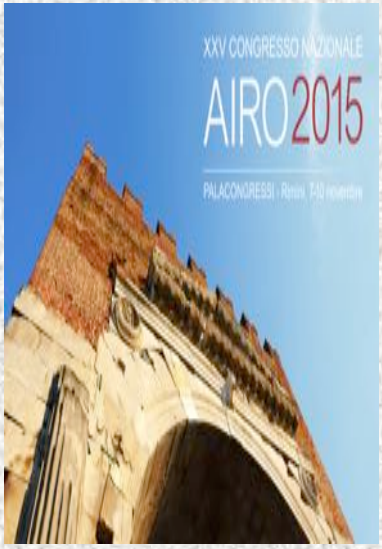
WORKSHOP

Trattamenti adiuvanti nei tumori dell'endometrio



Irradiazione pelvica adiuvante del tumore endometriale: indicazioni, volumi e tecnica

V. De Sanctis
Radioterapia Oncologica

"Sapienza"
Università di Roma

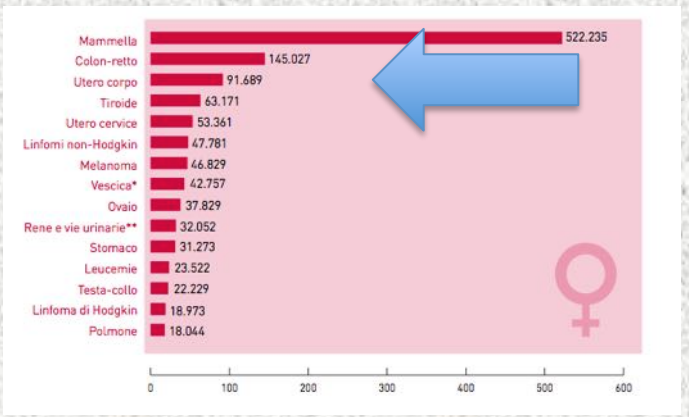
DICHIARAZIONE

Relatore: Vitaliana De Sanctis

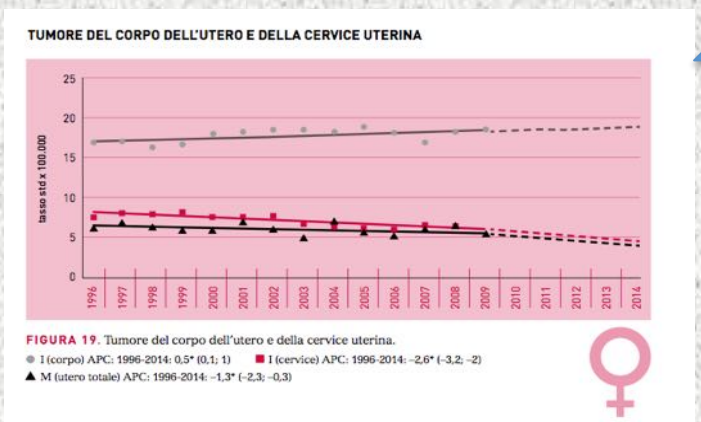
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
-

ENDOMETRIAL CANCER



Numero stimato di casi prevalenti in Italia per sesso.



stima dei trend tumorali di incidenza e mortalità (utero totale) 1996-2014.

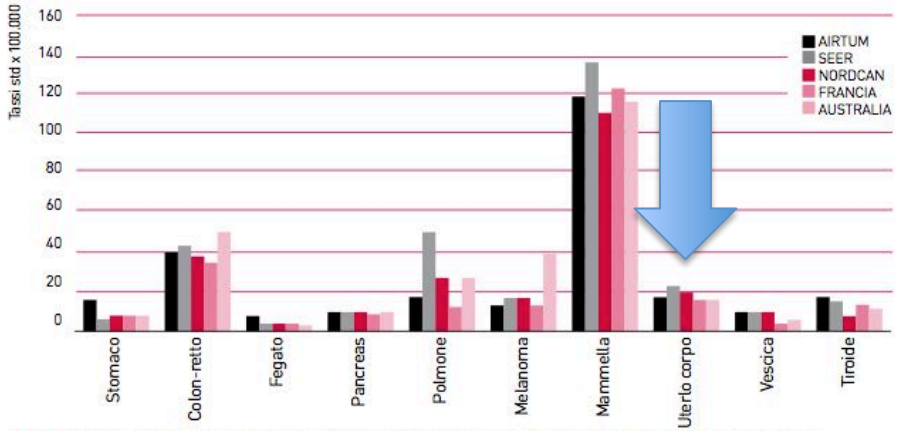


FIGURA 24B. Confronto geografico dei tassi di incidenza per i principali tumori, donne. Tassi di incidenza standardizzati sulla popolazione europea

Despite being the most common gynecological cancer in developed countries, there is evidence for many differences and discrepancies in the clinical management

Greggi, 2014

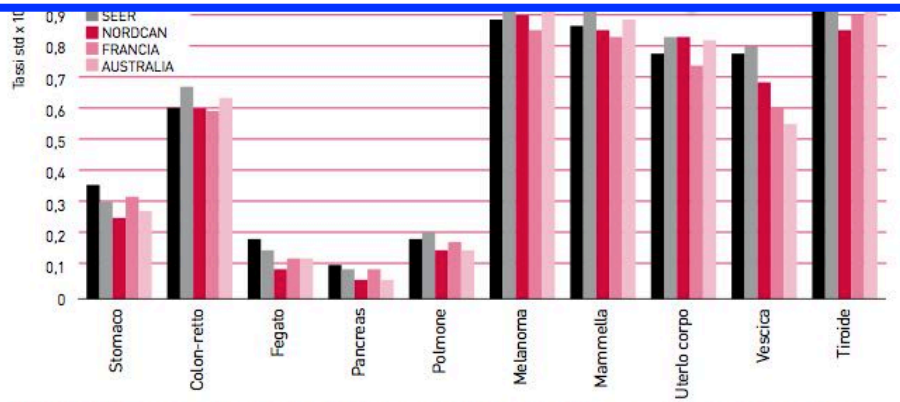


FIGURA 26B. Confronto geografico della sopravvivenza relativa a 5 anni per i principali tumori, donne.

Uterine Cancer Staging System.
FIGO 2010
FIGO Annual Report on 42.000 pts - 5y survival

Pecorelli S, Int J Gynecol Obstet 2009

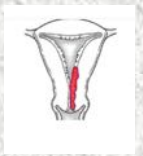
Stage I: 75-90%

A G123, invasion < 50% myometrium: 88%

B G123, invasion > 50% myometrium: 75%

Stage II: 70%

G123, endocervix stroma



Stage III: 45-60%

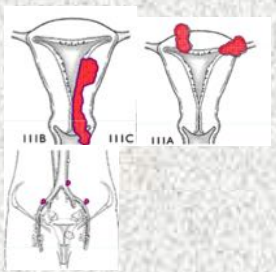
A G123, (+) serosa/ adnexa: 58%

B G123, (+) vagina/parametrium: 50%

C G123, (+) nodes: 47%

IIIC1: (+) pelvic nodes

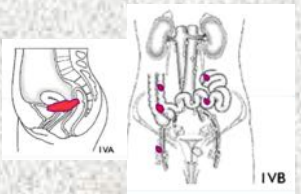
IIIC2: (+) PAN nodes



Stage IV: 15-20%

A G123, (+) GI, GU mucosa: 17%

B G123, distant mets, + groin nodes: 15%



Uterine Cancer Staging System.
FIGO 2010

Main changes include:

A) noninvasive tumors (1988 IA) and tumors with <50% myometrial invasion (1988 IB) are combined (2009 IA)

B) cervical glandular involvement does not affect staging (1988 IIA shifted to 2009 IA-IB);

C) peritoneal cytology does not affect staging (1988 IIIA with positive cytology only shifted to 2009 IA-II);

D) tumors with lymph node metastasis (1988 IIIC) are subdivided

IIIC1 (indicating positive pelvic nodes)
IIIC2 (indicating positive para-aortic nodes with or without positive pelvic nodes).

Uterine Cancer Staging System
FIGO 2010

positive peritoneal cytology

positive pelvic washings are no longer formally considered part of the staging system and, consequently, do not alter staging.

The 2010 staging system continues to require the collection of peritoneal cytology.

An estimated 11% of patients undergoing staging for endometrial cancer will have positive peritoneal cytology, most commonly in the presence of extra-uterine disease.

Shan,Gynecol Oncol 2005

The prognostic significance of isolated positive cytology in the absence of extra-uterine disease is controversial

Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: unraveling a mystery.
Wethington, Gynecol Oncol. 2009

The presence of positive peritoneal cytology in patients with otherwise low-risk tumors (grade 1 or 2, myometrial invasion <50%, no cervical involvement, no lymphovascular space invasion) had a significantly lower rate of recurrence (4.1% vs 32%) compared with other patients who had positive cytology and high-risk tumors.

