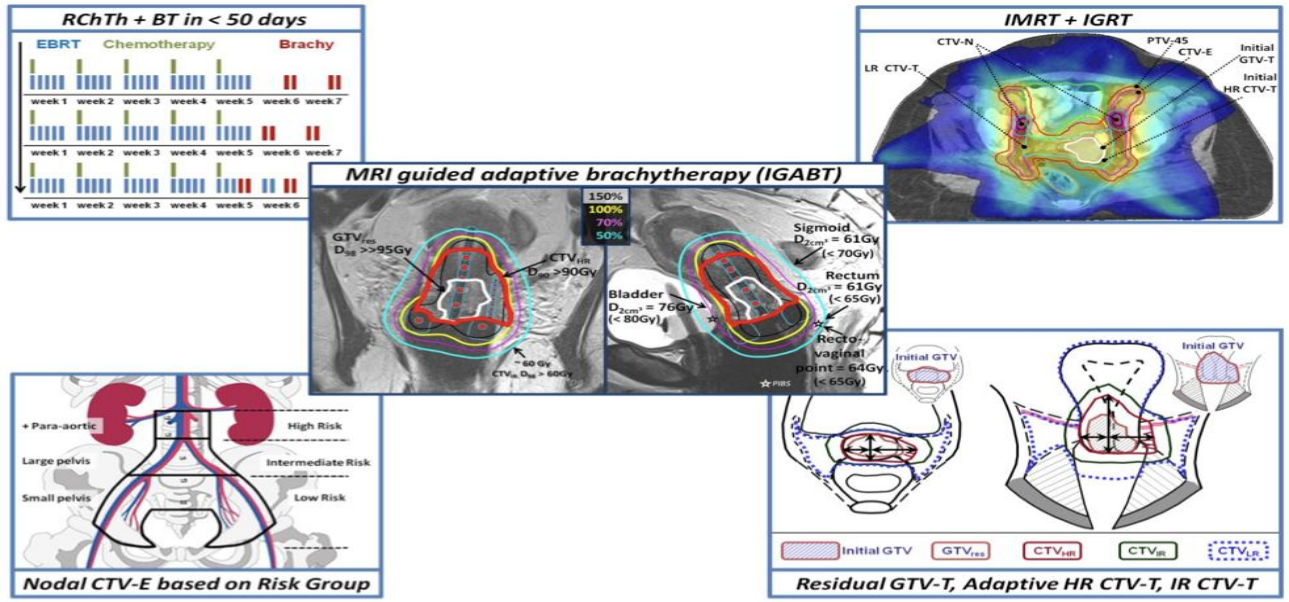
Schmid et al, J Clin Oncol 41:1933-1942. © 2023 by American Society of Clinical Oncology

Basis of EMBRACE 2

- Emerging evidence from the RetroEMBRACE and EMBRACE I studies has demonstrated that clinical outcome is related to dose prescription and technique.
- The next logical step is to demonstrate excellent clinical outcome with the most advanced EBRT and brachytherapy techniques based on an evidence based prospective dose and volume prescription protocol.

Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer

EMBRACE-II



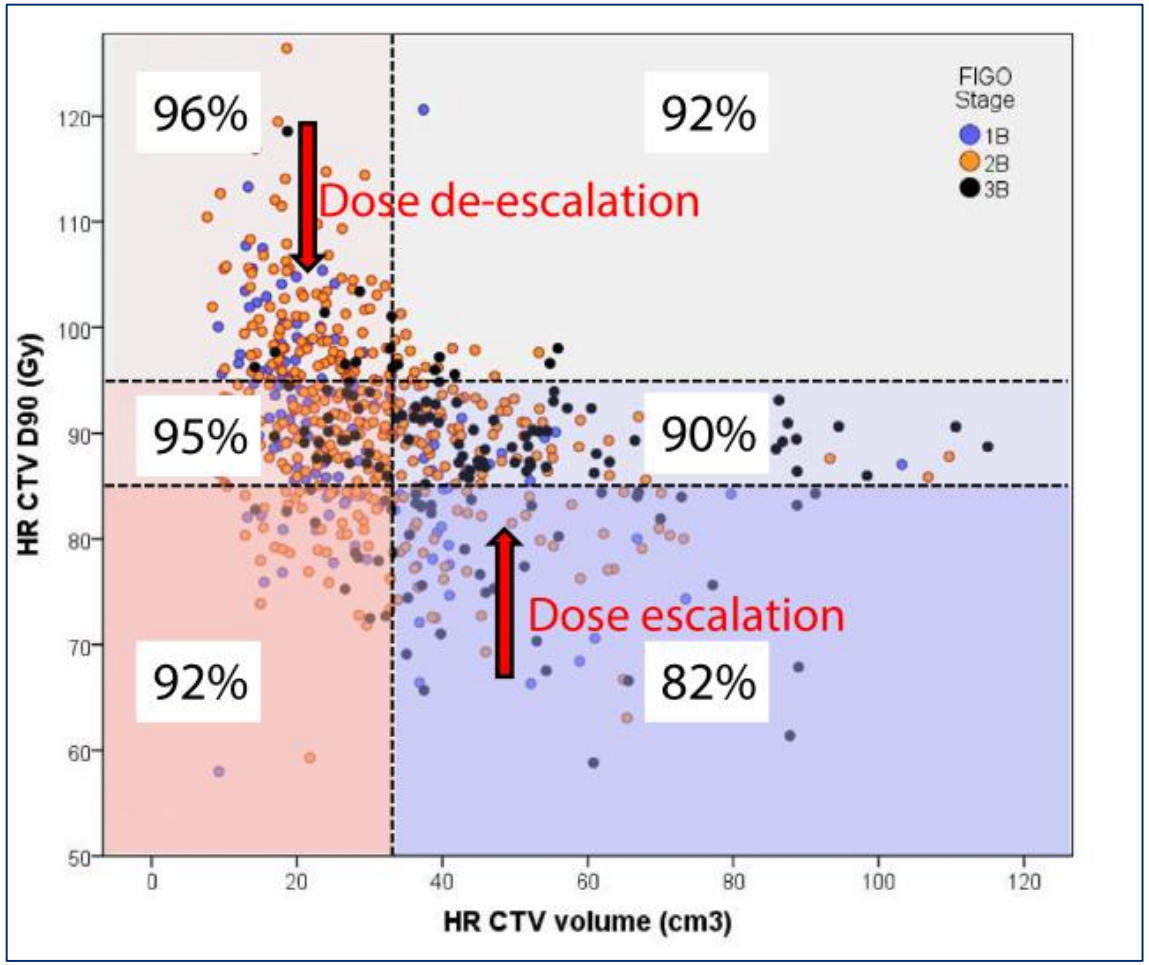
- Interventional
- Observational
- multicentre study

