Evidence and practice changing treatments in gynecological tumors

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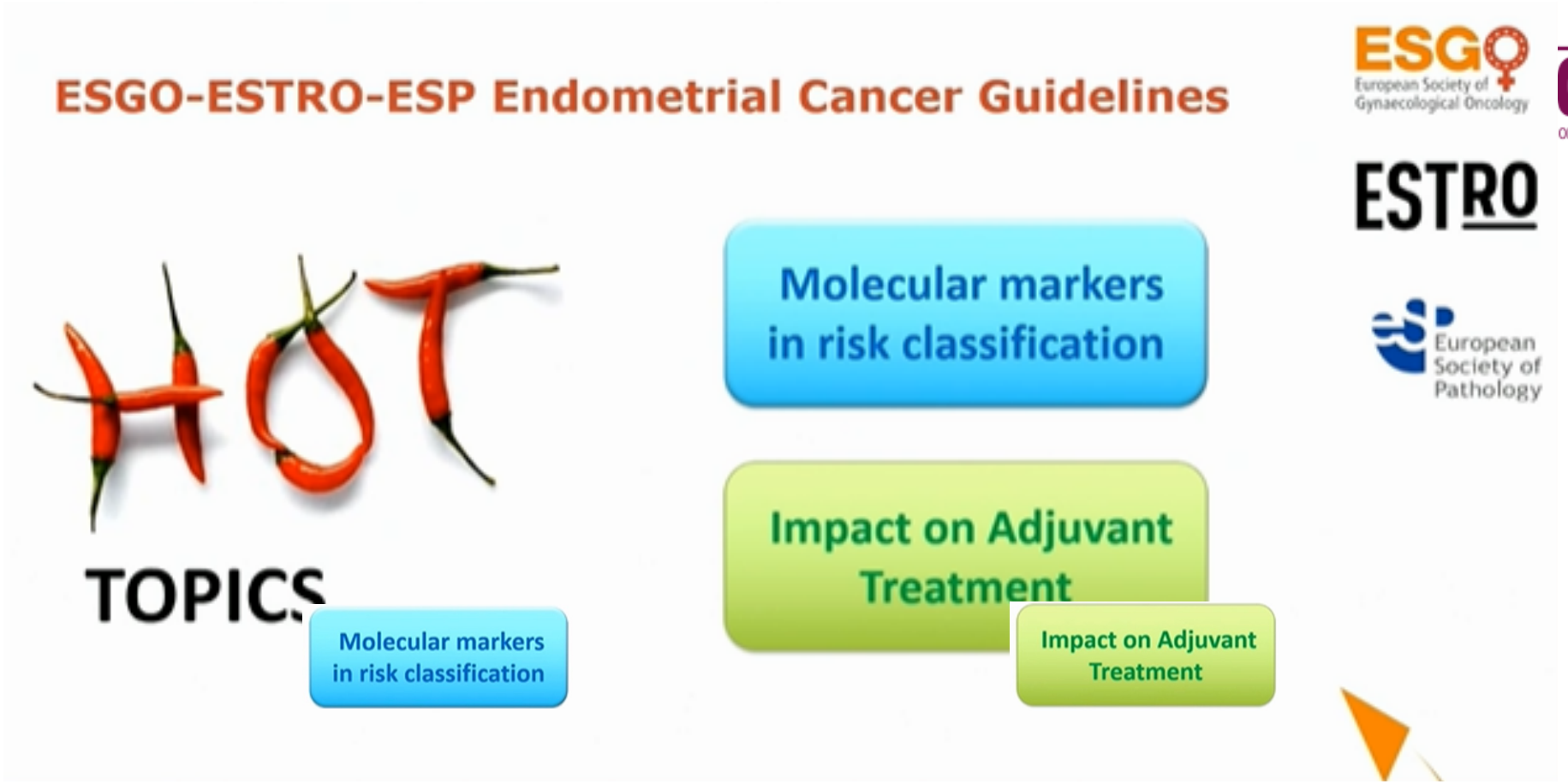
No conflict of interest

Endometrial Cancer

Guidelines



Oaknin A, Lancet Oncol - 2022

Guidelines

The molecular EC classification has the potential to improve patient management, reducing over- and undertreatment

Table 2. EC risk groups

Risk group	Description[a]
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR[b] and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; for stage III *POLE*mut cancers[c]
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype[b]

dMMR, mismatch repair deficient; EC, endometrial cancer; G1-G3, grade 1-3; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MSI-H, microsatellite instability high/hypermutated; NSMP, no specific molecular profile; p53-abn, p53-abnormal; *POLE*mut, polymerase epsilon-ultramutated.

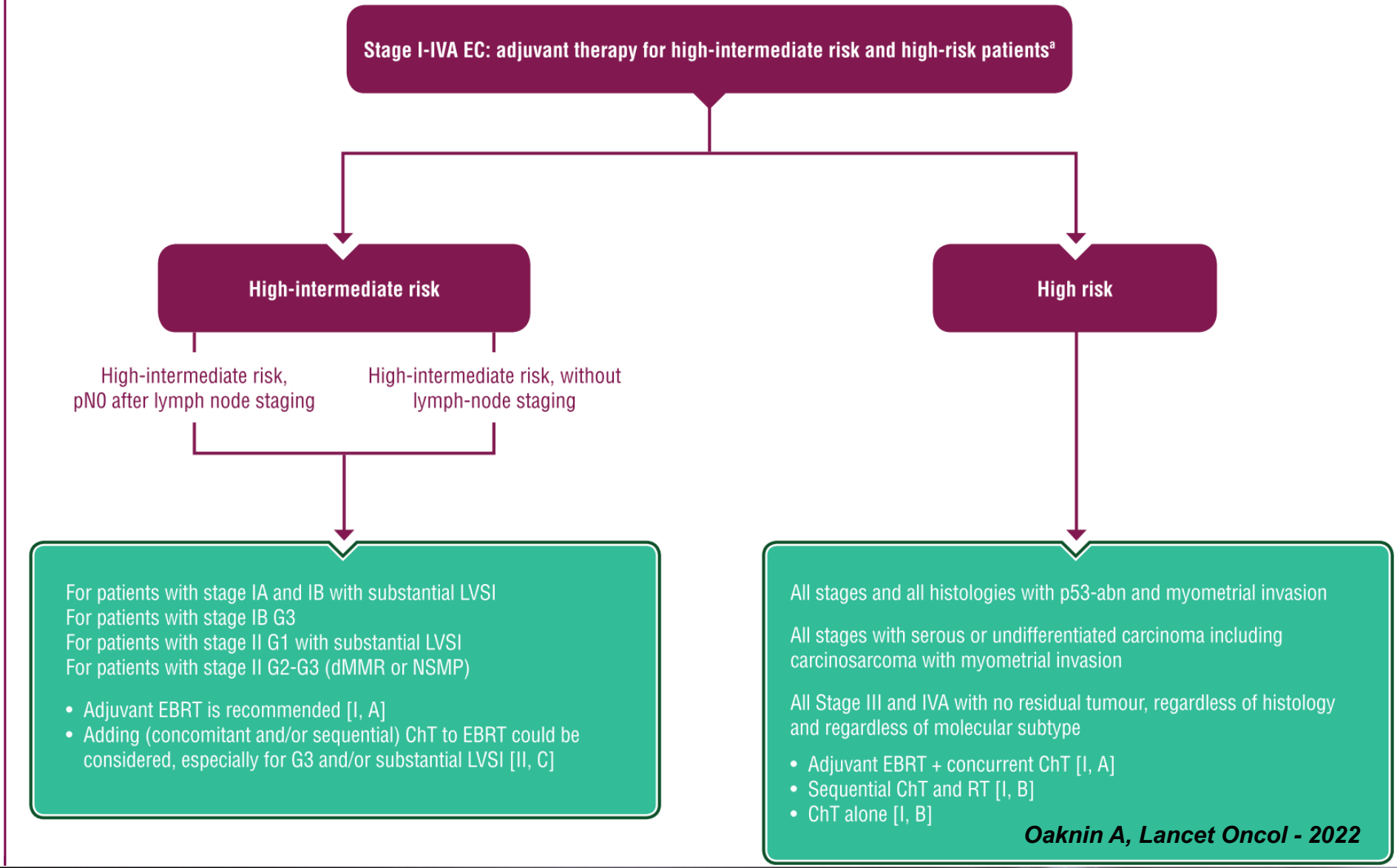
[a]Stage III-IVA if completely resected without residual disease; table does not apply to stage III-IVA with residual disease or for stage IV.

[b]dMMR and MSI-H: Both terms identify a similar EC population. Identification of a defective mismatch repair pathway by IHC (i.e. dMMR) or sequencing to determining microsatellite instability (i.e. MSI-H).

[c]*POLE*mut stage III might be considered as low risk. Nevertheless, currently there are no data regarding safety of omitting adjuvant therapy.