In this systematic review of over 50 studies

the prognosis associated with positive cytology varied based on the presence of other factors.

The prognostic significance of isolated positive cytology in the absence of extra-uterine disease is controversial

Positive peritoneal cytology is an independent risk-factor in early stage endometrial cancer.

Garg, Gynecol Oncol. 2013

patients with high-risk disease, such as grade 3 endometrioid, clear cell, or serous histology, were more likely to have positive cytology compared with those who did not have these high-risk factors (17.5% vs 7.5%, respectively; P<.0001). Positive cytology also predicted significantly poorer survival, irrespective of histology and tumor grade. The risk of death was significantly greater among patients who had positive cytology compared with that among patients who had negative peritoneal cytology and stage IA disease (hazard ratio, 4.6; 95% confidence interval, 3.79-5.66).

14,704 SEER

positive peritoneal cytology was an independent predictor of mortality, regardless of histologic subtype, among women with early stage (stage I or II) endometrial carcinoma.

The prognostic significance of isolated positive cytology in the absence of extra-uterine disease is controversial

Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: unraveling a mystery.

Wethington, Gynecol Oncol. 2009

Positive peritoneal cytology is an independent risk-factor in early stage endometrial cancer.

Garg, Gynecol Oncol. 2013

not consider positive cytology alone as a high-risk tumor criterion in the formulation of adjuvant treatment planning of patients with endometrial cancer.

Treatment decisions in women with endometrial cancer should be based on extent of disease, as determined by staging, and final pathologic tumor features.

Adjuvant treatment

2015

Postoperative Radiation Therapy for Endometrial Cancer:

American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline

Which women should receive postoperative external beam radiation?

To date, there is no documented improvement in overall survival for women with endometrial cancer treated with EBRT, and long-term complications including bowel and bladder dysfunction or secondary cancers have been reported.

•Patients with grade 3 cancer with ≥50% myometrial invasion or cervical stroma invasion may benefit from pelvic radiation to reduce the risk of pelvic recurrence.

•Patients with grade 1 or 2 tumors with ≥50% myometrial invasion may also benefit from pelvic radiation to reduce pelvic recurrence if other risk factors are present, such as age >60 years and/or LVSI. ***Vaginal brachytherapy may be a better option for patients with these features, especially if surgical staging was adequate and nodes were negative.***

A. Meyer et al. J Clin Oncol 33.

Prognostic factors in type 1 endometrial cancer

- **Grade**
- **Lympho-vascular space involvement**
- **Myometrial invasion**
- **Lymphnodes status**
- **Cervical stroma infiltration**
- **Tumor diameter (< 2 cm vs ≥ 2 cm)**
- **Age**

Sehouli, 2008

risk recurrence systems

RSS	Year	Number of patients	Criteria
PORTEC-1 (Creutzberg *et al*, 2000b)	2000	715	Low risk Endometrial adenocarcinoma stage Ia, grade 1 Intermediate risk Endometrial adenocarcinoma Stage I based on uterine factors Grade 1 histology and myometrial invasion of ⩾50% Grade 2 histology with any myometrial invasion Grade 3 histology with myometrial invasion <50% High-intermediate risk Age >60 years with grade 1 or 2 histology and myometrial invasion >50% Age >60 with grade 3 histology and myometrial invasion <50% High-risk Stage III–IV disease Uterine serous carcinoma or clear cell carcinoma of any stage
GOG-99 (Keys *et al*, 2004)	2004	382	Low risk Grade 1 or 2, endometrioid cancers confined to the endometrium stage IA Low-intermediate risk Age ⩽50 years + ⩽2 pathologic risk factors Age 50–69 years + ⩽1 pathologic risk factor Age ⩾70 years + no pathologic risk factors (Risk factors (1) grade 2 or 3 histology; (2) positive lymphovascular space invasion; (3) myometrial invasion to outer 1/3) High-intermediate risk (HIR) Any age + 3 pathologic risk factors Age 50–69 years + ⩾2 pathologic risk factors Age ⩾70 years + ⩾1 pathologic risk factor (Risk factors (1) grade 2 or 3 histology; (2) positive lymphovascular space invasion; (3) myometrial invasion to outer 1/3) High-risk Stage III–IV disease, regardless of histology or grade Uterine serous carcinoma or clear cell carcinoma of any stage

risk recurrence systems

SEPAL (Todo *et al*, 2010)	2010	671	Low risk Stage IA IB, endometrioid type, LVSI negative Intermediate risk Stage IA grade 3 endometrioid adenocarcinoma; any grade of non-endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma or other type of carcinoma), any LVSI Stage IB, grade 1–2 endometrioid adenocarcinoma, LVSI positive Stage IB, grade 3 endometrioid adenocarcinoma; any grade of non- endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma or other type of carcinoma), any LVSI Stage IC, stage II, any grade, any LVSI High risk Stage III–IV, any grade, any LVSI
ESMO (Colombo *et al*, 2013)	2013	—	Low risk Stage IA (grade 1 and grade 2) with endometrioid type Intermediate risk Stage IA grade 3 with endometrioid type Stage IB (grade 1 and grade 2) with endometrioid type High risk Stage IB grade 3 with endometrioid type All stages with non-endometrioid type

Miometrial invasion > 50%
Grade G3

→ **PORTEC-1**
GOG-99

Age > 60

→ **PORTEC 1 >60**
GOG-99 >70

Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma

Benedetti Panici 2015

CONCLUSION: Older women faced an intrinsic poorer survival whether or not they underwent lymphadenectomy, and, unexpectedly, irrespective of the presence of nodal metastasis. Only in older patients was obesity (body mass index >30) significantly associated with scarce prognosis.

> 65

Tumor diameter > 2 cm

→

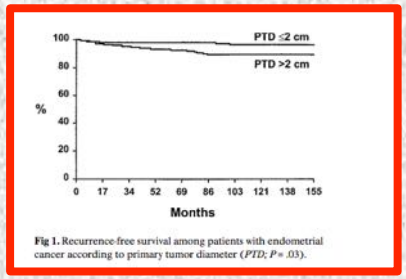


Fig 1. Recurrence-free survival among patients with endometrial cancer according to primary tumor diameter (*PTD*; *P* = .03).

Mariani, 2000

LVSI

strong marker of local and distant disease recurrence even in pN0 patients

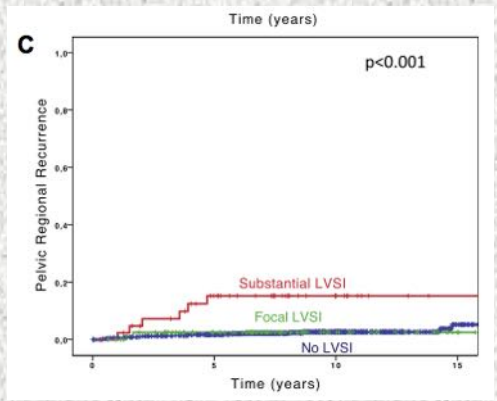
Morrow et al, 1991; Briet et al, 2005; Guntupalli et al, 2012

Laufer et al 2013; Simpkins et 2013•

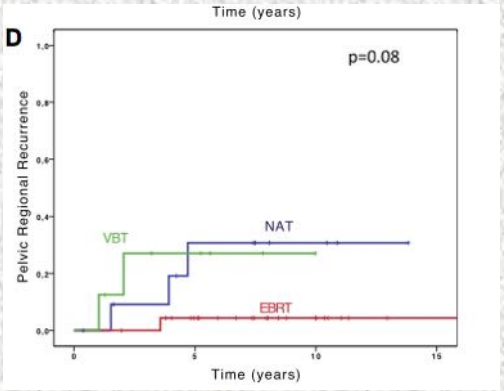
Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer – A pooled analysis of PORTEC 1 and 2 trials ☆

Tjalling Bosse [a,1], Elke E.M. Peters [a,1], Carien L. Creutzberg [b], Ina M. Jürgenliemk-Schulz [c], Jan J. Jobsen [d], Jan Willem M. Mens [e], Ludy C.H.W. Lutgens [f], Elzbieta M. van der Steen-Banasik [g], Vincent T.H.B.M. Smit [a], Remi A. Nout [b,*]

Bosse,2015



Conclusions: Substantial LVSI, in contrast to focal or no LVSI, was the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival. Therapeutic decisions should be based on the presence of substantial, not 'any' LVSI. Adjuvant EBRT and/or chemotherapy should be considered for stage I EC with substantial LVSI.



Just how accurate are the major risk stratification systems for early-stage endometrial cancer?