Aims to benchmark

- a high level of local, nodal and systemic control
- limiting morbidity
- using state of the art treatment including an advanced target volume selection and contouring protocol for EBRT and brachytherapy
- a multi-parametric BT dose prescription protocol (clinical validation of dose constraints)
- use of advanced EBRT (IMRT and IGRT) and brachytherapy (IC/IS) techniques (clinical validation).
- The study also incorporates translational research including imaging and tissue biomarkers

EMBRACE II
RATIONALE FOR CHANGE OF PRACTICE

1. Application of IC/IS brachytherapy



- Shows that suboptimal local control is predicted for the pts not achieving the 85 Gy constraint.
- The ability to reach dose constraints for both targets and OARs - involves increased use of IC/IS BT
- A significant number of pts, mainly with small tumours at the time of BT, CTVHR (<30 cm3), were treated to high doses which did not translate to higher local control
- There is therefore potential to de-escalate the dose in these patients to reduce OAR dose.

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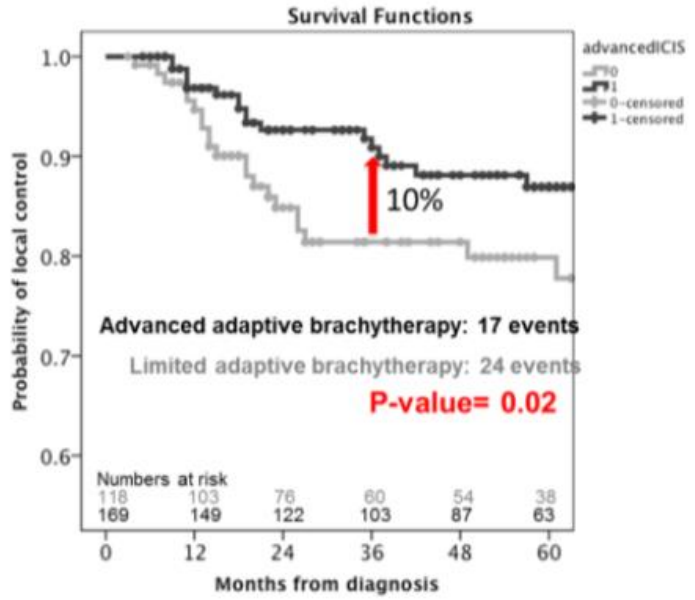
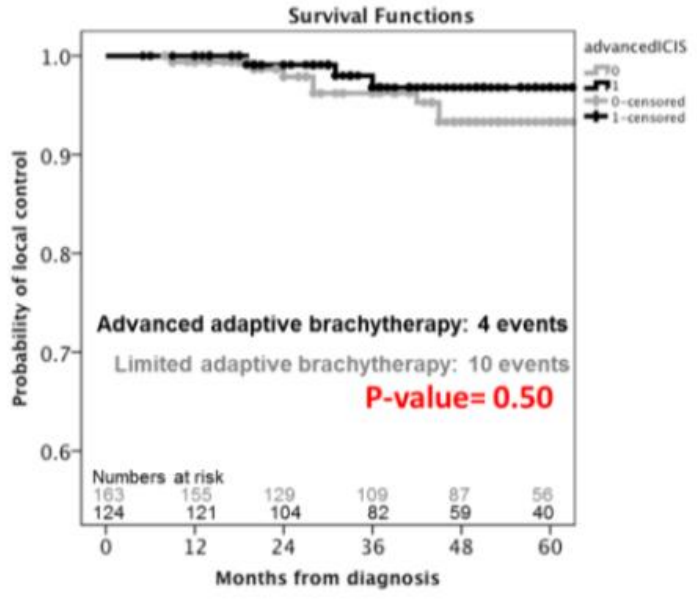
Local control

CTVHR ≥ 30 cm^3



CTVHR < 30 cm^3



gure 3.7. Local control for large (left panel) and small (right panel) CTV_{HR}, as depending on routine application of IC/IS technique. Advanced adaptive brachytherapy implies that >20% of the patients in the cohort were treated with IC/IS. Limited adaptive brachytherapy implies that the majority of patients (<20%) were treated with IC technique. Data from retroEMBRACE (Fokdal L. et al. 2015, RetroEMBRACE work in progress).

2. Vaginal Dose de-escalation

- It is hypothesized that limiting the dose to the ICRU recto-vaginal point to < 65 Gy and the EBRT dose to 45 Gy will reduce the incidence of G2 or higher vaginal stenosis from 21% to 14%

- In BT - the relative vaginal loading is usually around 50%. If the vaginal loading is decreased to 33%, it should reduce the ICRU recto-vaginal dose significantly

- A well defined lower EBRT target border for EBRT, and a specific vaginal dose reporting system referring to the Posterior-Inferior Border of the Symphysis (PIBS) , should reduce the EBRT dose to the lower and mid vagina.

3. IMRT and IGRT

- With the implementation of consistent target contouring protocol -IMRT and daily IGRT and a 5 mm PTV margin, the V43Gy can be significantly reduced

	Pelvic Irradiation	Pelvic RT + PA vol
EMBRACE 1 – V43 Gy	**2500 cm3**	**3200 cm3**
IMRT, IGRT with 5 mm PTV margin	**1500 cm3**	**2200 cm3**

4. Nodal Target Selection

- RetroEMBRACE and EMBRACE I outcome indicates that PA failure is the major challenge for nodal control.