Oaknin A, Lancet Oncol - 2022

Guidelines



Oaknin A, Lancet Oncol - 2022

Guidelines

Current Prognostic and Predictive Biomarkers for Endometrial Cancer in Clinical Practice: Recommendations/Proposal from the Italian Study Group

Gian Franco Zannoni[1,2], Emma Bragantini[3], Francesca Castiglione[4], Matteo Fassan[5], Giancarlo Troncone[6], Frediano Inzani[1], Anna Pesci[7], Angela Santoro[1] and Filippo Fraggetta[8,9]*

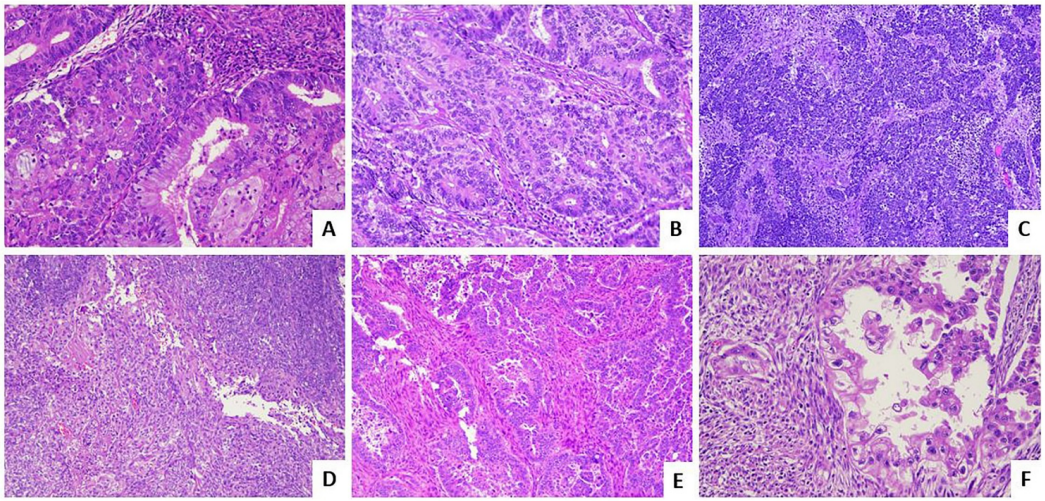


FIGURE 1 | Histological subtypes of endometrial carcinoma: an overview. **(A)** An endometrioid carcinoma G1 FIGO with mucinous features (LSAB, 10×). **(B)** An endometrioid carcinoma G2 FIGO (LSAB, 10×). **(C)** An endometrioid carcinoma G3 FIGO with basaloid features (LSAB, 4×). **(D)** An endometrioid carcinoma G3 FIGO with spindle cell features (LSAB, 4×). **(E)** A serous carcinoma (LSAB, 10×). **(F)** A clear cell carcinoma (LSAB, 20×).

Zannoni GF, Front. Oncol. 2022

Follow-up

original reports

Effectiveness of Intensive Versus Minimalist Follow-Up Regimen on Survival in Patients With Endometrial Cancer (TOTEM Study): A Randomized, Pragmatic, Parallel Group, Multicenter Trial

Paolo Zola, MD[1]; Giovannino Ciccone, MD, PhD[2]; Elisa Piovano, MD, PhD[3]; Luca Fuso, MD, PhD[4]; Daniela Di Cuonzo, MSc, PhD[2]; Anna Castiglione, MSc[2]; Eva Pagano, MSc[2]; Elena Peirano, MD[1]; Fabio Landoni, MD[5]; Enrico Sartori, MD[6]; Fabrice Narducci, MD[7]; Oscar Bertetto, MD[8]; Annamaria Ferrero, MD, PhD[4]; and the TOTEM Collaborative Group

42 hospitals (I-F)

1871 pts

Absolute improvement 5% of the 5y-OS with INT regimen

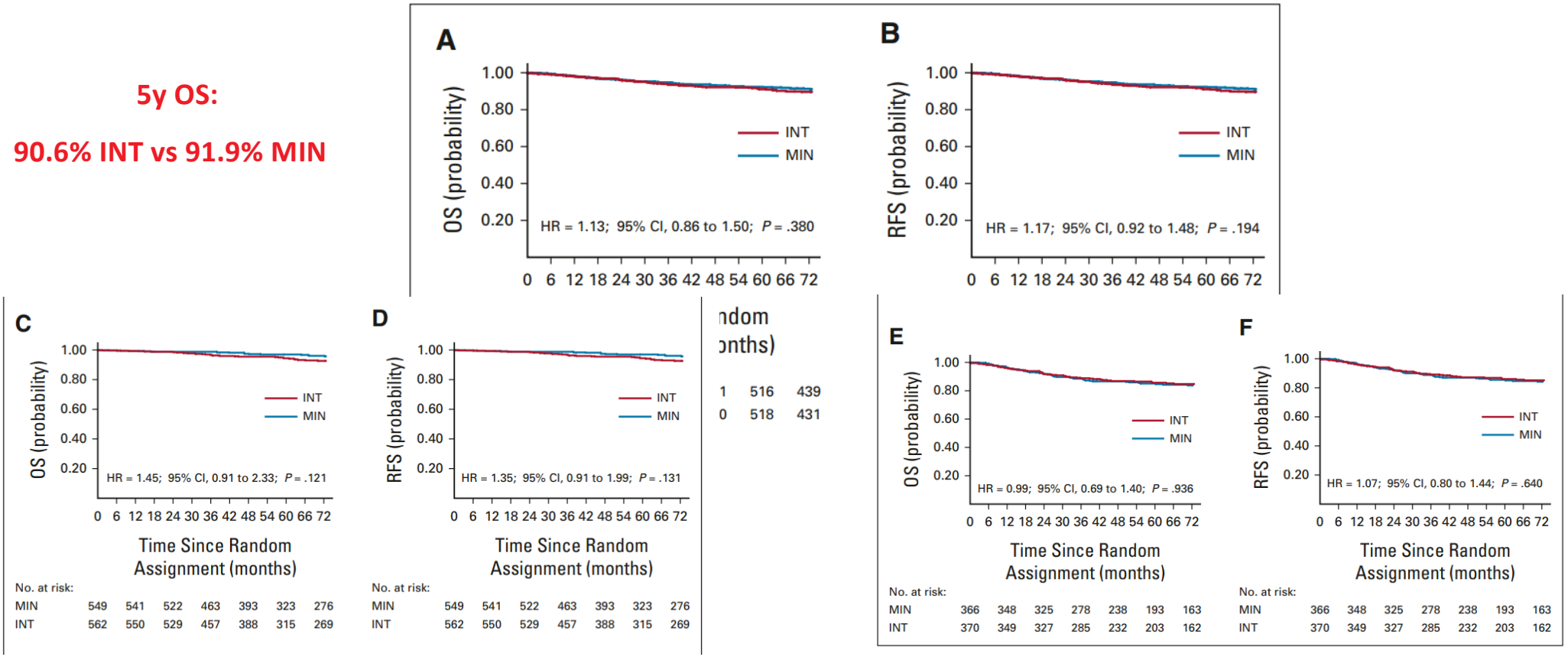
Zola P, JCO 2022

Follow-up

5y OS:

90.6% INT vs 91.9% MIN

FIG 2. OS and RFS in the overall population (A, B), in low-risk patients (C, D), and in high-risk patients (E, F), by follow-up regimen. HR, hazard ratio; INT, intensive; MIN, minimalist; OS, overall survival; RFS, relapse-free survival.



CONCLUSION An INT follow-up in endometrial cancer–treated patients does not improve OS, even in high-risk patients. According to available evidence, there is no need to routinely add vaginal cytology, laboratory, or imaging investigations to the MIN regimens used in this trial.

Zola P, JCO 2022

Follow-up

TABLE A1. Follow-Up Visits and Examinations by Risk of Relapse (LoR, A; HiR, B) and Follow-Up Regimen

A. LoR Follow-Up Regimen and Procedures	Months Since Random Assignment														
	0	4	6	8	12	16	18	20	24	30	36	42	48	54	60
MIN															
Clinical examination	X		X		X		X		X	X	X	X	X	X	X
INT															
Clinical examination	X	X		X	X	X		X	X	X	X	X	X	X	X
Vaginal cytology					X				X		X		X		X
CT scan of the chest, abdomen, and pelvis					X				X						

Zola P, JCO 2022

RT Technique

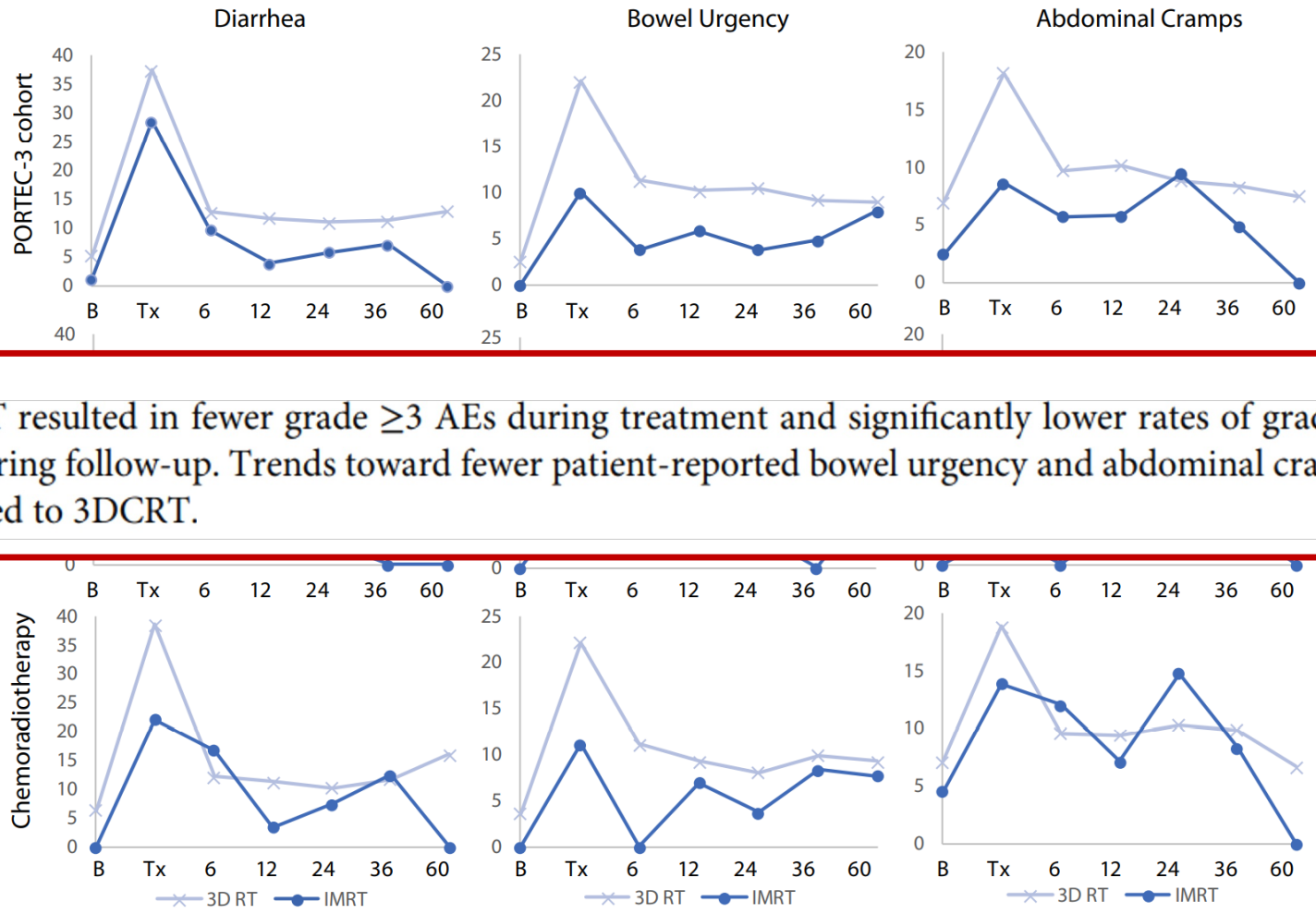
Clinical Investigation

Radiation Therapy Techniques and Treatment-Related Toxicity in the PORTEC-3 Trial: Comparison of 3-Dimensional Conformal Radiation Therapy Versus Intensity-Modulated Radiation Therapy