S Bendifallah[*,1,2], G Canlorbe[1], P Collinet[3], E Arsène[3], F Huguet[4], C Coutant[5], D Hudry[5], O Graesslin[6], E Raimond[6], C Touboul[7], E Daraï[1,8] and M Ballester[1,8]

British Journal of Cancer (2015)

SEPAL (Todo et al, 2010)	2010	671	Low risk Stage IA IB, endometrioid type, LVSI negative Intermediate risk Stage IA grade 3 endometrioid adenocarcinoma; any grade of non-endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma or other type of carcinoma), any LVSI Stage IB, grade 1–2 endometrioid adenocarcinoma, LVSI positive Stage IB, grade 3 endometrioid adenocarcinoma; any grade of non- endometrioid carcinoma (serous adenocarcinoma, clear cell adenocarcinoma or other type of carcinoma), any LVSI Stage IC, stage II, any grade, any LVSI High risk Stage III–IV, any grade, any LVSI
ESMO (Colombo et al, 2013)	2013	—	Low risk Stage IA (grade 1 and grade 2) with endometrioid type Intermediate risk Stage IA grade 3 with endometrioid type Stage IB (grade 1 and grade 2) with endometrioid type High risk Stage IB grade 3 with endometrioid type All stages with non-endometrioid type
ESMO modified (Bendifallah et al, 2014)	2014	496	Low-risk ESMO/LVSI- Low-risk ESMO/LVSI+ Intermediate-risk ESMO/LVSI- Intermediate-risk ESMO/LVSI+ High-risk ESMO/LVSI- High-risk ESMO/LVSI+

Abbreviations: ESMO = European Society for Medical Oncology; LVSI = lymphovascular space invasion.

A clue towards improving the European Society of Medical Oncology risk group classification in apparent early stage endometrial cancer? Impact of lymphovascular space invasion

S Bendifallah, BJC 2014

- ***Low risk***
  - **ESMO/LVSI-**
  - **ESMO/LVSI+**
- ***Intermediate risk***
  - **ESMO/LVSI-**
  - **ESMO/LVSI+**
- ***High risk***
  - **ESMO/LVSI-**
  - **ESMO/LVSI+**

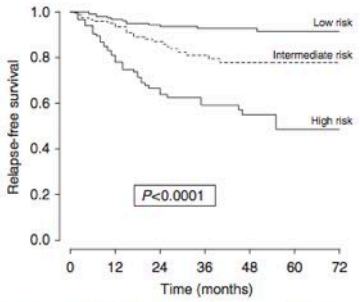


Figure 1. Recurrence-free survival according to ESMO risk classification.

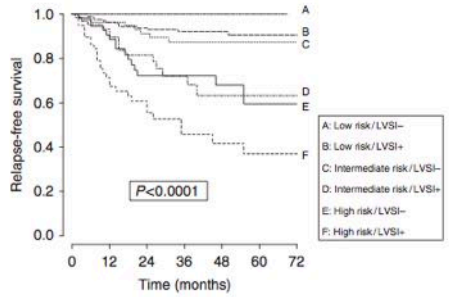


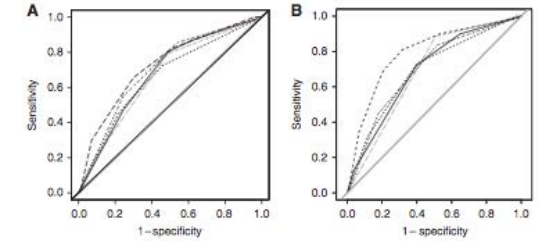
Figure 2. Recurrence-free survival according to modified ESMO risk classification.

Conclusions: The current modified classification could be helpful to better define indications for nodal staging and adjuvant therapy, especially for patients with intermediate risk EC.

Just how accurate are the major risk stratification systems for early-stage endometrial cancer?

S Bendifallah*[,1,2], G Canlorbe[1], P Collinet[3], E Arsène[3], F Huguet[4], C Coutant[5], D Hudry[5], O Graesslin[6], E Raimond[6], C Touboul[7], E Daraï[1,8] and M Ballester[1,8]

British Journal of Cancer 2015

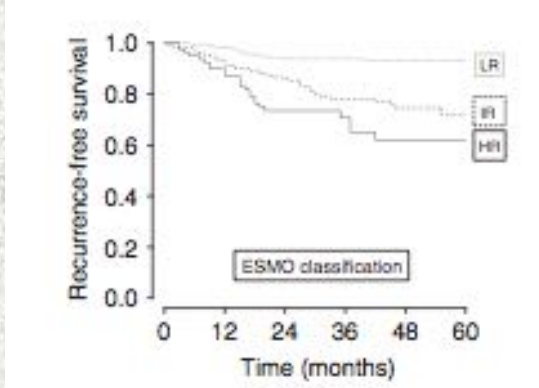


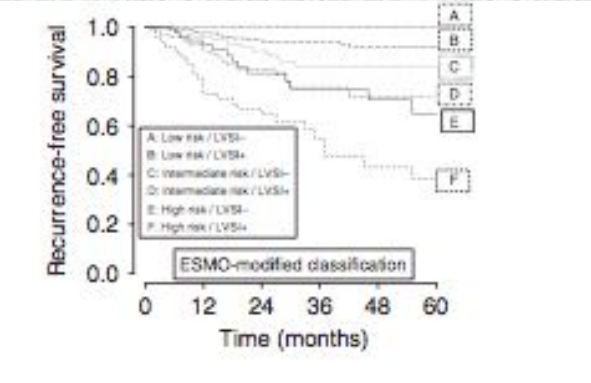
Classification	A	B	Legend
	Recurrence	Lymph node metastasis	
	C-index (95% CI)	AUC (95% CI)	
PORTEC-1 [8]	0.68 (0.66–0.70)	0.69 (0.66–0.72)	
GOG-99 [15]	0.65 (0.63–0.67)	0.69 (0.67–0.71)	
SEPAL [12]	0.66 (0.63–0.69)	0.68 (0.66–0.70)	
ESMO [2]	0.71 (0.68–0.74)	0.70 (0.68–0.72)	
ESMO modified [16]	0.73 (0.70–0.76)	0.80 (0.78–0.72)	

None of the five major RSS showed high accuracy in stratifying the risk of recurrence or nodal metastases in patients with early-stage EC

Just how accurate are the major risk stratification systems for early-stage endometrial cancer?

S Bendifallah*[,1,2], G Canlorbe[1], P Collinet[3], E Arsène[3], F Huguet[4], C Coutant[5], D Hudry[5], O Graesslin[6], E Raimond[6], C Touboul[7], E Daraï[1,8] and M Ballester[1,8]





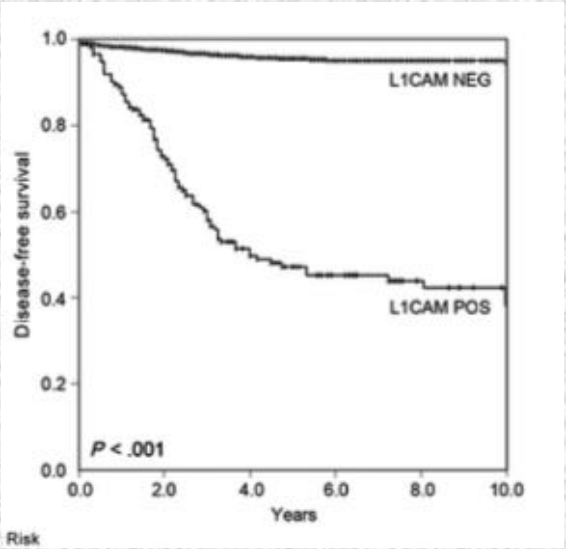
Therefore there is a need to rivisit existing RSS using additional tools as biological markers to better stratify risk for these patients

L1CAM in Early-Stage Type I Endometrial Cancer: Results of a Large Multicenter Evaluation

Alain G. Zeimet, Daniel Reimer, Monica Huszar, Boris Winterhoff, Ulla Puistola, Samira Abdel Azim, Elisabeth Müller-Holzner, Alon Ben-Arie, Léon C. van Kempen, Edgar Petru, Stephan Jahn, Yvette P. Geels, Leon F. Massuger, Frédéric Amant, Stephan Polterauer, Elisa Lappi-Blanco, Johan Bulten, Alexandra Meuter, Staci Tanouye, Peter Oppelt, Monika Stroh-Weigert, Alexander Reinthaller, Andrea Mariani, Werner Hackl, Michael Netzer, Uwe Schirmer, Ignace Vergote, Peter Altevogt, Christian Marth, Mina Fogel