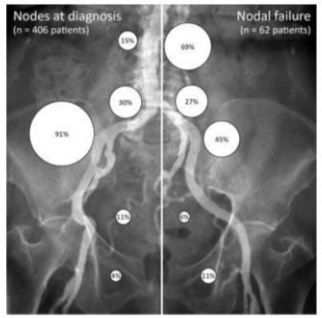


Figure 3.13. Patterns of spread for lymph node disease at time of diagnosis (left panel) and at time of first nodal failure (right panel) (Nomden C. et al. EMBRACE work in progress).

- This can be addressed using
  - pre-therapeutic laparoscopic para-aortic lymph node dissection
  - by increasing the use of para-aortic irradiation in selected patients
    - The number of pelvic nodes >3
    - location - common iliac
    - PET avid nodes
    - to a lesser extent size of nodes

Lymph Node positivity

- FDG PET positive
- CT or MRI : short axis ≥ 1 cm
- MRI : short axis between 0.5-1.0 cm with pathological morphology:
  - irregular border,
  - high signal intensity and/or
  - round shape

5. Overall Treatment Time

To improve OTT, efficient organization of the whole multimodal treatment is required.

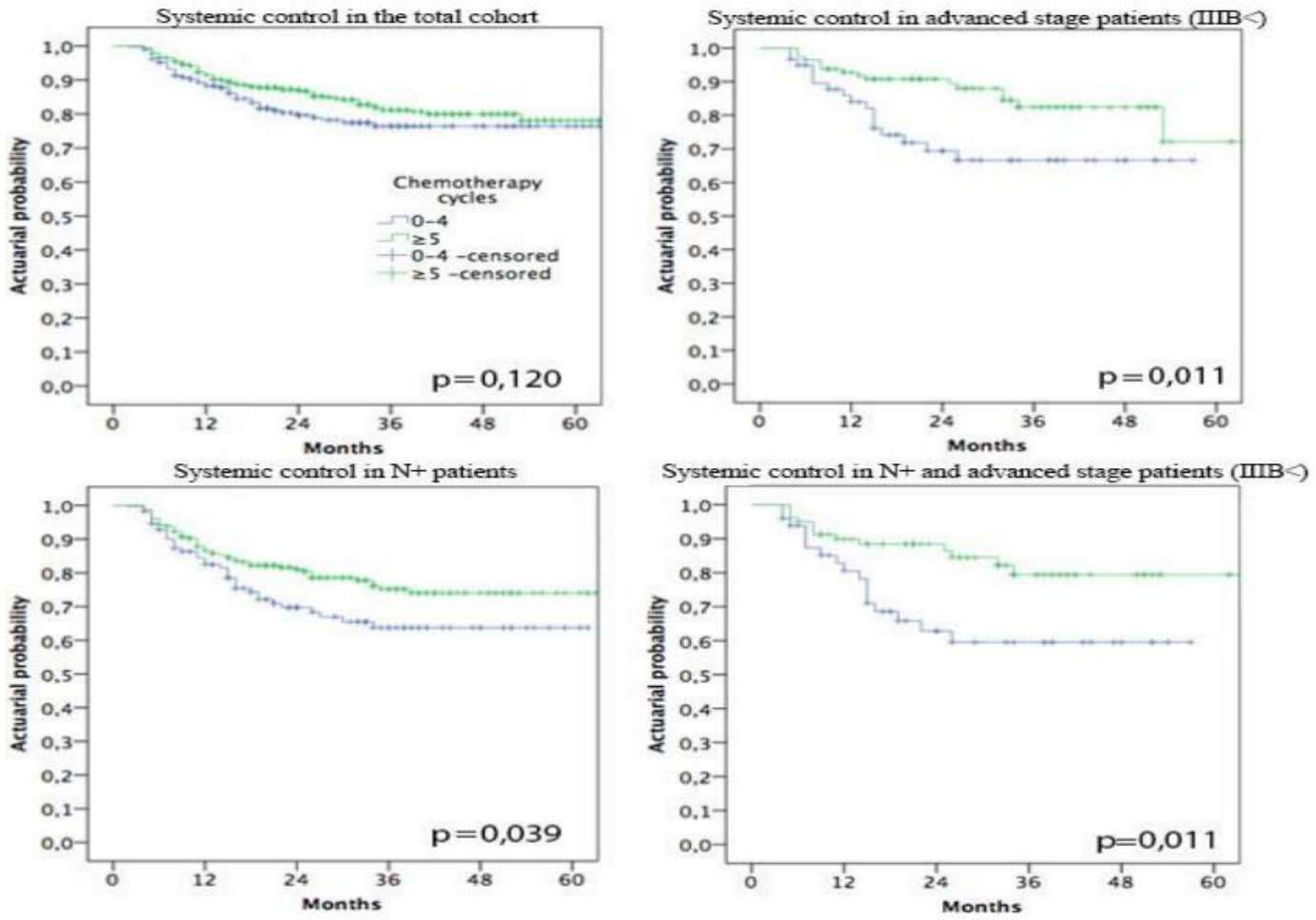
- Delivering EBRT in a max. of 25 fractions and use of SIB (in pts with LN involvement)
- Minimizing treatment interruptions as much as possible
- Planning the timing of BT carefully.
- OTT <50 days

Prolongation of OTT results in decreased pelvic control rate of 0.85% per day for all the pts

6. Chemotherapy

- EMBRACE II protocol emphasizes on administration of adequate doses of chemotherapy according to evidence from the EMBRACE I study and in accordance with inter- national guidelines.