Bastiaan G. Wortman, MD,* Cathalijne C.B. Post, MD,* Melanie E. Powell, MD, PhD,† Pearly Khaw, MD, PhD,‡ Anthony Fyles, MD, PhD,§ Romerai D'Amico, MD, PhD,‖ Christine Haie-Meder, MD, PhD,¶ Ina M. Jürgenliemk-Schulz, MD, PhD,# Mary McCormack, MD, PhD,** Viet Do, MD, PhD,†† Dionyssios Katsaros, MD, PhD,‡‡ Paul Bessette, MD, PhD,§§ Marie Hélène Baron, MD, PhD,‖‖ Remi A. Nout, MD, PhD,* Karen Whitmarsh, MD, PhD,¶¶ Linda Mileshkin, MD, PhD,## Ludy C.H.W. Lutgens, MD, PhD,*** Henry C. Kitchener, MD, PhD,††† Susan Brooks, MD, PhD,‡‡‡ Hans W. Nijman, MD, PhD,§§§ Eleftheria Astreinidou, PhD,* Hein Putter, PhD,‖‖‖ Carien L. Creutzberg, MD, PhD,* and Stephanie M. de Boer, MD, PhD*

Wortman BG, IJROBP 2022

RT Technique



Conclusions: IMRT resulted in fewer grade ≥3 AEs during treatment and significantly lower rates of grade ≥2 diarrhea and hematologic AEs during follow-up. Trends toward fewer patient-reported bowel urgency and abdominal cramps were observed after IMRT compared to 3DCRT.

Fig. 2. Inciden … nt in months at baseline, during a… erapy. *Abbrevia-tions*: B = baseline; … x = during treatment (time in mor…

Fig. 3. Percentage of patients who reported "quite a bit" or "very much" of diarrhea, bowel urgency or abdominal cramps in the total PORTEC-3 cohort, during and after radiation therapy only and after chemoradiation therapy. *Abbreviations*: B = baseline; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; Tx = during treatment (time in months).

Wortman BG, IJROBP 2022

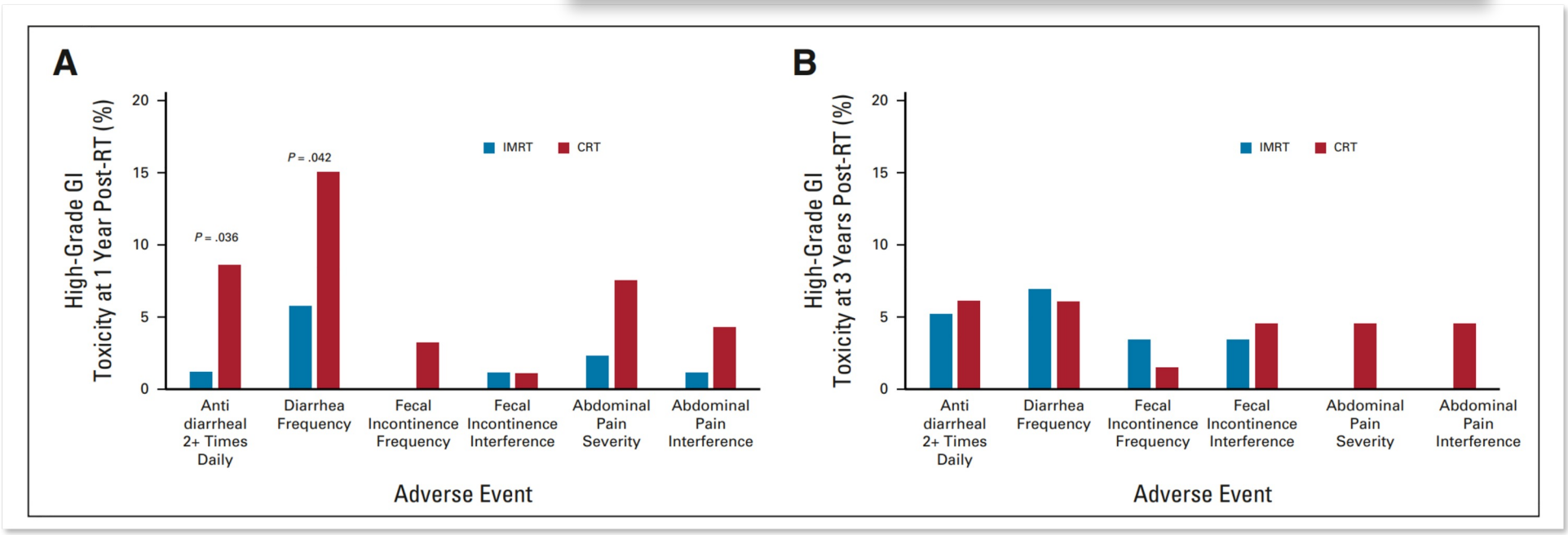
RT Technique

NRG Oncology-RTOG 1203 update

(Klopp AH, Yeung AR, Deshmukh S, et al. J Clin Oncol 2018)

Intensity-Modulated Radiation Therapy Reduces Patient-Reported Chronic Toxicity Compared With Conventional Pelvic Radiation Therapy: Updated Results of a Phase III Trial

Anamaria R. Yeung, MD[1]; Snehal Deshmukh, MS[2]; Ann H. Klopp, MD, PhD[3]; Karen M. Gil, PhD[4]; Lari Wenzel, PhD[5]; Shannon N. Westin, MD, MPH[3]; Andre A. Konski, MD, MBA, MA[6]; David K. Gaffney, MD[7]; William Small Jr, MD[8]; J. Spencer Thompson, MD[9]; Desiree E. Doncals, MD[4]; Guilherme H.C. Cantuaria, MD[10]; David P. D'Souza, MD[11]; Amy Chang, MD[12]; Vijayananda Kundapur, MD[13]; Dasarahally S. Mohan, MD[14]; Michael L. Haas, MD[15]; Yong Bae Kim, MD[16]; Catherine L. Ferguson, MD[17]; Stephanie L. Pugh, PhD[2]; Lisa A. Kachnic, MD[18]; and Deborah W. Bruner, PhD[19]



289 EC/CC pts IMRT arm less high-level diarrhea at 1y (6 versus 15%); 3y better GU

Yeung AR, JCO 2022

Target agents

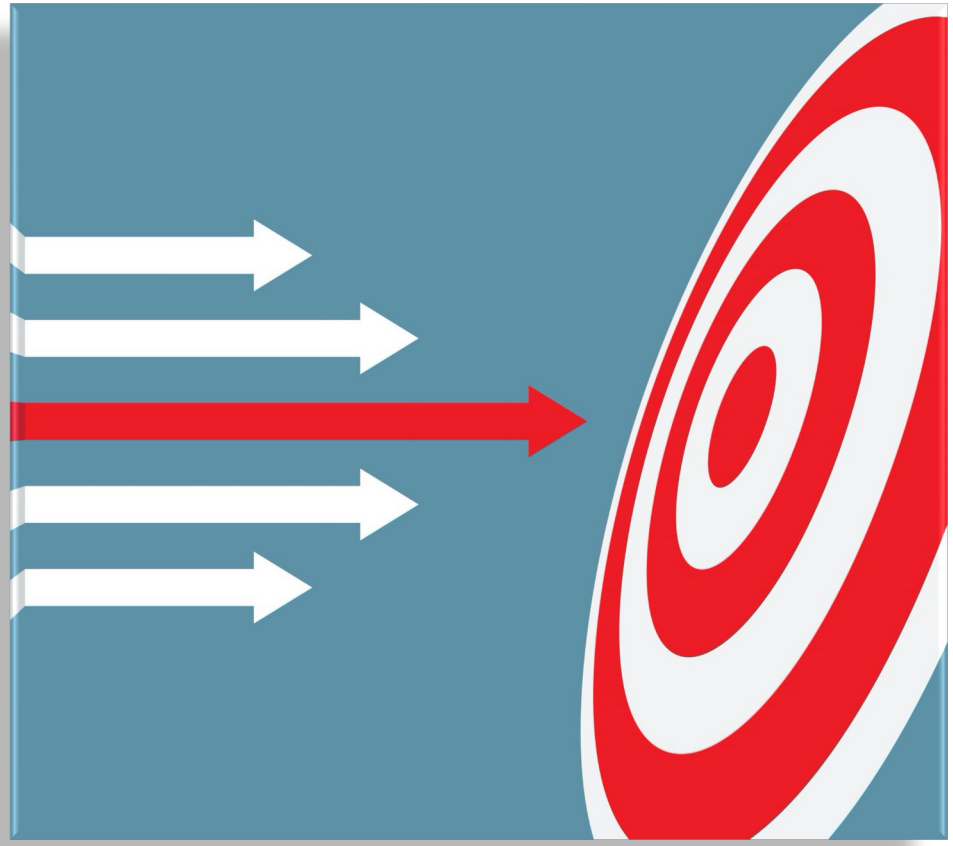
LOCALLY ADVANCED/RECURRENT EC

dMMR/MSI-H EC:

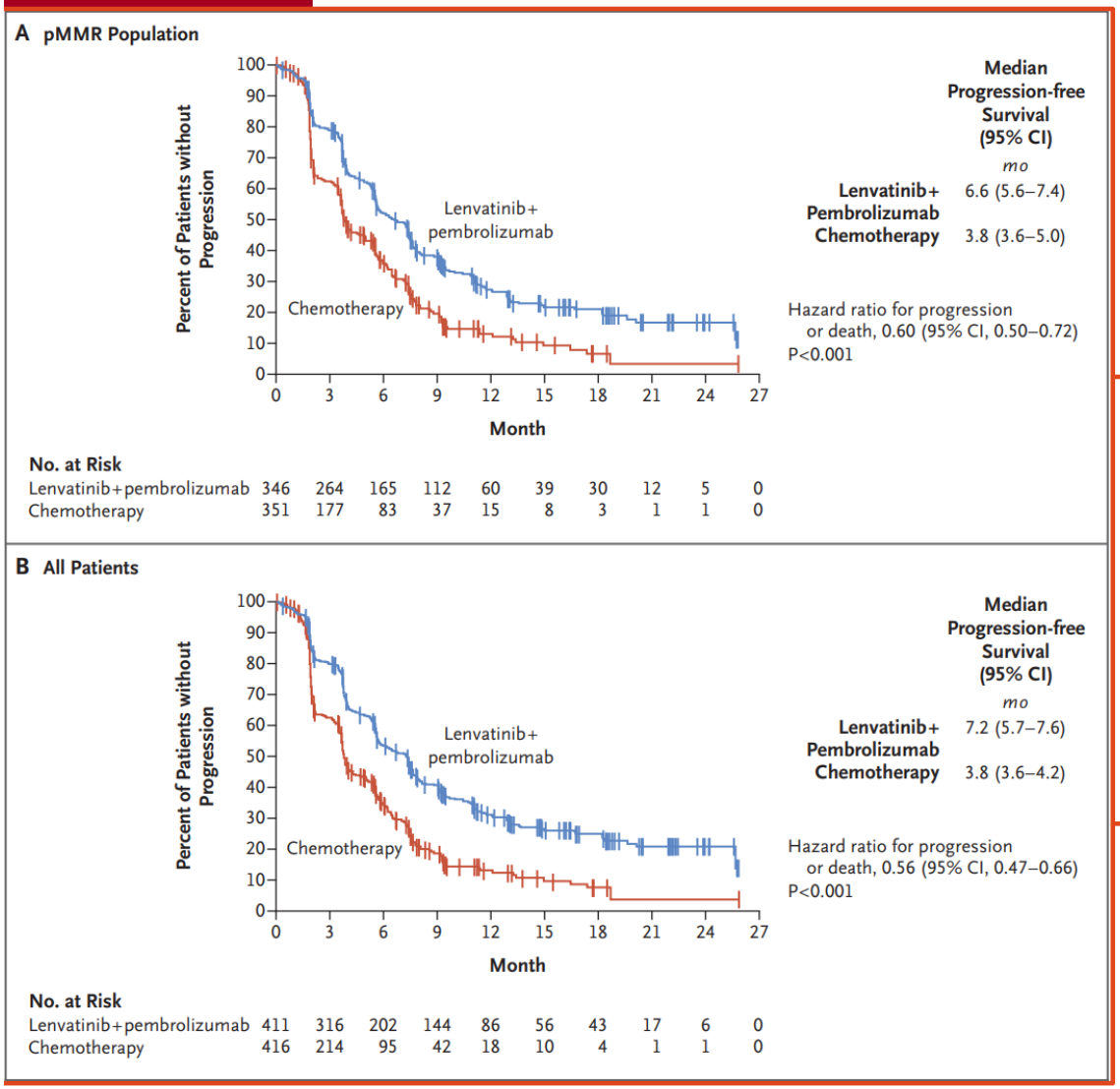
Pembrolizumab (USA)
Dostarlimab (USA, EU)

pMMR/MSS:

Lenvatinib+Pembrolizumab (USA)
(> 66.9%TRAE)



Target agents



Study 111–KEYNOTE-146 trial: treatment with **lenvatinib** in combination with **pembrolizumab** had compelling efficacy in patients with previously treated advanced EC **regardless of tumor MSI status**

Study 309–KEYNOTE-775 trial:

treatment with **lenvatinib** plus **pembrolizumab** led to significantly **longer PFS** and **OS** than chemotherapy of the treating physician's choice, **both in the pMMR population and in the overall trial population** of patients with advanced EC who had disease progression after the receipt of previous systemic platinum-based therapy

Makker V. JCO 2020
Makker V. N Engl J Med 2022

Target agents

GARNET trial (cohorts A1 and A2 update):


JAMA Oncology | Original Investigation

Clinical Activity and Safety of the
Antibody Dostarlimab for Patients
Repair–Deficient Endometrial Can
A Nonrandomized Phase 1 Clinical

Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET—a phase I, single-arm study

- in patients with previously treated recurrent or advanced **dMMR/MSI-H** or **pMMR/MSS** endometrial cancer, dostarlimab was associated with significant clinical activity
  - ORR: **45.4%** and **15.4%**; median PFS: **6.0** mo (range: 4.1-18.8) and **2.7** mo (range: 2.6-2.8); median OS: NR (range: 27.1-NR) and 16.9 mo (range: 13.0-21.8)
  - Median DoR not reached in dMMR/MSI-H group and 19.4 mo in pMMR/MSS group
- Dostarlimab was well tolerated with most TRAES of grade 1-2 and low rate of discontinuation

Oaknin A, et al. JAMA 2020
Oaknin A, et al. J Immunother Cancer 2022

Cervical Cancer

EMBRACE I studies

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

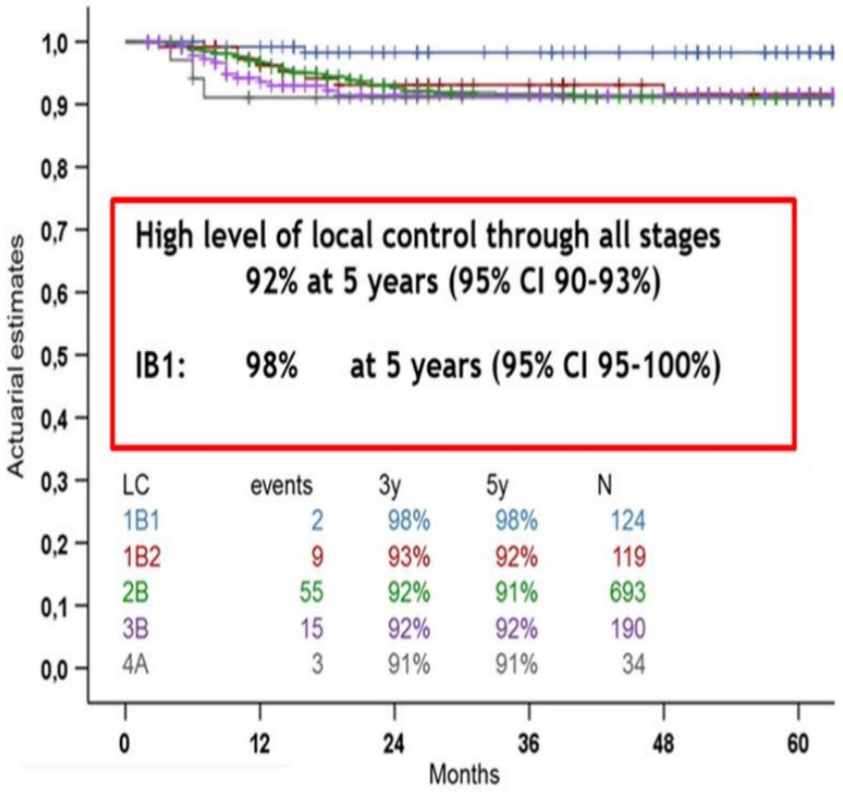
*Richard Pötter, Kari Tanderup, Maximilian Paul Schmid, Ina Jürgenliemk-Schulz, Christine Haie-Meder, Lars Ulrik Fokdal, Alina Emiliana Sturdza, Peter Hoskin, Umesh Mahantshetty, Barbara Segedin, Kjersti Bruheim, Fleur Huang, Bhavana Rai, Rachel Cooper, Elzbieta van der Steen-Banasik, Erik Van Limbergen, Bradley Rumwell Pieters, 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**

Lancet Oncol 2021

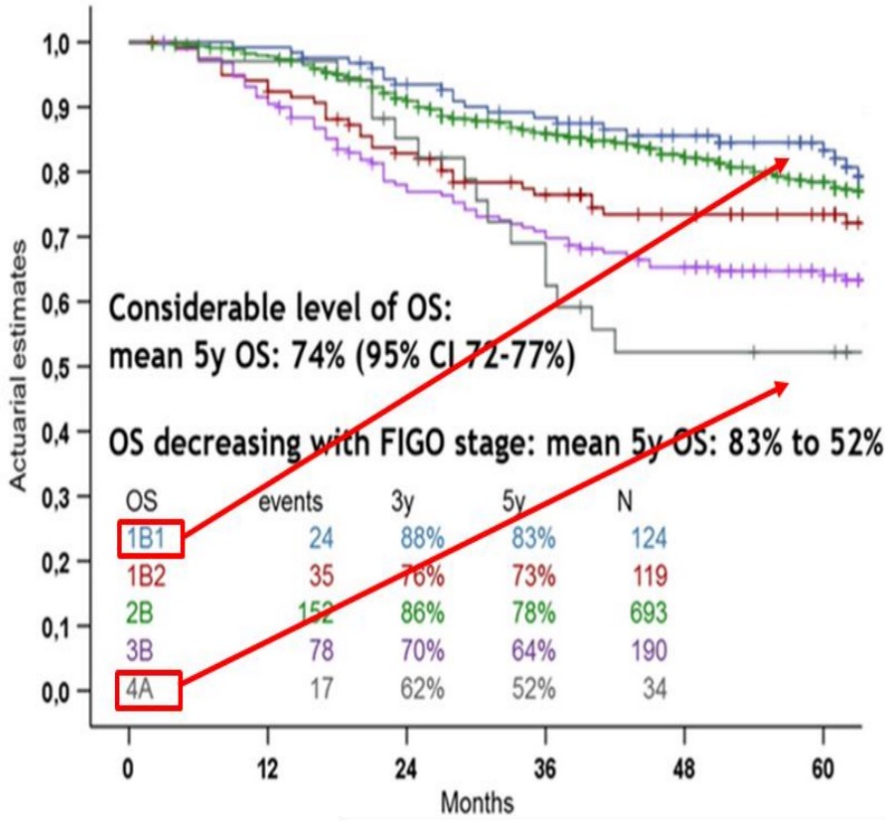
EMBRACE I studies

1341 pts

Local control and FIGO$_{2009}$ stage EMBRACE I (KM estimates)



Overall survival and FIGO$_{2009}$ stage EMBRACE I (KM-estimates)



EMBRACE I studies

Prognostic Implications of Uterine Cervical Cancer Regression During Chemoradiation Evaluated by the T-Score in the Multicenter EMBRACE I Study.