J Natl Cancer Inst;2013

DFS



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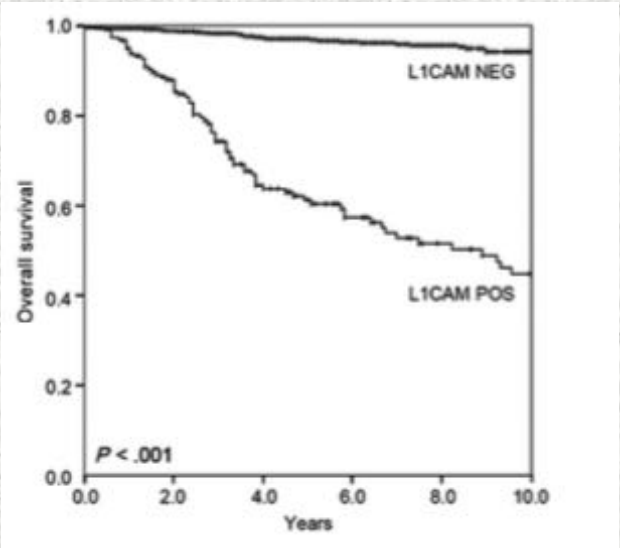

L1CAM in Early-Stage Type I Endometrial Cancer: Results of a Large Multicenter Evaluation

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J Natl Cancer Inst;2013

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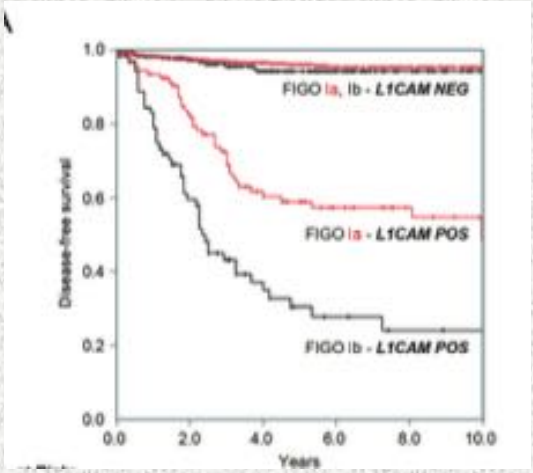
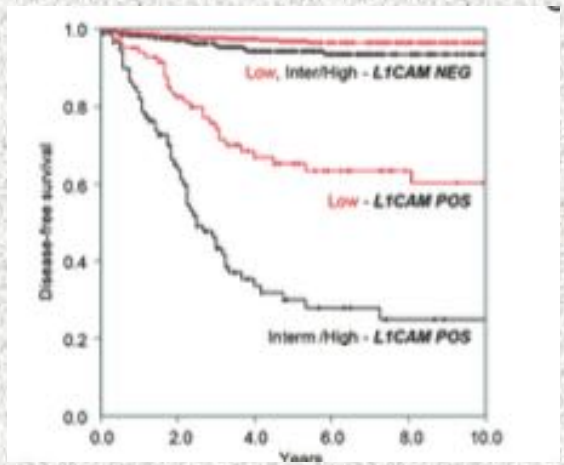
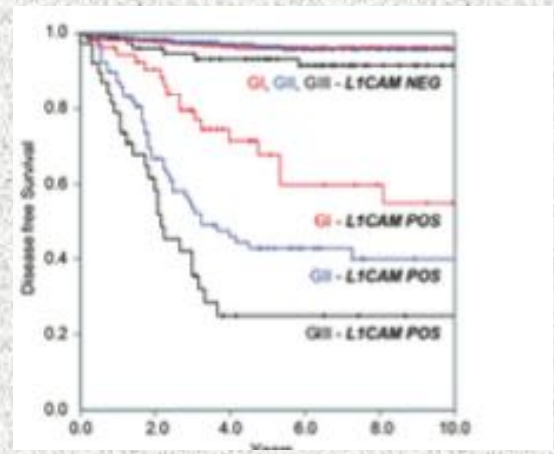


FIGO stage



Risk stratification



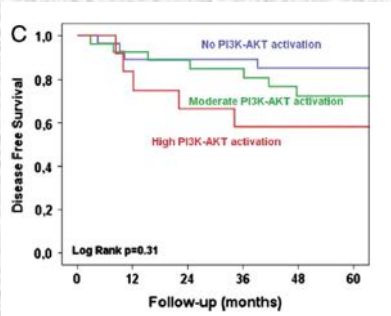
Grade

Improved risk assessment of endometrial cancer by combined analysis of MSI, PI3K–AKT, Wnt/β-catenin and P53 pathway activation☆

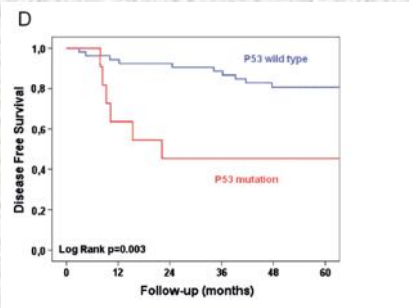
Remi A. Nout [a,*,1], Tjalling Bosse [f,1], Carien L. Creutzberg [a], Ina M. Jürgenliemk-Schulz [b], Jan J. Jobsen [c], Ludy C.H.W. Lutgens [d], Elzbieta M. van der Steen-Banasik [e], Ronald van Eijk [f], Natalja T. ter Haar [f], Vincent T.H.B.M. Smit [f]

Gynecologic Oncology 2012

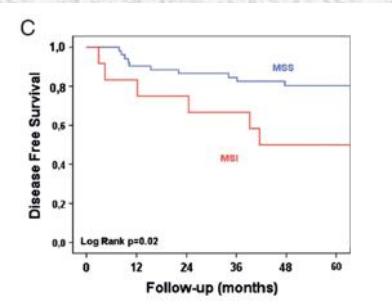
PI3K–AKT pathway

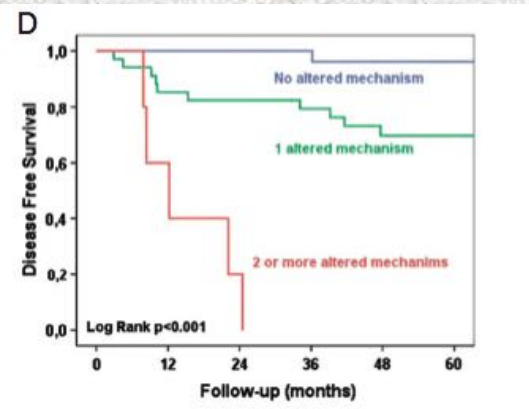


P53



MSI





Conclusions

Activation of multiple oncogenic pathways in EEC was the most powerful prognostic factor for decreased DFS, resulting in an individual risk assessment superior to the current approach based on clinico-pathological factors.

Prognostic factors in type 1 endometrial cancer

- Grade
- Lympho-vascular space involvement
- Myometrial invasion
- Lymphnodes status
- Cervical stroma infiltration <10–15% of all uterine cancers
- Tumor diameter (< 2 cm vs ≥ 2 cm)
- Age

Sehouli, 2008

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2016

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,g,l,m]		
	G1	G2	G3
Surgically staged:[d] Stage II[o,p] →	Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± chemotherapy[n] (category 2B for chemotherapy)

GOG 99 (2004) [7]	IB/IC		Yes	No	4-Year	4-Year	4-Year	4-Year	4-Year	4-Year	4-Year	4-Year
No RT arm (N = 202)	IIA (occult)	pT1			7%[a]	2%[a]	8%	5%	92%	95%	86%	92%
WPRT arm (N = 190)	Any grade											
	Excluded											
	Serous/clear cell											
PORTEC-2 (2010) [9]	Stage IC (grade 1 or 2 and age >60)		No	–	WPRT	IVRT	WPRT	IVRT	WPRT	IVRT	WPRT	IVRT
WPRT (N = 214)	Stage IB (grade 3 and age >60)				5-Year	5-Year	5-Year	5-Year	5-Year	5-Year	5-Year	5-Year
IVRT (N = 213)	Stage IIA except >50% DOI with grade 3	pT1			2.1%	5.1%	5.7%	8.3%	78%	83%	80%	85%
	Excluded serous/clear cell histology											

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2016

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,g,l,m]		
	G1	G2	G3
Surgically staged:[d] Stage II[o,p] →	Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± chemotherapy[n] (category 2B for chemotherapy)

Minimal stromal invasion without risk factors

	Maggi [3]	Susumu [2]
Protocol regimens	RT arm: Pelvic XRT + para-aortic RT if any (+)LNs Chemotherapy arm: CAP q28d × 5 cycles	RT arm: Pelvic XRT +/− Para-aortic RT +/− IVB Chemotherapy arm: CAP q28d × at least 3 cycl
Included cases	LND optional Excluded serous/clear cell histology	LND optional Endometrioid only
	FIGO stages: IC (G3) IIA/B (G3) if ≥50% myoinvasion III (any)	FIGO stages: IC-IIIC AND >50% myoinvasion <75 years old
N	RT arm: 166 Chemotherapy arm: 174	RT arm: 192 Chemotherapy arm: 192
5-Year PFS	RT arm: 63% Chemotherapy arm: 63%	RT arm: 83.5% Chemotherapy arm: 81.8%
HR (recur)	0.88 (0.63 to 1.23)	1.07 (0.65 to 1.76)
5-Year OS	RT arm: 69% Chemotherapy arm: 66%	RT arm: 85.3% Chemotherapy arm: 86.7%
HR (death)	0.95 (0.66 to 1.36)	0.72 (0.4 to 1.29)

LVSI

Prognostic factors in type 1 endometrial cancer

- Grade
- Lympho-vascular space involvement
- Myometrial invasion
- Lymphnodes status
- Cervical stroma infiltration
- Tumor diameter (< 2 cm vs ≥ 2 cm)
- Age

Stage III C1
Stage III C2

Sehouli, 2008

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2016

Total hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic and para-aortic lymph nodes dissection

(>20 pelvic nodes; >10 aortic nodes).