- >/=5cycles of chemotherapy



Impact of number of chemotherapy cycles on systemic control. Advanced stage is defined as stage III and IV (Fortin I. et al. 661 Abstract ASTRO 2015, EMBRACE work in progress)

Study design

- **Interventional, prospective** study with some area of **observational** research

Primary Endpoints	Secondary Endpoints
1.Local control 2. Nodal control, 3. systemic control, 4. overall survival 5. morbidity and quality of life.	1. Cancer specific survival 2. Disease Specific Survival

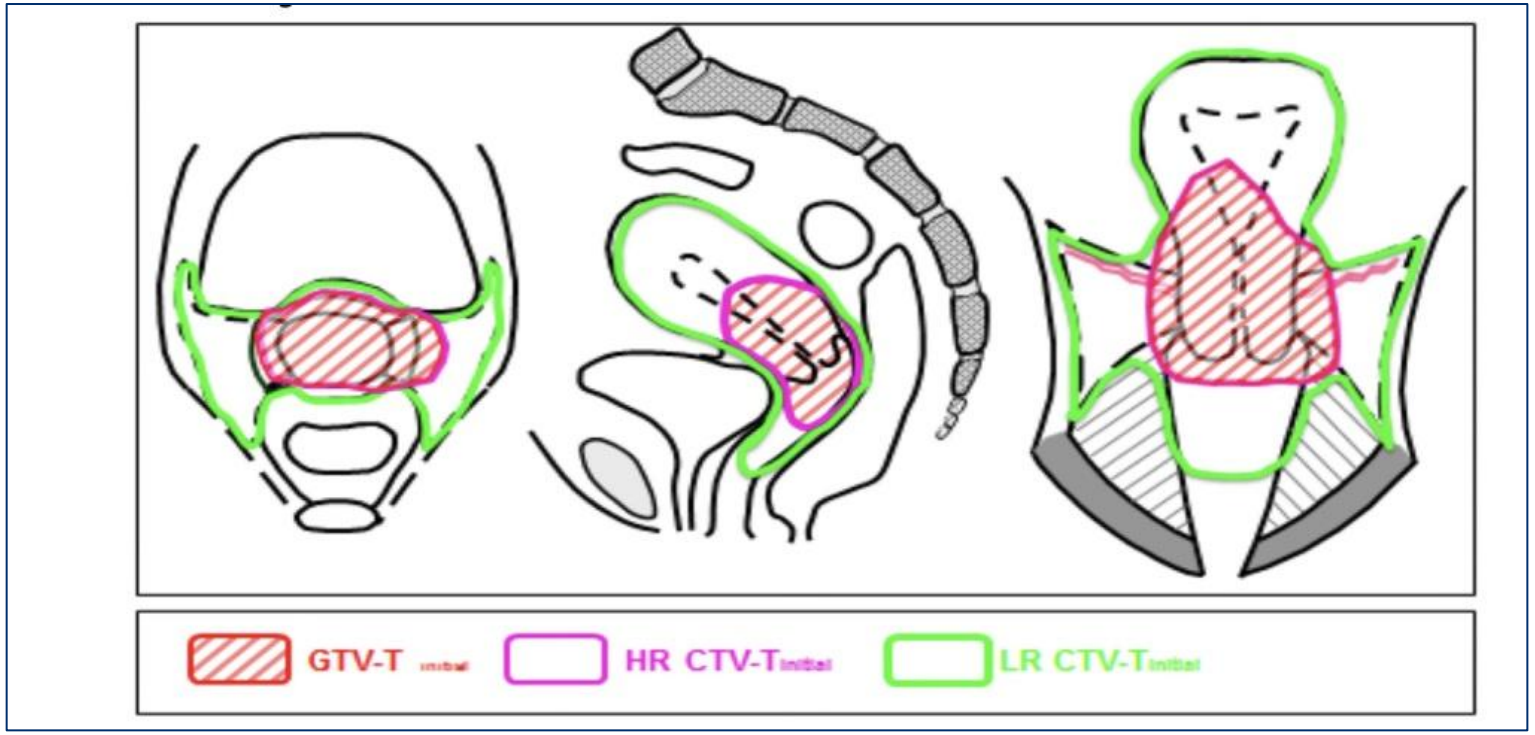
Interventions/Proposed change of Practice

1. Increased use of IC/IS BT
2. Reduction of BT vaginal source loading
3. Protocol for target and OAR contouring for EBRT and BT
4. Adaptation of EBRT nodal elective CTV according to risk of nodal and systemic recurrence
5. Use of IMRT/VMAT and daily IGRT for EBRT delivery (45 Gy/25 frs to elective target volume)
6. Use of SIB for pathological lymph nodes
7. Systematic application of con. CT
8. Reduction of OTT

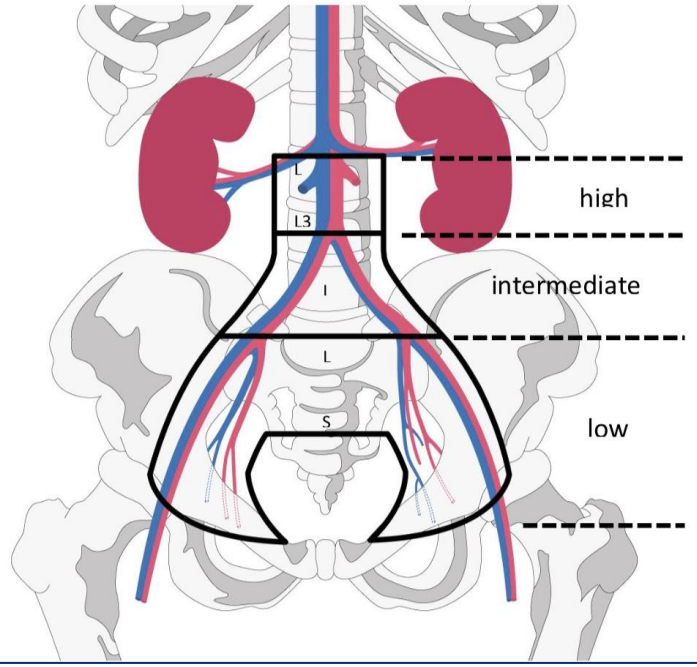
Dose to pathological LNs

- Total dose to PTV-Ns - 60 Gy EQD2 can be achieved with the following fractionation schedules:
- Inside true pelvis: EBRT with SIB 55Gy/25 frs physical dose. This is equivalent to 56 Gy EQD2 EBRT + 3-4 Gy EQD2 from BT which results in a total dose of ~60 Gy EQD2.
- Outside true pelvis: EBRT with SIB 57.5 Gy/25 frs physical dose. This is equivalent to ~59 Gy EQD2 and BT dose contribution is negligible

EBRT – PRIMARY TUMOR TARGETS



EBRT- NODAL TARGETS (ELECTIVE)



Risk Group LN	Definition	EBRT lymph node regions
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion	**"Small Pelvis"** internal iliac external iliac obturator presacral
Intermediate Risk (IR LN)	Not low risk No high risk features	**"Large Pelvis"** Nodes included in "Small Pelvis" and common iliac region (including the aortic bifurcation). In addition: • inguinal in case of distal vaginal involvement. • Mesorectal space in case of mesorectal nodes and advanced local disease
High Risk (HR LN)	Based on nodal pathology • ≥ 1 pathologic node at common iliac or above • OR ≥ 3 pathologic nodes	**"Large Pelvis + Para-aortic"** Nodes included in "Large Pelvis" and para-aortic region with the upper border of CTV minimum at the level of renal veins (usually incl. L2), and at least 3 cm cranial of the highest pathological node in case of para-aortic nodes].