Lindegaard JC, Petric P, Schmid MP, Nesvacil N, Haie-Meder C, Fokdal LU, Sturdza AE, Hoskin P, Mahantshetty U, Segedin B, Bruheim K, Huang F, Rai B, Cooper R, van der Steen-Banasik E, Van Limbergen E, Pieters BR, Tan LT, Nout RA, De Leeuw AAC, **Kirchheiner K**, Spampinato S, Jürgenliemk-Schulz I, Tanderup K, Kirisits C, Pötter R.

Int J Radiat Oncol Biol Phys. 2022 Jun 1;113(2):379-389. doi: 10.1016/j.ijrobp.2022.02.005. Epub 2022 Feb 12.

PMID: 35157992

Lindegaard JC, IJROBP 2022:

T-Score and prognosis

Dose-effect relationship between vaginal dose points and vaginal stenosis in cervical cancer: An EMBRACE-I sub-study.

Westerveld H, **Kirchheiner K**, Nout RA, Tanderup K, Lindegaard JC, Spampinato S, Sturdza A, Nesvacil N, Bruheim K, Hellebust TP, Pieters BR, Kirisits C, Jürgenliemk-Schulz IM, Pötter R, de Leeuw AAC.

Radiother Oncol. 2022 Mar;168:8-15. doi: 10.1016/j.radonc.2021.12.034. Epub 2022 Jan 19.

PMID: 35063582

Westerveld H, Radiother Oncol 2022:

PIBS and vaginal stenosis

Risk Factors for Late Persistent Fatigue After Chemoradiotherapy in Patients With Locally Advanced Cervical Cancer: An Analysis From the EMBRACE-I Study.

Smet S, Spampinato S, Pötter R, Jürgenliemk-Schulz IM, Nout RA, Chargari C, Mahantshetty U, Sturdza A, Segedin B, Bruheim K, Hoskin P, Rai B, Huang F, Cooper R, Van der Steen-Banasik E, Sundset M, Van Limbergen E, Tan LT, Lutgens LCHW, Villafranca E, Pieters BR, Tanderup K, **Kirchheiner K.**

Int J Radiat Oncol Biol Phys. 2022 Apr 1;112(5):1177-1189. doi: 10.1016/j.ijrobp.2021.11.022. Epub 2021 Nov 25.

PMID: 34838868

Smet S, IJROBP 2022:

Late persistent fatigue

Severity and Persistency of Late Gastrointestinal Morbidity in Locally Advanced Cervical Cancer: Lessons Learned From EMBRACE-I and Implications for the Future.

Spampinato S, Jensen NBK, Pötter R, Fokdal LU, Chargari C, Lindegaard JC, Schmid MP, Sturdza A, Jürgenliemk-Schulz IM, Mahantshetty U, Hoskin P, Segedin B, Rai B, Bruheim K, Wiebe E, Van der Steen-Banasik E, Cooper R, Van Limbergen E, Sundset M, Pieters BR, Lutgens LCHW, Tan LT, Villafranca E, Smet S, Jastaniyah N, Nout RA, Kirisits C, Chopra S, **Kirchheiner K**, Tanderup K, Embrace Collaborative Group.

Int J Radiat Oncol Biol Phys. 2022 Mar 1;112(3):681-693. doi: 10.1016/j.ijrobp.2021.09.055. Epub 2021 Oct

Spampinato S, IJROBP 2022:

Late GI morbidity

EMBRACE I studies

Prognostic Implications of Uterine Cervical Cancer Regression During Chemoradiation Evaluated by the T-Score in the Multicenter EMBRACE I Study

400→1318 pts

Conclusions

Repetitive quantification of the local tumor extension in LACC by a single number (T-score, TS) based on integrated evidence from clinical examination and MRI constitutes a new multidisciplinary platform for linking regression during chemoradiation with BT application technique, DVH parameters, and outcome in a multicenter setting. Local tumor regression of LACC during chemoradiation evaluated by the TS was found to open the therapeutic window in relation to local control, survival, and morbidity.

Location	Nominal Scale	FIGO$_{2009}$ No of patients Points
Uterine cervix	<20 mm§ (%)	0
	20-40 mm§ (%)	1
	>40 mm§ (%)	2
	Disrupted* (%)	3
Parametrium left	Not involved (%)	0
	Proximal (%)	1
	Distal (%)	2
	Pelvic wall (%)	3
Parametrium right	Not involved (%)	0
	Proximal (%)	1
	Distal (%)	2
	Pelvic wall (%)	3
Bladder	Not involved (%)	0
	Bladder wall (%)	1
	Bullous edema (%)	2
	Mucosa (%)	3
Ureter	Not involved (%)	0
	Unilateral# (%)	1
	Bilateral# (%)	2
Rectum	Not involved (%)	0
	Mesorectum (%)	1
	Rectal wall (%)	2
	Mucosa (%)	3
Uterine corpus	Not involved (%)	0
	Lower third (%)	1
	Middle third (%)	2
	Upper third (%)	3
Vagina	Not involved (%)	0
	Upper third (%)	1
	Middle third (%)	2
	Lower third (%)	3
T-score	Median (range)	
	Mean (SE)	

Lindegaard JC, IJROBP 2019

EMBRACE I studies

Radiotherapy and Oncology
Volume 168, March 2022, Pages 8-15

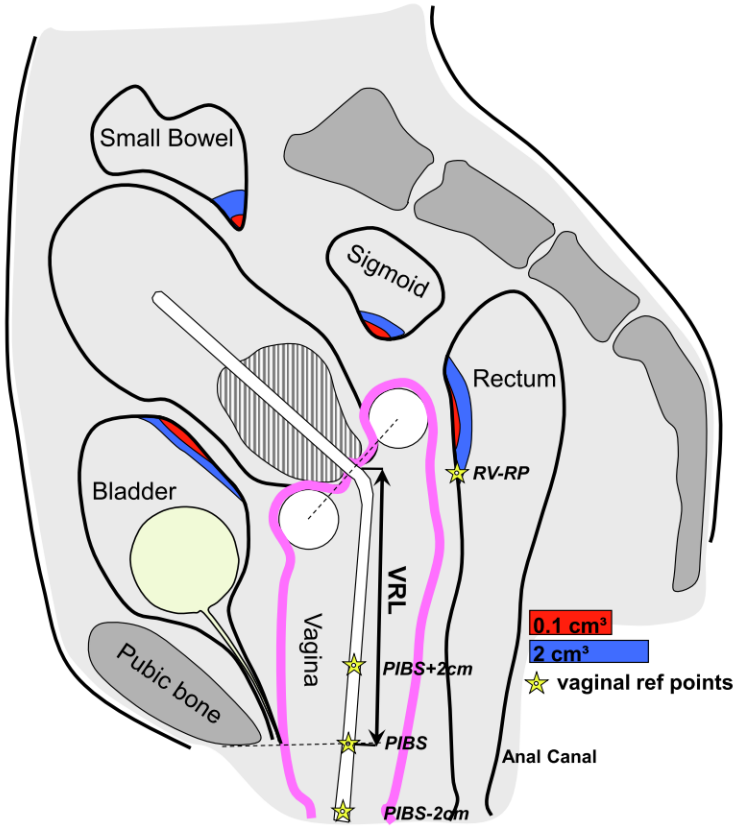
Dose-effect relationship between vaginal dose points and vaginal stenosis in cervical cancer: An EMBRACE-I sub-study

Highlights

- Doses to the vaginal dose points predicts well the risk of vaginal morbidity.
- Higher doses to the vaginal PIBS points are associated with vaginal stenosis.
- A shorter vaginal reference length is associated with ≥grade 2 vaginal stenosis.

Posterior-Inferior Border of Symphysis (PIBS)

301 pts



Dose levels < 50 Gy for PIBS EBRT + BT; < 5 Gy for PIBS-2 cm EBRT → **Lower risk of vaginal stenosis**

The current dose constraint for the RectoVaginal-Reference Point → 65 Gy *Westerveld H, Radiother Oncol 2022*

EMBRACE I studies

993 pts

Risk Factors for Late Persistent Fatigue After Chemoradiotherapy in Patients With Locally Advanced Cervical Cancer: An Analysis From the EMBRACE-I Study

Stéphanie Smet, MD,[*,†] Sofia Spampinato, PhD,[‡] Richard Pötter, MD,[§] Ina M. Jürgenliemk-Schulz, MD, PhD,[‖] Remi A. Nout, MD, PhD,[¶,#] Cyrus Chargari, MD, PhD,[**] Umesh Mahantshetty, MD,[††,‡‡] Alina Sturdza, MD, FRCPC,[§] Barbara Segedin, MD, PhD,[§§,‖‖] Kjersti Bruheim, MD, PhD,[¶¶] Peter Hoskin, MD, FRCR,[##] Bhavana Rai, MD, DNB,[***] Fleur Huang, MD,[†††] Rachel Cooper, MD, FRCR,[‡‡‡] Elzbieta Van der Steen-Banasik, MD,[§§§] Marit Sundset, MD,[‖‖‖] Erik Van Limbergen, MD, PhD,[¶¶¶] Li Tee Tan, MD,[****] Ludy C.H.W. Lutgens, MD, PhD,[††††] Elena Villafranca, PhD,[‡‡‡‡] Bradley R. Pieters, MD, PhD,[§§§§] Kari Tanderup, PhD,[‡] and Kathrin Kirchheiner, MSc, PhD[§]

late persistent grade ≥1 fatigue→>33%pts; 6% suffer from late persistent grade ≥2