Continue to be recommended

THE COCHRANE COLLABORATION®

Lymphadenectomy for the management of endometrial cancer (Review)

Frost JA, Webster KE, Bryant A, Morrison J

2015

Authors' conclusions

This review found no evidence that lymphadenectomy decreases risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease. Evidence on serious adverse events suggests that women who undergo lymphadenectomy are more likely to experience surgery-related systemic morbidity or lymphoedema/lymphocyst formation. Currently, no RCT evidence shows the impact of lymphadenectomy in women with higher-stage disease and in those at high risk of disease recurrence.

MRC ASTEC trial *Lancet 2009*

Benedetti P et al, *J Natl Cancer Inst 2008*

large proportion of low-risk women,

no clear indication was given for postoperative adjuvant therapy

neither trial evaluated appropriately the role of para-aortic lymphadenectomy

No lymphoadenectomy in early stage low risk endometrial cancer type I

Table IV. Association of pelvic lymph node metastasis with primary tumor diameter and grade among patients with low-risk endometrial cancer (endometrioid histologic subtype, myometrial invasion ≤ 50%, and histologic grade 1-2)

		Positive pelvic lymph nodes							
		Primary tumor diameter ≤2 cm		*Primary tumor diameter >2 cm*		*Histologic grade 1*		*Histologic grade 2*	
Study	*Cases (No.)*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Schink et al[10]	87	0/39	0	4/48	8	1/57	2	3/30	10
Current study	187	0/59	0*	8/107	7*	5/126	4	4/61	7
Creasman et al[9]	393	NA	NA	NA	NA	3/162	2	14/231	6
TOTAL	667	0/98	0	12/155	8	9/345	3	21/322	7

NA, Not available.
*Calculated for the 166 patients for whom the information about primary tumor diameter was available.

Low incidence of pelvic lymph nodes

Table V. Recurrence and survival among patients with low-risk endometrial cancer (endometrioid histologic subtype, myometrial invasion ≤50%, and histologic grade 1-2) and no lymphadenectomy

Study	*Cases (No.)*	*Adjuvant therapy*	*Median follow-up (mo)*	*Recurrence*		*Site*
				No.	*%*	
No adjuvant therapy						
Lim et al[28]	315†	None	45	14	4	Local (n = 8), distant (n = 6)
Carey et al[6]	227	None	54	10	4	Local (n = 6), distant (n = 3), local plus distant (n = 1)
Leijon et al[7]	248	None	42	9	4	Local (n = 6), distant (n = 3)
Poulsen et al[8]	641	None	68-92	45	7	Local (n = 24), distant (n = 21)
Larson et al[29]	102‡	None	40-46	3	3	Local (n = 3)
Current study	126	None	88	2	2	Local (n = 1), distant (n = 1)
TOTAL	1659	None		83	5	Local (n = 48, 3%), distant (n = 34, 2%), local plus distant (n = 1, 0.1%)
Adjuvant therapy						
Piver and Hempling[30]	90	Brachytherapy§	NA	0	0	—
Lim et al[28]	91‖	Brachytherapy	45	4	4	Local (n = 2), distant (n = 2)
Weiss et al[26]	75	Brachytherapy	48	3	4	Local (n = 1), distant (n = 1), local plus distant (n = 1)
Aalders et al[5]	126	Brachytherapy	3-10 y	7	6	Local (n = 5), distant (n = 2)
Faught et al[31]	161	Brachytherapy¶	80% ≥5 y	0	0	—
TOTAL	543			14	2.5	Local (n = 8, 1%), distant (n = 5, 1%), local plus distant (n = 1, 0.2%)

Low relapse rate

Low-risk corpus cancer: Is lymphadenectomy or radiotherapy necessary?

Andrea Mariani, MD,[a] Maurice J. Webb, MD,[a] Gary L. Keeney, MD,[b] Michael G. Haddock, MD,[c] Giliola Calori, MS,[d] and Karl C. Podratz, MD, PhD[a]

Rochester, Minnesota, and Milan, Italy

Am J Obstet Gynecol 2000

RESULTS: The 5-year overall cancer-related and recurrence-free survivals were 97% and 96%, respectively. Primary tumor diameter and lymphatic or vascular invasion significantly affected longevity. No patient with tumor diameter ≤2 cm had positive lymph nodes or died of disease.

CONCLUSION: Patients who have International Federation of Gynecology and Obstetrics grade 1 or 2 endometrioid corpus cancer with greatest surface dimension ≤2 cm, myometrial invasion ≤50%, and no intraoperative evidence of macroscopic disease can be treated optimally with hysterectomy only. (Am J Obstet Gynecol 2000;182:1506-19.)

T <2 cm
MI <50%
G1-2

No lymphoadenectomy
No adjuvant therapy

Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging

Andrea Mariani, Sean C. Dowdy, William A. Cliby, Bobbie S. Gostout, Monica B. Jones, Timothy O. Wilson, Karl C. Podratz *

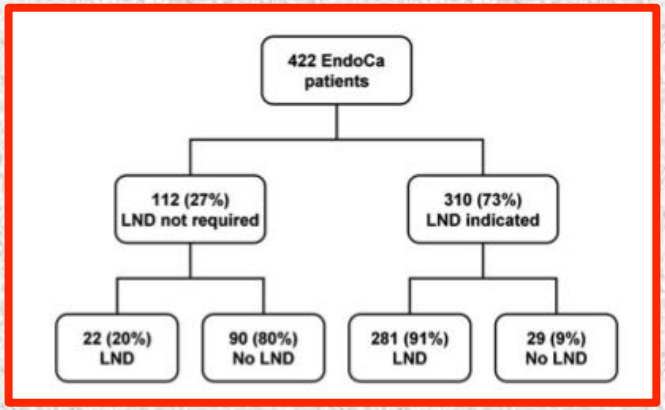
Division of Gynecologic Surgery, Mayo Clinic, Rochester, Minnesota, USA

Gynecol Oncol 2008

Guidelines for surgical management of endometrial cancer at Mayo Clinic, Rochester, Minnesota (2004–2006)

Hysterectomy
Bilateral salpingo-oophorectomy
Peritoneal cytology
Bilateral pelvic and para-aortic lymphadenectomy
  Para-aortic dissection up to renal vessels
  Excision of gonadal vessels at insertions (optional)
  Omit lymphadenectomy if no disease beyond corpus and
    (1) Endometrioid (grade 1 or 2), MI ≤50%, and PTD ≤2 cm; or
    (2) Endometrioid and no MI (independent of grade and PTD)
Omentectomy, staging biopsies, or cytoreduction for nonendometrioid or advanced disease

Abbreviations: MI, myometrial invasion; PTD, primary tumor diameter.



need for systematic pelvic and para-aortic lymphadenectomy and cytologic assessment

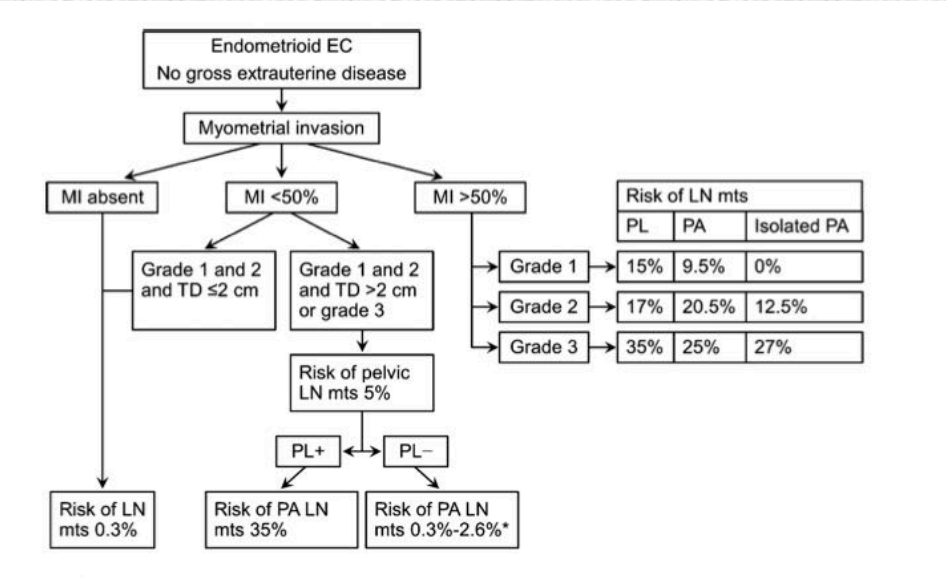
PTD >2 cm
nonendometrioid histologic subtype, grade 3 histology
depth of MI greater than 50%.

documented macroscopic extrauterine disease, when optimal cytoreduction was anticipated.