Dose constraints for EBRT for N0 and N1 patients..

	No lymph node involvement		Involved lymph nodes	
	Hard dose constraints	Soft dose constraints	Hard dose constraints	Soft dose constraints
PTV45	V42.75 Gy > 95% Dmax < 107%	V42.75 Gy = 95%	V42.75 Gy > 95%	V42.75 Gy = 95% Dmax < 107% for helper structure: PTV45 – (PTV-N(#) + 1 cm)
ITV45	Dmin > 95%		Dmin > 95%	
CTV-HR + 10 mm		Dmax < 103%		Dmax < 103% for helper structure: CTV-HR + 10 mm – (PTV-N(#) + 1 cm)
PTV-N(#)			D98% > 90% of prescribed LN dose Dmax < 107% of prescribed LN dose	D98% = 90% of prescribed LN dose
CTV-N(#)			D98% > 100% of prescribed LN dose	D50% > 102% of prescribed LN dose
Bowel	Dmax < 105%	V40Gy < 250 cm^{3*} V30Gy < 500 cm^{3*}	Dmax < 105% in regions outside 10–15 mm from PTV-N	When no para-aortic irradiation: V40Gy < 250 cm^{3*} V30Gy < 500 cm^{3*} For para-aortic irradiation: V40Gy < 300 cm^{3*} V30Gy < 650 cm^{3*}
Sigmoid	Dmax < 105%		Dmax < 105% in regions outside 10–15 mm from PTV-N	
Bladder	Dmax < 105%	V40Gy < 60%* V30Gy < 80%*	Dmax < 105% in regions outside 10–15 mm from PTV-N	V40Gy < 60%* V30Gy < 80%*
Rectum	Dmax < 105%	V40Gy < 75%* V30Gy < 95%*	Dmax < 105% in regions outside 10–15 mm from PTV-N	V40Gy < 75%* V30Gy < 95%*
Spinal cord	Dmax < 48 Gy		Dmax < 48 Gy	
Femoral heads	Dmax < 50 Gy		Dmax < 50 Gy	
Kidney	Dmean < 15 Gy	Dmean < 10 Gy	Dmean < 15 Gy	Dmean < 10 Gy
Body	Dmax < 107%		Dmax < 107% in regions outside 10–15 mm from PTV-N	
Vagina (if not involved)		$D_{PRS-2cm}$ < 5 Gy		$D_{PRS-2cm}$ < 5 Gy
Conformality		1.10 (V43/Volume of PTV) 1.55 (V36Gy/Volume of PTV)		1.10 (V43Gy/Volume of PTV) 1.55 (V36Gy/Volume of PTV)
Transposed ovaries	Dmean < 8 Gy	Dmean < 5 Gy	Dmean < 8 Gy	Dmean < 5 Gy
Duodenum	V55 < 15 cm^3		V55 < 15 cm^3	

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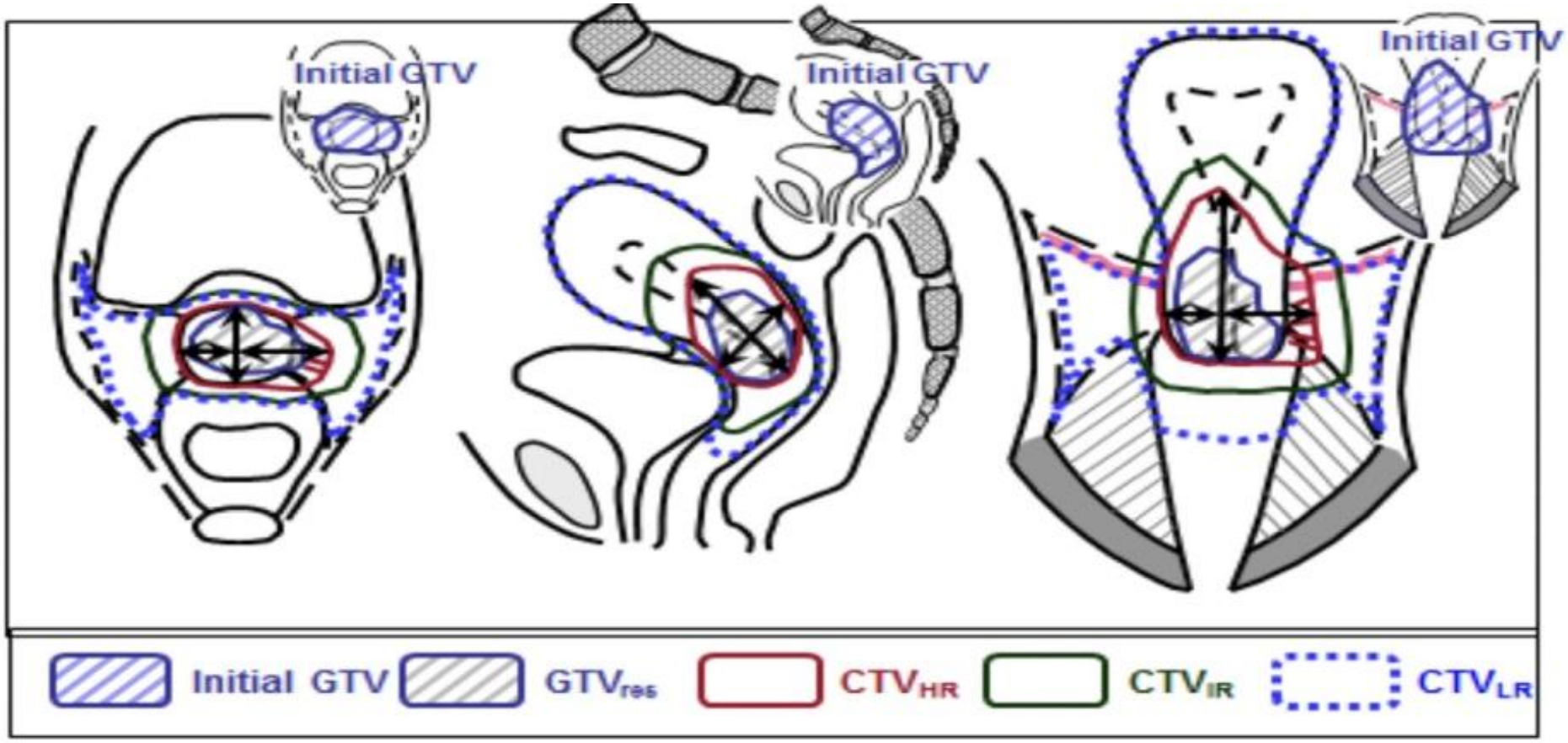
BRACHYTHERAPY