Baseline ≥1/≥2 fatigue	Late persistent grade ≥1/≥2 fatigue
preexisting comorbidities	size of irradiated volumes
WHO-PS score	level of radiation doses both from EBRT and brachytherapy (EBRT: V43Gy, V57Gy; EBRT + brachytherapy: V60Gy EQD2)
being underweight	baseline fatigue
severe pain	younger age
tumor volume	obesity
	late persistent organ-related morbidity

Smet S, Int J Radiation Oncol Biol Phys, 2022

EMBRACE I studies

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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1416 pts

CLINICAL INVESTIGATION

Severity and Persistency of Late Gastrointestinal Morbidity in Locally Advanced Cervical Cancer: Lessons Learned From EMBRACE-I and Implications for the Future

Sofia Spampinato, PhD,* Nina B.K. Jensen, MD, PhD,* Richard Pötter, MD,† Lars U. Fokdal, MD, PhD,* Cyrus Chargari, MD, PhD,‡ Jacob C. Lindegaard, MD, DMSc,* Maximilian P. Schmid, MD,† Alina Sturdza, MD,† Ina M. Jürgenliemk-Schulz, MD, PhD,§ Umesh Mahantshetty, DMRT, MD, DNB,‖ Peter Hoskin, MD, FRCR,# Barbara Segedin, MD, PhD,** Bhavana Rai, MD, DNB,†† Kjersti Bruheim, MD, PhD,‡‡ Ericka Wiebe, MD, MSc,§§ Elzbieta Van der Steen-Banasik, MD,‖‖ Rachel Cooper, MD, FRCR,## Erik Van Limbergen, MD, PhD,*** Marit Sundset, MD,††† Bradley R. Pieters, MD, PhD,‡‡‡ Ludy C.H.W. Lutgens, MD, PhD,§§§ Li Tee Tan, MD,‖‖‖ Elena Villafranca, MD,### Stéphanie Smet, MD,**** Noha Jastaniyah, MD,†††† Remi A. Nout, MD, PhD,‡‡‡‡ Christian Kirisits, DSc,† Supriya Chopra, MD,§§§§ Kathrin Kirchheiner, MSc, PhD,† Kari Tanderup, PhD,* and EMBRACE Collaborative Group,‖‖‖‖

Conclusions: The analysis showed that both EBRT and image guided adaptive brachytherapy contribute to GI symptoms after locally advanced cervical cancer treatment. Rectum D_{2cm3}, ICRU RV-RP , and bowel D_{2cm3} are risk factors for GI morbidity. The risk for various symptoms was lower with an EBRT prescription of 45 Gy than 50 Gy and increased with larger V57Gy. ©

Spampinato S, Int J Radiation Oncol Biol Phys, 2022

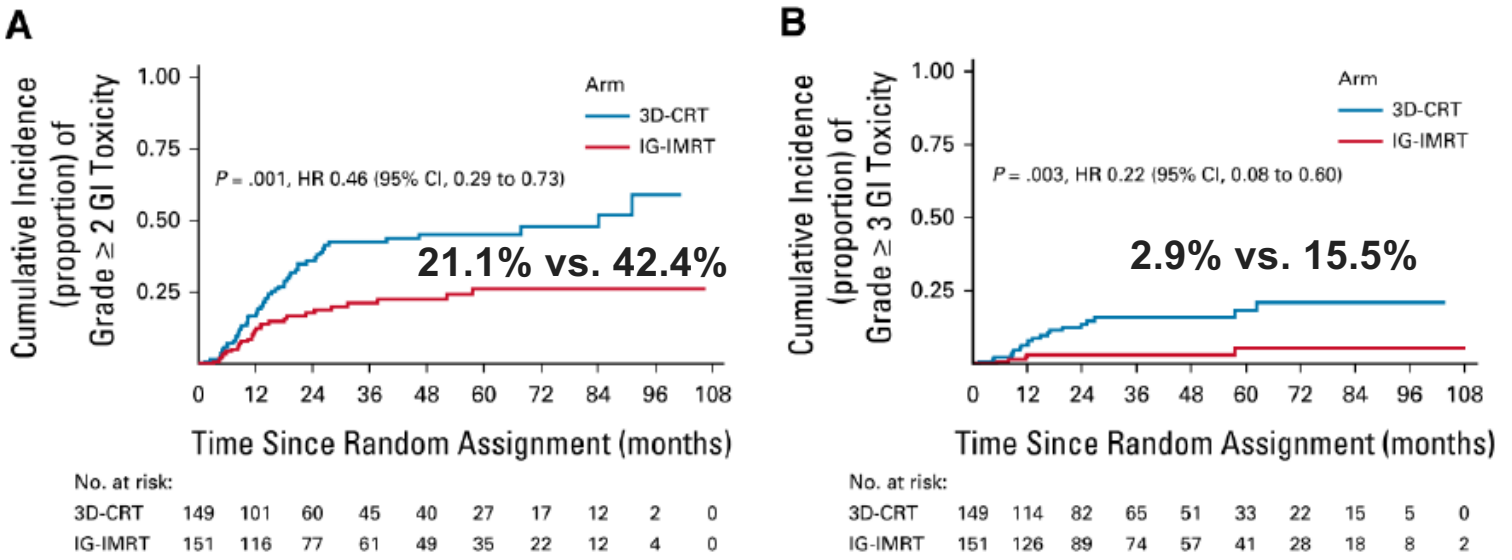
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

original reports

Late Toxicity After Adjuvant Conventional Radiation Versus Image-Guided Intensity-Modulated Radiotherapy for Cervical Cancer (PARCER): A Randomized Controlled Trial

Supriya Chopra, MD, DNB[1]; Sudeep Gupta, DM[2]; Sadhana Kannan, MSc[3]; Tapas Dora, MD[4]; Reena Engineer, DNB[5]; Akshay Mangaj, MD[5]; Amita Maheshwari, MD[6]; T. Surappa Shylasree, MD[6]; Jaya Ghosh, MD, DM[2]; Siji N. Paul, MSc[1]; Reena Phurailatpam, MSc[1]; Mayuri Charnalia, MSc[1]; Mitali Alone, BSc[7]; Jameena Swamidas, PhD[1]; Umesh Mahantshetty, MD[6]; Kedar Deodhar, MD[8]; Rajendra Kerkar, MD[6]; and Shyam K. Shrivastava, MD, DNB[5]

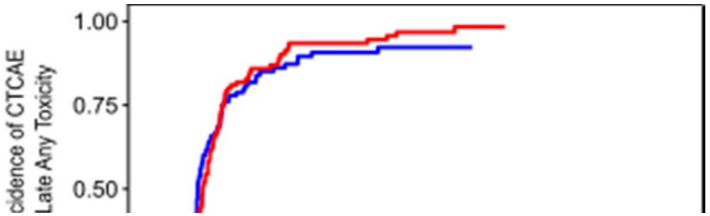
300 patients were randomly assigned (IG-IMRT 151 and 3D-CRT 149).



IG-IMRT results in reduced toxicity with no difference in disease outcomes.

Chopra, S et al. J Clin Oncol 39:3682-3692. © 2021

Technique



ELSEVIER

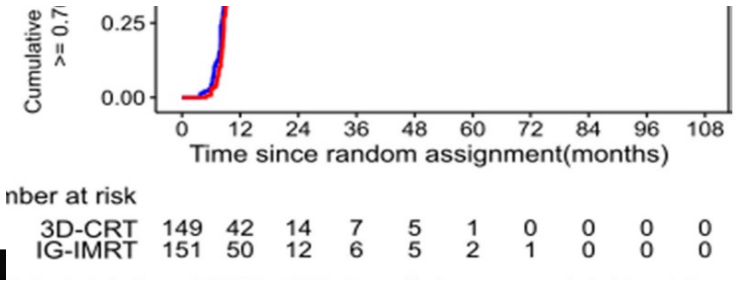
Original Articl

Late toxici
(PARCER):
(MOSES)

Supriya Chop
Lavanya Gurı

[a] Department of Radi
Mumbai; [b] Departmen
Advanced Centre for
Oncology, Homi Bhab
Cancer, Tata Memoria
Homi Bhabha Nationa

In summary, these results reiterate that CTCAE maximum grade method misses out a lot of important information for patient survivorship and there is need for better tool to summarize treatment related morbidities. The MOSES system appears a promising method of summating and reporting toxicity that has potential to provide a better correlation with patient-reported symptoms. MOSES can therefore be a valuable complement to CTCAE. External validation is however, needed in the future to test the applicability in different population groups.



Chopra S, Radiotherapy & Oncology 2022

Brachytherapy

Radiotherapy and Oncology 170 (2022) 70–78

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

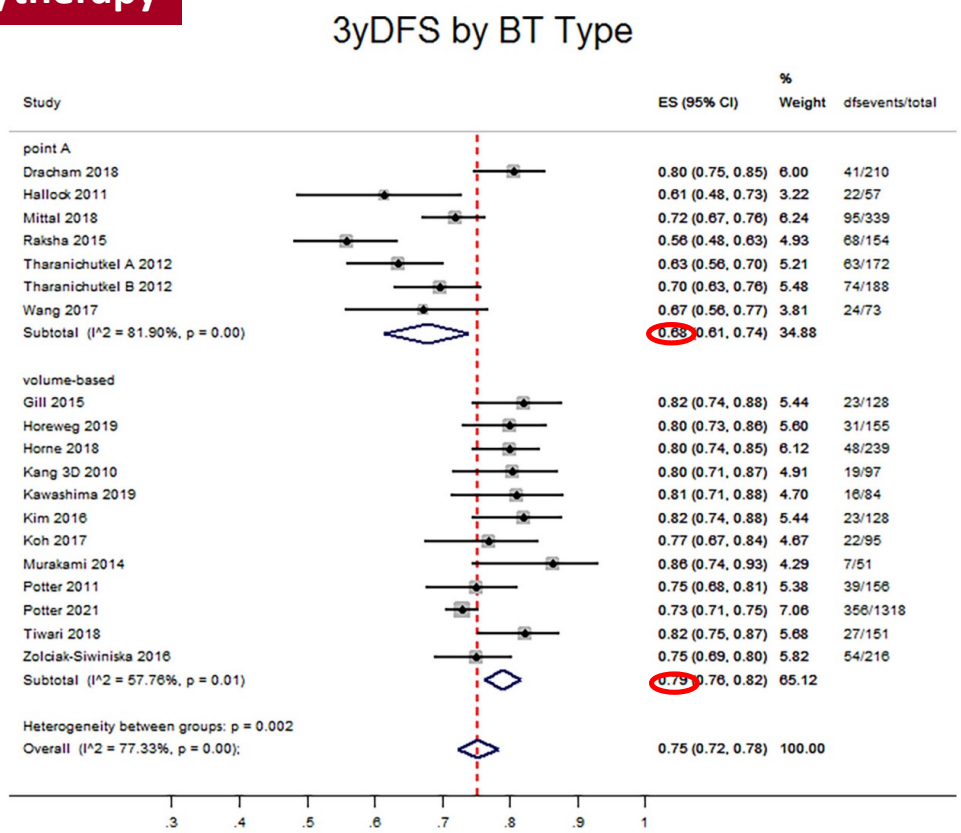
Original Article

Point-A vs. volume-based brachytherapy for the treatment of cervix cancer: A meta-analysis