Role of pelvic and para-aortic lymphadenectomy in endometrial cancer: Current evidence

Giorgio Bogani[1], Sean C. Dowdy[1], William A. Cliby[1], Fabio Ghezzi[2], Diego Rossetti[3], and Andrea Mariani[1]

J Obstet Gynaecol Res. 2014



in the majority of patients with para-aortic lymph node invasion, the area above the IMA is involved.

How does lymphadenectomy impact morbidity, QOL and costs?

higher risk of surgically related morbidity and lymphatic complications

longer operative times and higher complication rates than patients who have hysterectomy plus adnexectomy alone.

Also, the overall cost of surgical care is higher.

What is the role of SLN mapping?

SLN mapping should be as good as a systematic lymphadenectomy in the identification of patients with lymph node dissemination, while reducing the morbidity associated with an extensive surgical procedure.

The prospective multi-institutional SENTI-ENDO study suggested that in stage I and II EC patients, SLN biopsy has a sensitivity of 84%.

Darai,2015

one of the largest prospective single-institution cohorts, showed that applying an SLN mapping algorithm may be a safe and effective alternative to systematic lymphadenectomy

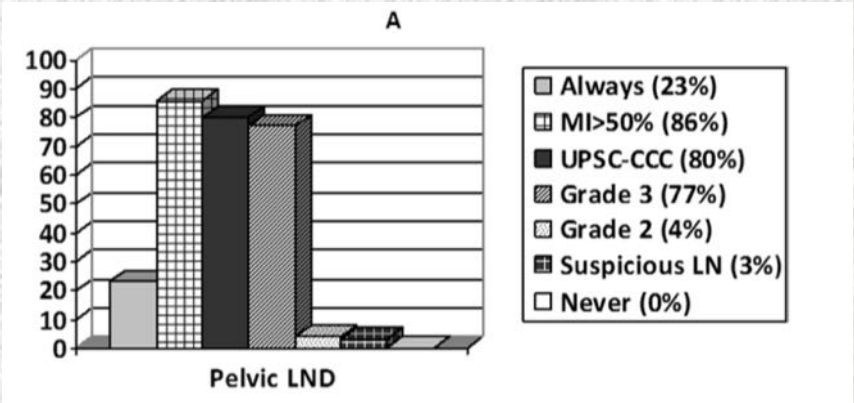
Barlin,2012

Ideally, SLN biopsy could be an effective alternative to systematic lymphadenectomy. However, available data are still insufficient to define its role in clinical practice.

Management of endometrial cancer in Italy: A national survey endorsed by the Italian Society of Gynecologic Oncology

Greggi, 2014

retroperitoneal LND



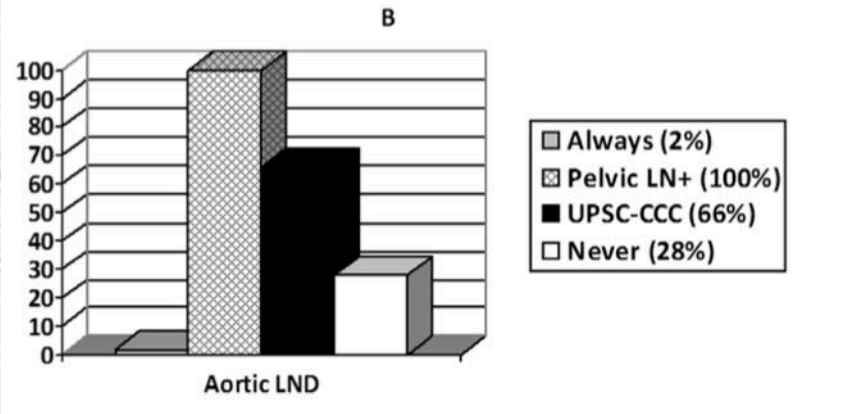
23% of centers perform it routinely

>50% myometrial infiltration (86%),
serous or clear cell histology (80%),
poorly differentiated tumors (77%),
moderately differentiated tumors (4%),
suspicious nodes (3%)

Management of endometrial cancer in Italy: A national survey endorsed by the Italian Society of Gynecologic Oncology

Greggi, 2014

Aortic LND



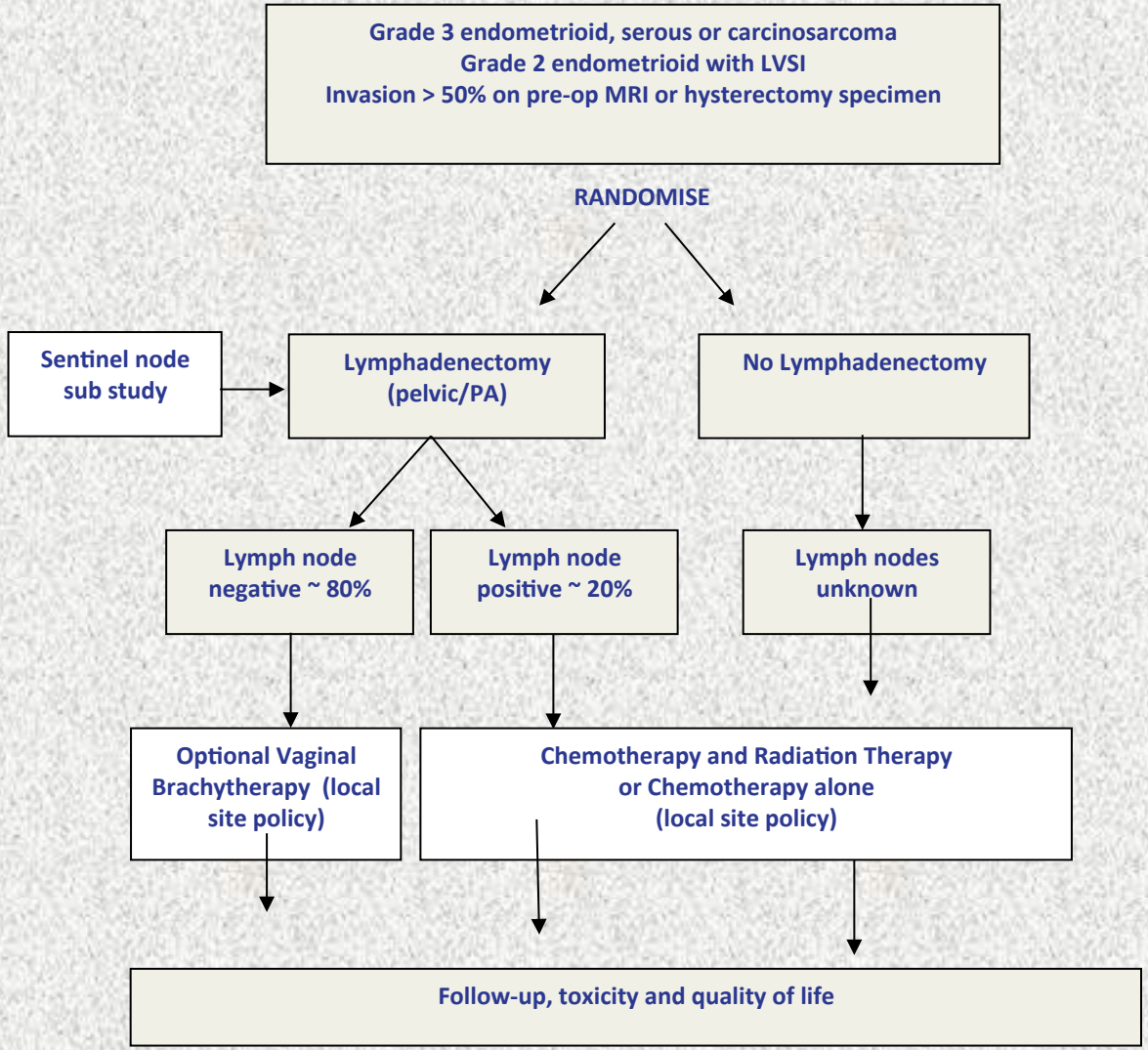
is never performed in 28% of institutions routinely in 2%,