FINAL PLAN EVALUATION

Target	D90 CTV HR EQD2 (10)	D98 CTV HR EQD2 (10)	D98 GTV res EQD2 (10)	D98 CTV IR EQD2 (10)	Point A EQD2 (10)
Planning Aims	>90 Gy <95 Gy	>75 Gy	>95Gy	>60 Gy	>65 Gy
Limits for Prescribed doses	>85 Gy	-	> 90 Gy	-	-

OAR	Bladder D2cc – EQD2(3)	Rectum D2cc – EQD2(3)	Rectovaginal point– EQD2(3)	Sigmoid D2cc – EQD2(3)	Bowel D2cc – EQD2(3)
Planning Aims	< 80 Gy	<65	<65	<70	<70
Limits for prescribed doses	<90 Gy	<75	< 75	<75	<75

FOLLOW UP

- Follow-up with gynaecological examination will occur at 6, 9, 12, 18, 24, 30, 36, 48 and 60 months after treatment.
- Pelvic MRI ± para-aortic CT - at 3 mths and repeated at 12 months after treatment or in case of suspected recurrence.
- For uncertain remission, further imaging will be carried out at 6 months.
- Morbidity, PRO and QoL will be scored at baseline and at each follow-up visit.

SUB STUDIES

Vaginal morbidity sub-study - Prospectively dosimetric and treatment parameters will be correlated with vaginal morbidity. The impact of regular vaginal dilatation on the vaginal adhesions, length and width will also be evaluated.

Translational tissue-based research - informed consent for collecting additional biopsy and blood will be obtained and research will focus on validating biomarkers of distant metastasis, local and nodal recurrence

Bio-imaging - will evaluate the value of multiparametric quantitative MR imaging as biomarker for identifying patients at increased risk of recurrence.

May 5, 2025, 08:55

EMBRACE II Trial at ESTRO 2025. Overall Results of on IGRT-IMRT+cisplatin +MR-IGABT in LA Cervix Cancer

The study involved multiple hypotheses

- MRI and PET-CT for staging
- Adaptive target definition
- highly conformal multi-parametric treatment planning
- image-guided delivery techniques like IGRT-IMRT
- LN-SIB
- PAO-RT
- MR-guided adaptive brachytherapy (MR-IGABT)

Study methods and Design

- N= 1482 patients from 49 centers
- The median age- 51 years(68% having a WHO PS of 0 and 30% with score 1)
- 50% had N1 disease, 8.6% had M1PAO .
- The median GTV-Tinit was 37 cm^3
- 74% of patients receiving IC-IS MR-IGABT.

- Median follow-up: 39 months (time to event/vital status).

RESULTS

	3 yr	5yr
LCR	93%	
Pelvic control	94%	
Distant control beyond pelvis	93%	
PFS	78%	
DSS	89%	
OS	87%	82%

Morbidity and Toxicity

- Late morbidity was tracked, with a total of 170 late events.
- Late G3-G5 morbidity occurred in 8.9% of patients, with urinary toxicity being the most prevalent.
- Late life-threatening morbidity (Grade 4) was observed in 1% of patients
- There were two treatment-related deaths reported.

Comparison with EMBRACE I

- When comparing EMBRACE II with EMBRACE I, the results showed improved disease control and survival outcomes, especially for high-risk patients (T4, T3, N2).
- data from EMBRACE-II - showing a 5% reduction in the event rate of extra-pelvic recurrences compared with EMBRACE-I
- Significant reduction in late toxicity (G3-G5) was observed, with overall risk reduction in disease progression and death, as well as a notable decrease in G3-G5 complications.

Key takeaways

- EMBRACE II confirmed hypotheses regarding treatment protocols and demonstrated substantial improvements in clinical outcomes and disease control.
- The treatment protocol, which included advanced radiation therapy techniques and integrated chemotherapy, proved to be effective while maintaining manageable toxicity rates.
- EMBRACE II is now considered the new standard of care for locally advanced cervical cancer, especially in high-risk groups, showing significant improvements in both disease control and the reduction of late-stage toxicity

Embrace III

- The next step is to identify patient-related, disease-related, and treatment-related risk factors and biomarkers for outcome to define risk groups, which can be used for intensification of multimodality treatment in high-risk patients and de-escalation of treatment in low-risk patients.

MAX Healthcare

EMBRACE-III Triplet

Improving cervical cancer care through personalized radiation therapy

PROMISE, **IMPACT**, and **REWIND** studies for image-guided adaptive brachytherapy.