Varsha Hande [a,b], Supriya Chopra [a,1,*], Babusha Kalra [a], May Abdel-Wahab [b], Sadhana Kannan [c], Kari Tanderup [d], Surbhi Grover [e,f], Eduardo Zubizarreta [b], Jose Alfredo Polo Rubio [b,1,*]

[a] *Department of Radiation Oncology, Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Homi Bhabha National Institute, Navi Mumbai, India;* [b] *Applied Radiation Biology and Radiotherapy Section, Division of Human Health, International Atomic Energy Agency, Vienna, Austria;* [c] *Department of Epidemiology and Clinical Trials Unit, Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Homi Bhaba National Institute, Navi Mumbai, India;* [d] *Department of Oncology, Aarhus University Hospital, Denmark;* [e] *Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States;* [f] *Botswana-UPenn Partnership, Gaborone, Botswana*

Brachytherapy



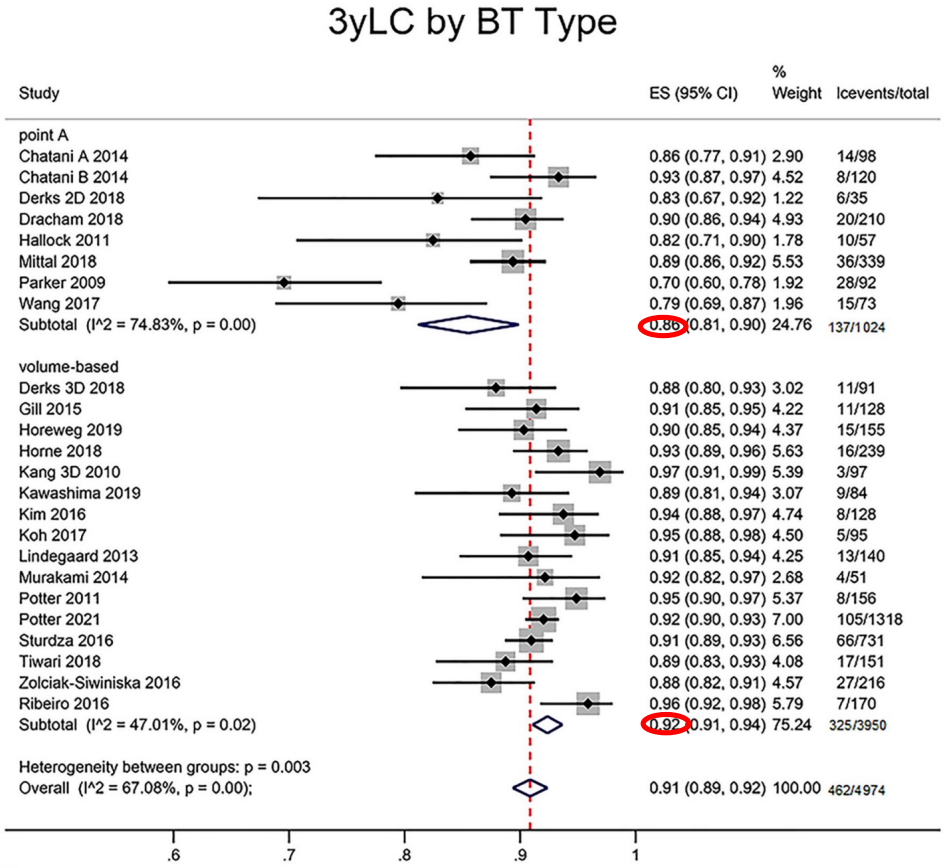
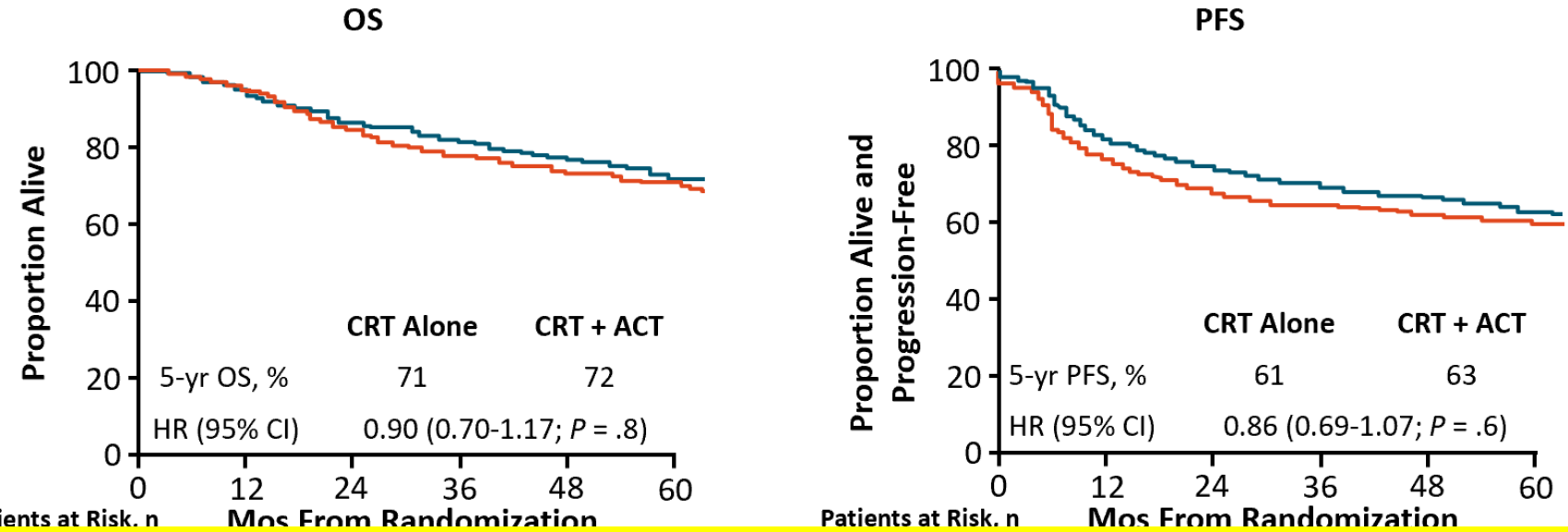


Fig. 2. 3yDFS Forest Plot: Forest Plot showing 3-year disease-free survival between point-A studies and volume-based studies. I^2: Heterogeneity ES = Estimate Siz CI = 95% Confidence Interval.

Conclusion: Volume-based BT results in superior 3-year DFS and 3-year LC. In the absence of randomized trials, this meta-analysis provides the best evidence regarding transition to 3D planning.

OUTBACK: OS and PFS



Adjuvant CT after standard cisplatin-based chemoradiation for LACC did not improve OS or PFS
Pelvic CRT with concurrent weekly cisplatin→standard of care

PFS with CRT + ACT vs CRT alone

- Sensitivity analyses found no significant differences in OS or PFS in CRT + ACT arm for those who did vs did not complete CRT

except for those aged < vs ≥60 yr, where younger patients had greater OS and PFS benefit with CRT + ACT (interaction *P* = .01 and .03, respectively)

Mileshkin. ASCO 2021. Abstr LBA3. Reproduced with permission.

Mileshkin LR JCO, 06/2021, Volume 39, 18S

Adjuvant Chemotherapy

Overall survival

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

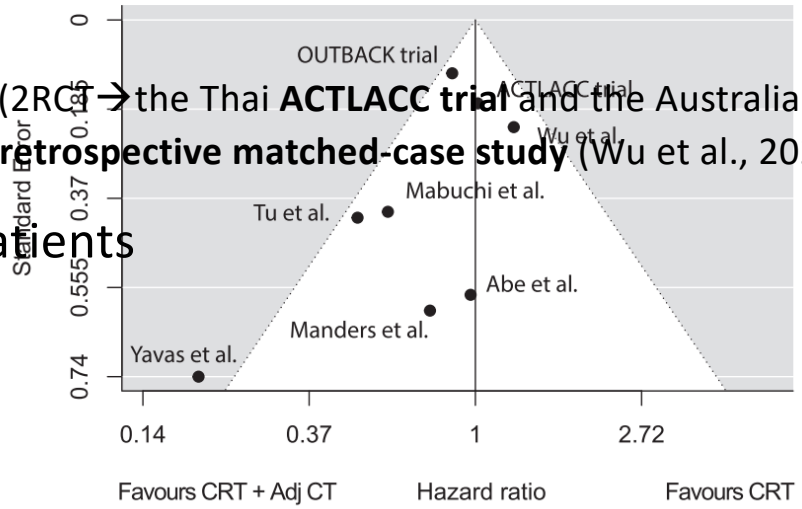
journal homepage: www.elsevier.com/locate/critrevonc

A systematic review and meta-analysis of adjuvant chemotherapy after chemoradiation for locally advanced cervical cancer

Nanda Horeweg [a,*,1], Prachi Mittal [b], Patrycja L. Gradowska [c], Ingrid Boere [d], Supriya Chopra [f,2]

8 studies (2RCT → the Thai **ACTLACC trial** and the Australian-led intern
one **large retrospective matched-case study** (Wu et al., 2021))

2150 patients



Rejection of the hypothesis that adjuvant chemotherapy after chemoradiation and brachytherapy improves survival in unselected patients with locally advanced cervical cancer