100% pelvic nodes suspected or positive at frozen sections
66% serous or clear cell histology

STATEC

Selective **T**argeting of **A**djuvant **T**herapy for **E**ndometrial **C**ancer

University College London Hospital



Prognostic factors in type 1 endometrial cancer

- **Grade**
- **Lympho-vascular space involvement**
- **Myometrial invasion**
- **Lymphnodes status**
- **Cervical stroma infiltration**
- **Tumor diameter (< 2 cm vs ≥ 2 cm)**
- **Age**
- **Stage III-IV**

Sehouli, 2008

Low risk

pT1A
pT1B
without risk factors

LESS IS BETTER

Reduction
of toxicities treatment-related

High risk

pT1B with risk factor
pT2 with risk factor
Advanced stage

MORE IS BETTER

Increase
of the therapeutic load

Early stage
Low risk
70%

LESS
IS BETTER

Reduction
of toxicities treatment-related

OS 93%
DSS 99%

indicating that these women are far more likely to die of comorbidities than of endometrial cancer itself

only 16% of deaths in low-risk patients are cancer-related

86% of recurrences
92% of cancer-related deaths

occur in this risk groups.

OS 15%-45%

High risk

30%

MORE
IS BETTER

Increase
of the therapeutic load

SIGNIFICANT PELVIC RECURRENCE IN HIGH-RISK PATHOLOGIC STAGE I–IV ENDOMETRIAL CARCINOMA PATIENTS AFTER ADJUVANT CHEMOTHERAPY ALONE: IMPLICATIONS FOR ADJUVANT RADIATION THERAPY

ARNO J. MUNDT, M.D.,* RUSSELL MCBRIDE, B.A.,* JACOB ROTMENSCH, M.D.,*†
STEVEN E. WAGGONER, M.D.,† S. DIANE YAMADA, M.D.,† AND PHILIP P. CONNELL, M.D.*

Int. J. Radiation Oncology Biol. Phys. 2001

Table 2. Pattern of failure

		Pelvic			Extrapelvic			
Total	Recurred	Any	VR	Non-VR	Any	PA	Abd.	Distant
43	29 67.4%	17 39.5%	14 32.6%	9 20.9%	23 55.5%	5 11.6%	13 30.3%	18* 41.8%

Conclusions: PVR is common in high-risk pathologic Stage I–IV endometrial cancer patients after adjuvant chemotherapy alone. These results support the continued use of locoregional RT in patients undergoing adjuvant chemotherapy. Further studies are needed to test the addition of chemotherapy to locoregional RT.

Adjuvant chemotherapy *vs* radiotherapy in high-risk endometrial carcinoma: results of a randomised trial

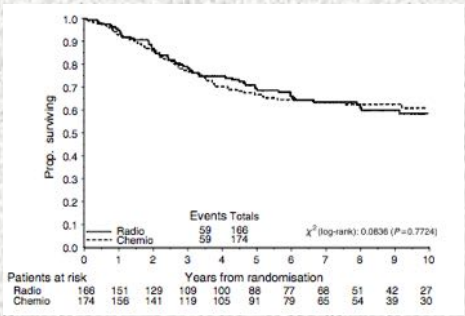
Maggi, Br J Cancer 2006

stage IcG3, IIG3 with myometrial invasion >50%, and III

345

EBRT
45 – 50 Gy

adjuvant CT
cisplatin,
dox
cycloph x 5



median follow-up of 95.5 month

5 yrs OS 63 and 66

EBRT
60 relapse

21% distant (extra-abdominal or liver)
7% local
5% concurrent distant and local ,
3% unknown type i

CT
56 relapse

16% distant
11% local
5% concurrent local and distant
1% unknown type

Radiotherapy delayed local relapses and CT delayed metastases but these trends did not achieve statistical significance.

node positive endometrial cancer treated surgically and with adjuvant radiotherapy

Author (year)	No. of patients	Overall survival (%)	Disease-free survival (%)
Onda et al. (1997) [13]	30/173	84	NA
Nelson et al. (1999) [14]	17	72	81
Mundt et al. (2001) [8]	30	NA	34
Patel et al. (2007) [5]	23/107	60	NA
Klopp et al. (2009) [4]	50/71	73	NA
Lee et al. (2012) [3]	62/66	81	71

The survival outcome and patterns of failure in node positive endometrial cancer patients treated with surgery and adjuvant radiotherapy with curative intent

Chrishanthi Rajasooriyar[1], David Bernshaw[2], Srinivas Kondalsamy-Chennakesavan[3], Linda Mileshkin[2], Kailash Narayan[2]

J Gynecol Oncol 2014

93% had nodes detected on nodal sampling or lymph node resection 7% on PET.

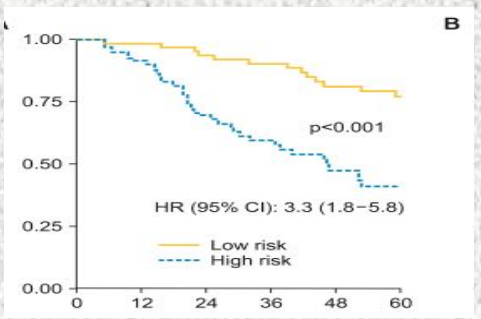
126 pts

EBRT
45-50 Gy

75% pelvic,
7% common iliac,
18% para-aortic

38% received concurrent chemotherapy
17% sistemic CT

5-year OS 61%. DSS 67%



Low risk G1-2
High risk G3, type 2

Fifty-four patients (43%) relapsed

6% exclusively in pelvis.

The extrapelvic failure in the low risk group was 23% (15/65) and 59% (36/61) in the high risk group.

94% extrapelvic nodal or distant parenchymal sites

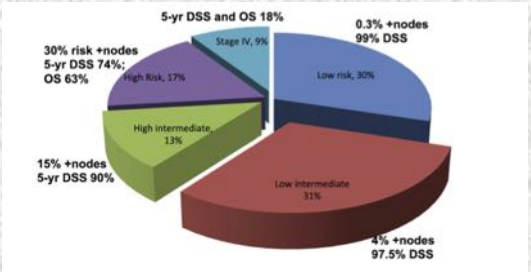
Review

Improving oncologic outcomes for women with endometrial cancer: Realigning our sights

Sean C. Dowdy *

Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN 55905, USA

MORE IS BETTER



Early stage
High risk

			OS	PFS	RR
Chemotherapy vs radiotherapy					
JGOG 2933 [21]	IC–IIIC	CAP (n = 192) Pelvic RT (n = 193)	5-year: 86.7% vs 85.3% HR = 0.72 [0.40–1.29] p = 0.27	5-year: 81.8% vs 83.5% HR = 1.07 [0.65–1.76] p = 0.73	Overall: 17.2% vs 15.5% Intrapelvic: 7.3% vs 6.7% Extrapelvic: 13.5% vs 16.1%
GICOG [22]	IC grade 3 IIA–B grade 3 and ≥50% m.i. III	CAP (n = 177) pelvic RT ± lumbo-aortic RT (n = 168)	5-year: 66% vs 69% HR = 0.95 [0.66–1.36] p = 0.78	5-year: 63% vs 63% HR = 0.88 [0.63–1.23] p = 0.45	Distant: 21% vs 26% Local: 16% vs 12%
GOG122 [23]	III or IV ≤2 cm post-surgery	CD (n = 190) abdominal RT ± pelvic and para-aortic RT (n = 198)	**5-year: 55% vs 42%** **HR = 0.68 [0.52–0.89]** **p = 0.004**	**5-year: 50% vs 38%** **HR = 0.71 [0.55–0.91]** **p = 0.007**	Overall: 50% vs 54%