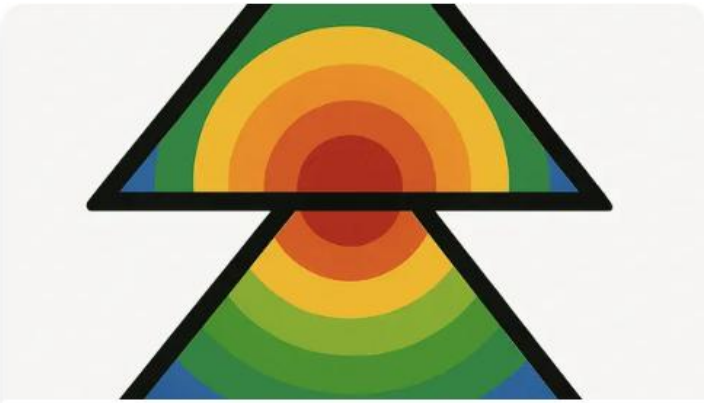
About Us | Join Us

Clinical Studies

Participate in groundbreaking research that shapes the future of radiation therapy for cervical cancer.

REWIND

Retrospective Real-World Interpretation of Data

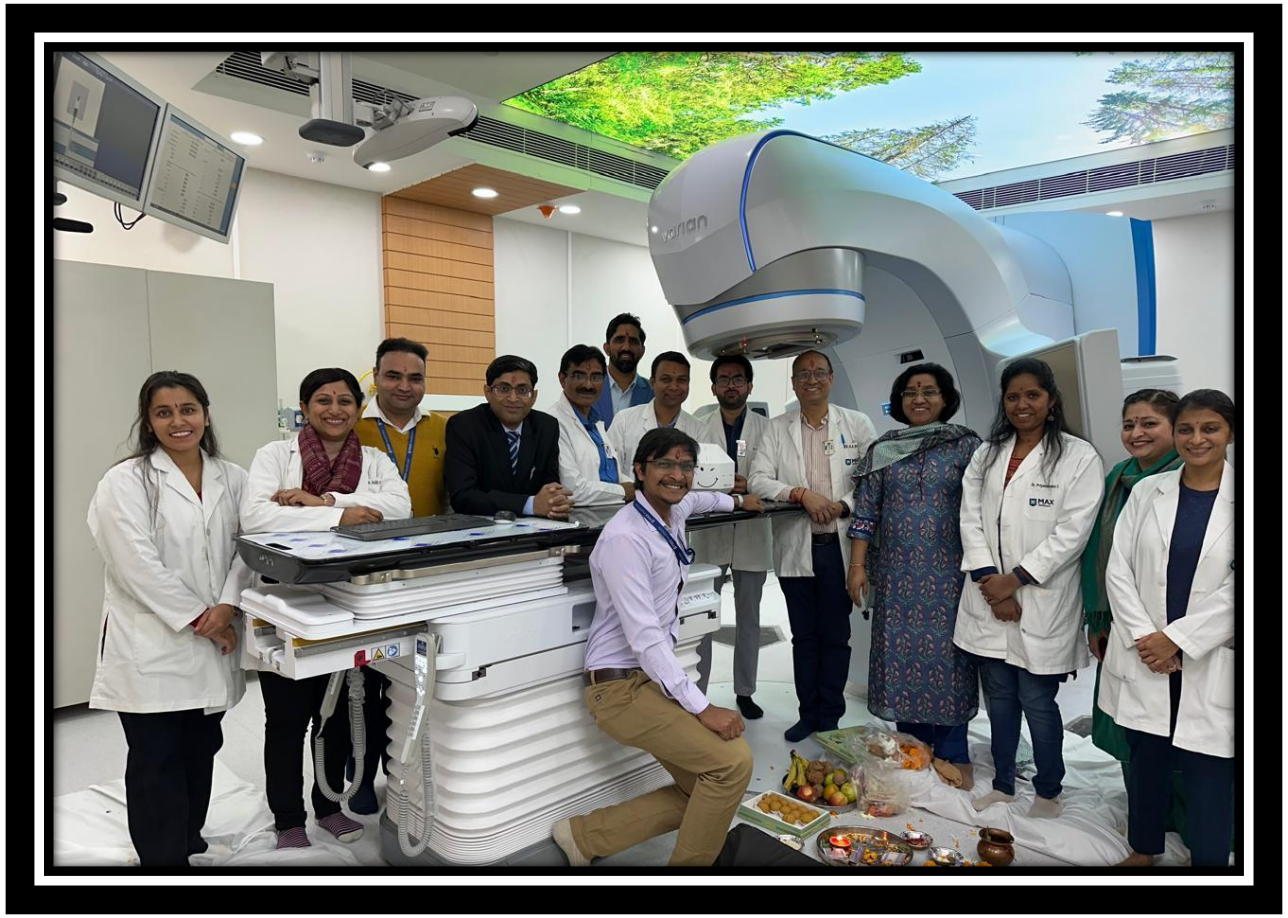


IMPACT

CT-based Image Guided Adaptive Brachytherapy

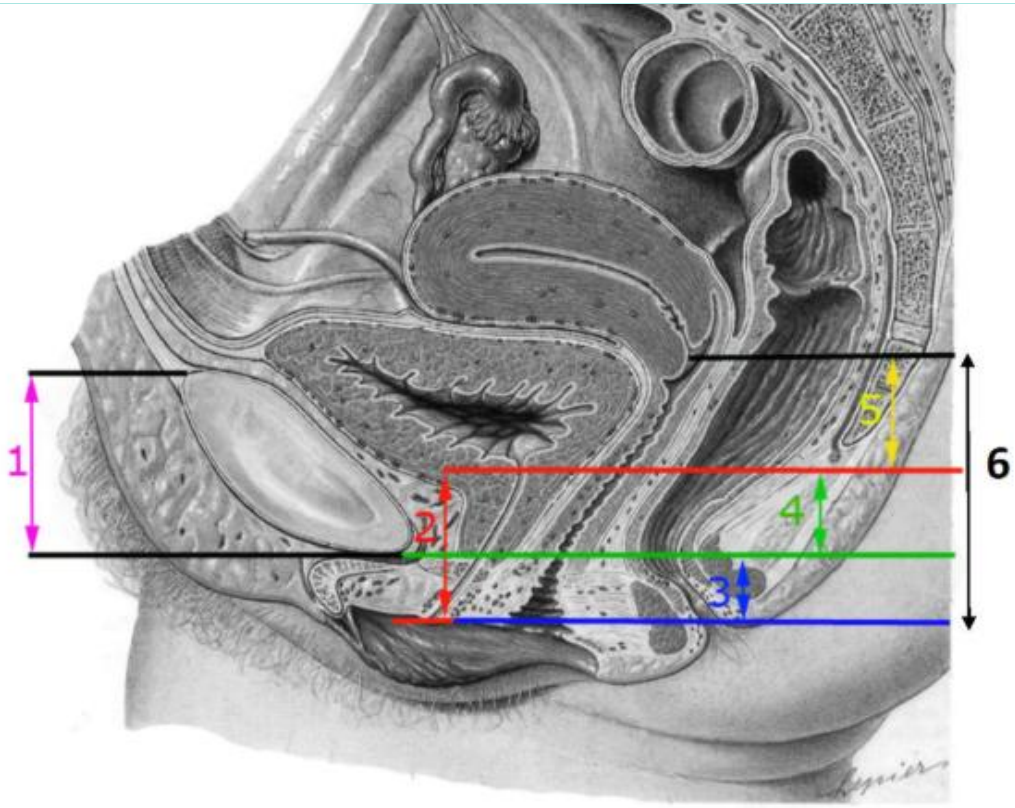
PROMISE

Prospective Real-world MRI-based Treatment


varian


Thank You!

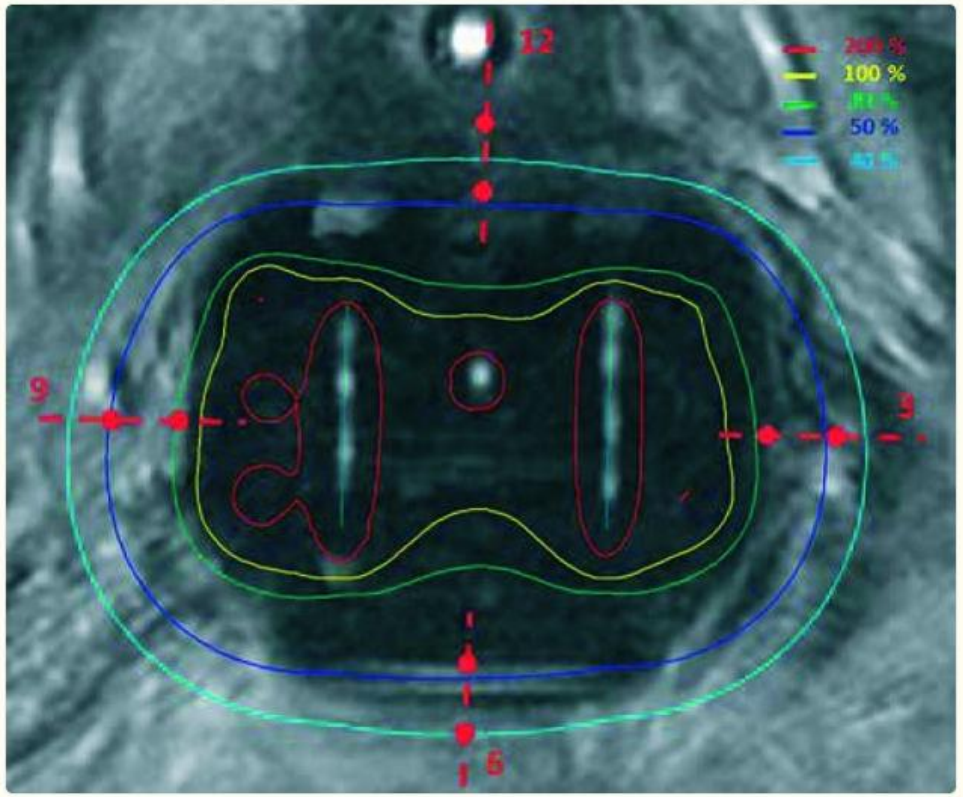
The PIBS vaginal-dose point was defined 2 cm posterior from the Posterior-Inferior Border of the pubic symphysis and for BT at the point of this line where it crosses the applicator tandem. From there, two additional points 2 cm up and down along the vaginal axis, are defined with PIBS+2 representing the mid of the vagina and PIBS-2 representing the introitus level



1. **Pubic symphysis length**: 32 mm [1]
2. **Urethral length**: 36-38 mm [2,3]
3. **Lower Vagina: from introitus to posterior-inferior border of symphysis (PIBS)[4]**
4. **Mid vagina: from posterior-inferior border of symphysis (PIBS) to urethrovesical junction [4]**
5. **Upper vagina: from urethrovesical junction to cervical os [4]**
6. = 3+4+5: **Vaginal length** : 63-77 mm [5,6]

Bladder filling status seems to impact more on the uterine motion and rectal filling more on the motion of the cervix and upper vagina.
A systematic review of organ motion in cervix cancer summarises studies on uterine and cervix movements (Jadon R. et al. 2014).
For the cervix, the reported mean movement ranges in the anterior-posterior direction between 2-21 mm, with standard deviations ranging between 3.5-10 mm; superior-inferior 2-16 (SD range 3-8 mm); lateral 0-10 mm (SD range 1-7 mm).
For the uterine part corresponding figures are anterior-posterior 4-14 mm (SD range 9-12 mm); superior-inferior 2-10 (SD range 7- 12 mm); lateral 0-7 mm (SD range 1-8 mm

To exactly determine these vaginal top points, one can focus on the MRI para-axial image containing the ovoids, where the source path inside the ovoids can be visualized. In this plane, points at the surface and at 5 mm depth of the left ovoid, at the central needle level (3 o'clock), and the equivalent points in the right ovoid (9 o'clock) can be defined. In the tangential line connecting both ovoids at the anterior part, the middle point (12 o'clock) and the point at 5 mm depth can be established. Similarly, the equivalent points in the posterior part (6 o'clock) and at 5 mm depth are also determined. With that procedure, the extra eight points on the MRI axial image for BT are defined.



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Determination of eight additional reference points for BT in the upper vagina from axial MRI