Horeweg N, Critical Reviews in Oncology / Hematology 172 (2022)

Target agents

CALLA Study Design

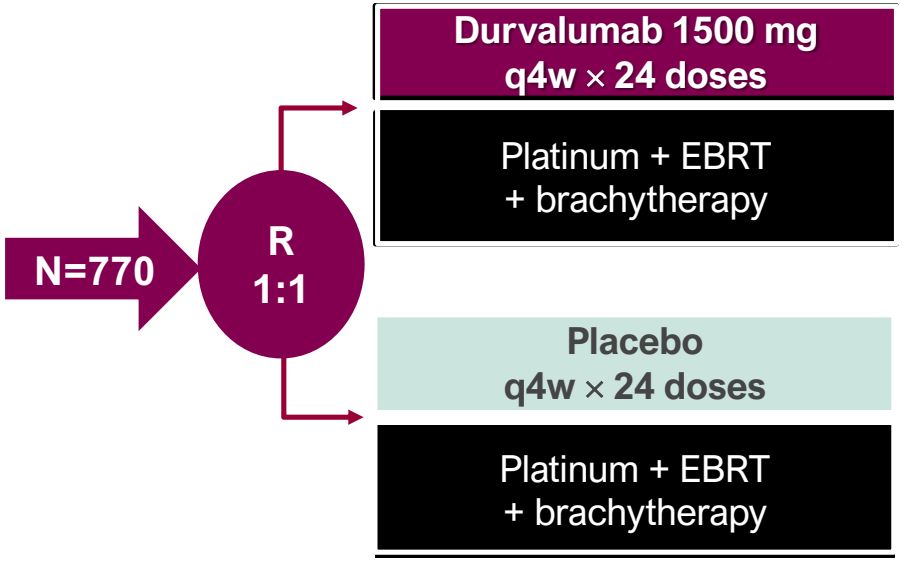
15 countries, **120** sites

Eligible population

- Women aged ≥18 years
- Histologically confirmed cervical adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma
- High-risk LACC (FIGO 2009)
  - Stages IB2 to IIB, node positive (N≥1)
  - Stages IIIA to IVA with any node (N≥0)
- WHO ECOG performance status of 0 or 1

Stratification factors

- Disease stage
  - FIGO Stage IB2–IIB and LN+
  - FIGO Stage ≥III and LN−
  - FIGO Stage ≥III and LN+
- Region of world



Primary Endpoint:

Progression-Free Survival[a] (Investigator-assessed)

Key Secondary Endpoints:

- Overall survival
- Objective response rate
- Duration of response
- Incidence of local or distant progression / 2˚ malignancy
- Safety and tolerability

Chemoradiotherapy Regimen

Platinum agent	Cisplatin 40 mg/m^2 or carboplatin AUC2 q1w × 5 weeks
EBRT	45 Gy in 25 fractions at 1.8 Gy/fraction, 5 fractions per week
Brachytherapy	High-dose rate: 27.5–30 Gy; Low/pulsed-dose rate: 35–40 Gy

Key Milestones

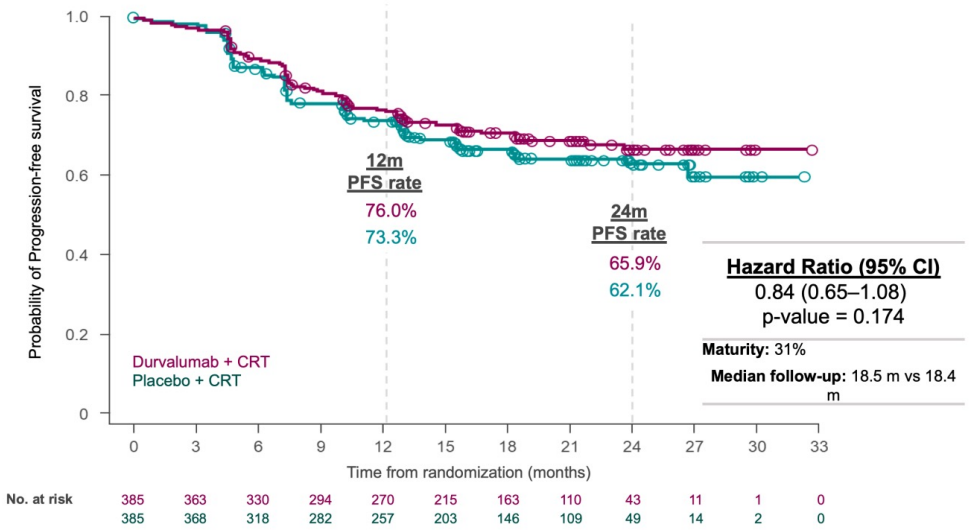
First patient in	February 2019
Last patient in	December 2020
Data cut off	January 20, 2022

[a]According to RECIST 1.1 or histopathologic confirmation of local tumor progression using CT or MRI scans.

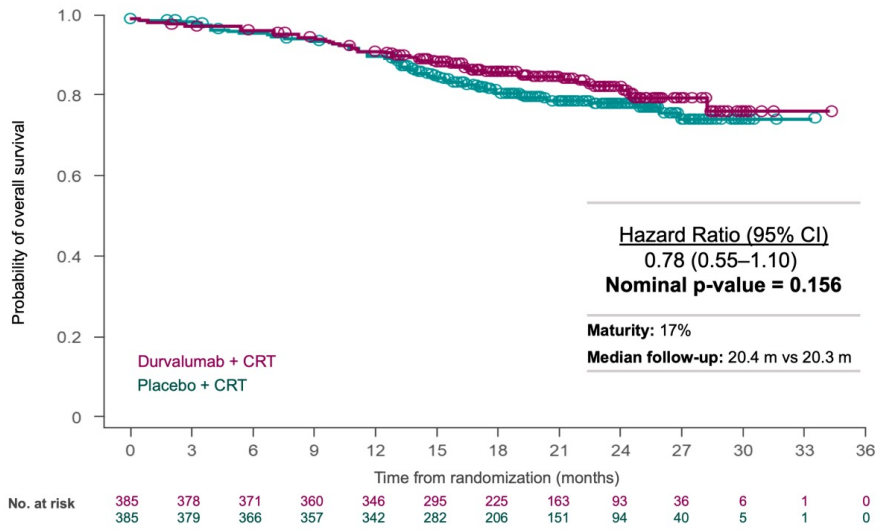
Target agents

Progression-Free and Overall Survival

PFS



OS



Courtesy Prof. Lorusso

Target agents

Secondary Efficacy Endpoints

	Durvalumab + CRT (n = 385)	Placebo + CRT (n = 385)
Objective Response Rate[a] , n (%)	318 (82.6)	310 (80.5)
CR, n (%)	165 (42.9)	155 (40.3)
PR, n (%)	153 (39.7)	155 (40.3)
Local Disease Progression Events, n (%)	42 (10.9)	40 (10.4)
Hazard Ratio (95% CI), 2-sided p-value	**1.06 (0.69–1.63), *P*=0.795**	
Local Disease Progression, % (95% CI)		
12 months	8.2 (5.7–11.3)	8.2 (5.7–11.3)
24 months	13.1 (9.3–17.6)	12.7 (9.0–17.1)
Distant Disease Progression Events, n (%)	52 (13.5)	69 (17.9)
Hazard Ratio (95% CI), 2-sided p-value	**0.75 (0.53–1.06), *P*=0.103**	
Distant Disease Progression, % (95% CI)		
12 months	12.3 (9.1–15.8)	15.7 (12.2–19.6)
24 months	16.1 (12.4–20.2)	21.0 (16.8–25.5)

Courtesy Prof. Lorusso

[a]By blinded independent central review using RECIST v1.1; includes unconfirmed complete or partial response.

Target agents

CALLA: Safety and Tolerability

Parameter, n (%)	Durvalumab + CRT (N = 385)	Placebo + CRT (N = 385)
Any AE leading to discontinuation of any study treatment	65 (16.9)	50 (13.0)
▪ Possibly related to any study treatment	48 (12.5)	37 (9.6)
Any AE leading to discontinuation of Durvalumab/Placebo only	33 (8.6)	22 (5.7)
▪ Possibly related to durvalumab/placebo	12 (3.1)	5 (1.3)
Any AE leading to discontinuation of durvalumab/placebo only	34 (8.8)	30 (7.8)
▪ Possibly related to CRT only	25 (6.5)	22 (5.7)

- All grade AEs occurring in ≥15% of patients receiving durva + CRT vs Pbo + CRT included: anemia (56% vs 54.4), nausea (55.5% vs 52.3%), diarrhea (45.7% vs 49.5%), vomiting (27.3 vs 27.6), and UTI (25.7 vs 24.5)
- Most common grade 3/4 AEs in both arms included: anemia, neutropenia, neutrophil count decrease, white blood count decrease, and leukopenia

Parameter, n (%)	Durvalumab + CRT (N = 385)	Placebo + CRT (N = 385)
Any AE	379 (98.2)	377 (98.2)
▪ Possibly related to any study treatment	350 (90.9)	337 (87.8)
▪ Possibly related to Durvalumab/Placebo only	194 (50.4)	139 (36.2)
Any AE of CTCAE grade 3/4	199 (51.7)	196 (51.0)
▪ Possibly related to any study treatment	160 (41.6)	166 (43.2)
▪ Possibly related to durvalumab/placebo only	31 (8.1)	25 (6.5)
Any AE with outcome of death	13 (3.4)	5 (1.3)
▪ Possibly related to any study treatment	5 (1.3)*	1 (0.3)†
▪ Possibly related to durvalumab/placebo only	1 (0.3)‡	0

*Any study treatment: Durvalumab/Placebo only or CRT only or durvalumab/placebo + CRT: Urinary tract infection, blood loss anemia, pulmonary embolism, sepsis, endocrinopathy;. †Pneumonia. ‡Endocrinopathy.

Monk. IGCS 2022. Abstr O001.

Phase III CALLA trial

- durvalumab in combination with and following chemoradiation did not significantly improve PFS in patients with high-risk locally advanced cervical cancer vs chemoradiation alone (HR: 0.84; *P* = .174) or OS (HR: 0.78; *P* = .156)[1]
  - Safety was comparable in both arms
  - No new or unexpected toxicity

Molise ART

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