MORE IS BETTER

Chemotherapy+radiotherapy

			OS	PFS	RR
Chemotherapy + radiotherapy vs radiotherapy alone					
NSGO-EORTC [25]	I (91%)	Chemo + pelvic RT ± VB (n = 187) Pelvic RT ± VB (n = 191)	5-year: 83% *vs* 76% HR = 0.66 [0.40–1.08] p = 0.10	**5-year: 79% vs 72%** **HR = 0.64 [0.41–0.99]** **p = 0.04**	Overall: 15% *vs* 24%
MaNGO ILIADE-III [25]	IIB IIIA–C	CD + pelvic RT ± VB (n = 80) Pelvic RT ± VB (n = 76)	5-year: 78% *vs* 73% HR = 0.74 [0.36–1.52] p = 0.41	5-year: 74% *vs* 61% HR = 0.61 [0.33–1.12] p = 0.10	Overall: 19% *vs* 32%
Kuoppala [26]	IA–B grade 3 IC–IIIA	Cisplatin/epirubicin/cyclophosphamide + pelvic RT (n = 84) Pelvic RT (n = 72)	median: 37 *vs* 23 months p = 0.15	median: 25 *vs* 18 months p = 0.13	Overall: 22.6% *vs* 18% p = 0.50 Distant: 20.2% *vs* 13.8%
GOG 34 [27]	I–II occulte[2]	Doxorubicin + pelvic RT ± para-aortic RT (n = 92) Pelvic RT ± para-aortic RT (n = 89)	5-year: 61% *vs* 66%	-	Extra-pelvic: 16.3% *vs* 22.5%

MORE
IS BETTER

Sequential chemotherapy and radiotherapy in the sandwich method for advanced endometrial cancer

Study	Study Type	No. of Patients	Stage of Disease	Pathological Type	Treatment Regimens	3-Year PFS	3-Year OS	NOS Star
Lan et al (2013)[13]	Retrospective	25	III–IV	UPSC + other types	"Sandwich" protocol with unclear detail	62.4%	81.8%	5/9
Einstein et al (2012)[14]	Prospective	14	III–IV	UPSC	3 cycles of paclitaxel and carboplatin + radiotherapy + 3 cycles of chemotherapy	NA	50%	6/9
Geller et al (2011)[15]	Retrospective	39	III–IV	UPSC + other types	3 cycles of docetaxel and carboplatin + radiotherapy + 3 cycles of chemotherapy	71%	NA	5/9
Secord et al. (2009)[16]	Retrospective	45	III–IV	UPSC + other types	"Sandwich" protocol with unclear detail	69%	88%	6/9
Lupe et al. (2009)[17]	Prospective	43	III–IV	UPSC + other types	4 cycles of paclitaxel and carboplatin + radiotherapy + 2 cycles of chemotherapy	NA	68%	6/9

NA = not available; NOS = Newcastle-Ottawa scale; OS = overall survival; PFS = progression-free survival; UPSC = uterine papillary serous carcinoma.

Review

Improving oncologic outcomes for women with endometrial cancer: Realigning our sights

Sean C. Dowdy *

Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN 55905, USA

MORE
IS BETTER???

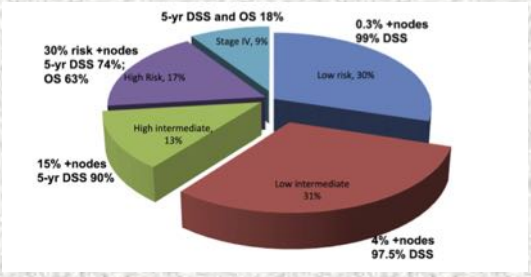


Table 1
Ongoing randomized trials of particular interest for patients with endometrial cancer. Note the wide variation in inclusion criteria.

Trial	Treatment	Patient cohort	Primary completion date
ENGOT-EN2-DGCG/EORTC 55102	Chemotherapy vs. observation	Stage I/II (grade 3 or type II histology)	January 2018
GOG 249	Pelvic radiation vs. brachytherapy and chemotherapy	GOG 99 high intermediate risk, stage II, or stage I/II with type II histology	Completed February 2013; results early 2014
PORTEC 3	Pelvic radiation with or without concomitant and post-radiation	Stages I (grade 3 with LVSI or >50% MI; type II histology), II, IIIA, and IIIC	Completed; results December 2018
GOG 258	Chemo alone vs. pelvic radiation with concomitant and post-radiation chemo	Stage I/II (type II with positive cytology), stages III–IVA	February 2016

Current opinion on bevacizumab on endometrial cancer treatment

Stefano Bogliolo, Chiara Cassani, Barbara Gardella, Valentina Musacchi, Luciana Babilonti, Pier Luigi Venturini, Simone Ferrero† & Arsenio Spinillo

Expert Opin Biol Ther 2015

A prospective feasibility study of radiation and concurrent bevacizumab for recurrent endometrial cancer☆,☆☆,★

Akila N. Viswanathan [a,*], Hang Lee [b], Ross Berkowitz [c], Suzanne Berlin [d], Susanna Campos [d], Colleen Feltmate [c], Neil Horowitz [c], Michael Muto [c], Cheryl A. Sadow [e], Ursula Matulonis [d]

Gynecologic Oncology 2014

1- and 3-year progression-free survival (PFS was) 80%/67% and overall survival (OS) was 93%/80%.

Conclusions. Delivering bevacizumab with concurrent radiation provides excellent local tumor control and survival for women with recurrent endometrioid endometrial cancer, particularly those with unresectable nodes. Caution must be used in those at highest risk of developing metastatic disease given the increased risk of thromboembolic events. This regimen may be considered for recurrent gynecologic malignancies in future trials.

NRG Oncology/RTOG 0921: A Phase 2 Study of Postoperative Intensity-Modulated Radiotherapy With Concurrent Cisplatin and Bevacizumab Followed by Carboplatin and Paclitaxel for Patients With Endometrial Cancer

Akila N. Viswanathan, MD, MPH[1]; Jennifer Moughan, MS[2]; Brigitte E. Miller, MD[3]; Ying Xiao, PhD[4]; Anuja Jhingran, MD[5]; Lorraine Portelance, MD[6]; Walter R. Bosch, DSc[7]; Ursula A. Matulonis, MD[8]; Neil S. Horowitz, MD[9]; Robert S. Mannel, MD[10]; Luis Souhami, MD[11]; Beth A. Erickson, MD[12]; Kathryn A. Winter, MS[2]; William Small Jr, MD[13]; and David K. Gaffney, MD, PhD[14]

Cancer July 1, 2015

34 pts

hysterectomy and lymph node removal, and had >1 of the following high-risk factors: grade 3 carcinoma with >50% myometrial invasion, grade 2 or 3 disease with any cervical stromal invasion, or known extrauterine extension confined to the pelvis.

IMRT and concurrent cisplatin on days 1 and 29 of radiation and bevacizumab (at a dose of 5 mg/kg on days 1, 15, and 29 of radiation) followed by adjuvant carboplatin and paclitaxel for 4 cycles.

primary endpoint was grade >3 AEs occurring within the first 90 days

23.3% grade > 3 treatment-related nonhematologic toxicitie

Term	Grade[a]
Headache	3
Fatigue	3
Syncope	3
Thromboembolic event[b]	4
Hyponatremia	3
Hyperglycemia	3
Vaginal infection	3
Vaginal inflammation	3
ALT increased	3
Febrile neutropenia	4
Fatigue	3

2-year OS 96.7%
DFS 79.1%

Risk-scoring models for individualized prediction of overall survival in low-grade and high-grade endometrial cancer

Mariam M. AlHilli [a], Andrea Mariani [a], Jamie N. Bakkum-Gamez [a], Sean C. Dowdy [a], Amy L. Weaver [b], Preema P. Peethambaram [c], Gary L. Keeney [d], William A. Cliby [a], Karl C. Podratz [a,*]

Gynecologic Oncology 133 (2014)

925 low-grade G1-2

older age at surgery, cardiovascular disease, pulmonary dysfunction, advanced stage, primary tumor diameter greater than 2 cm, pelvic lymph node status, and 30-day postoperative complications were independently predictive of compro- mised OS.

1281 pts

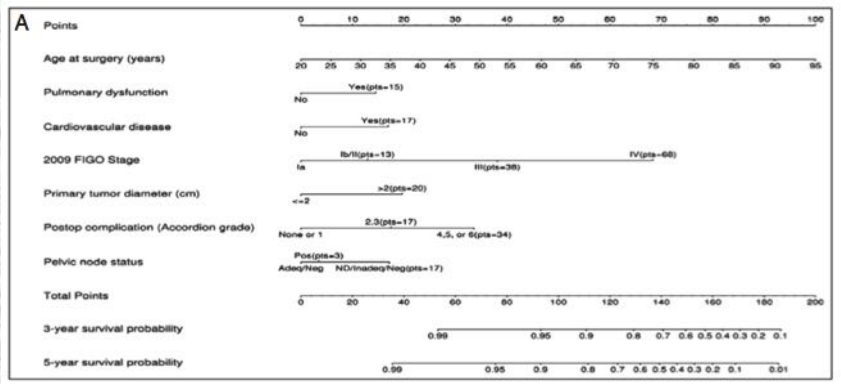
356 high-grade

older age at surgery, ASA score N 2, lymphovascular space invasion (LVSI), cervical stromal invasion, metastatic involvement of para-aortic nodes, and adjuvant therapy retained independent significance in the multivariable modeling for the high-risk cohort

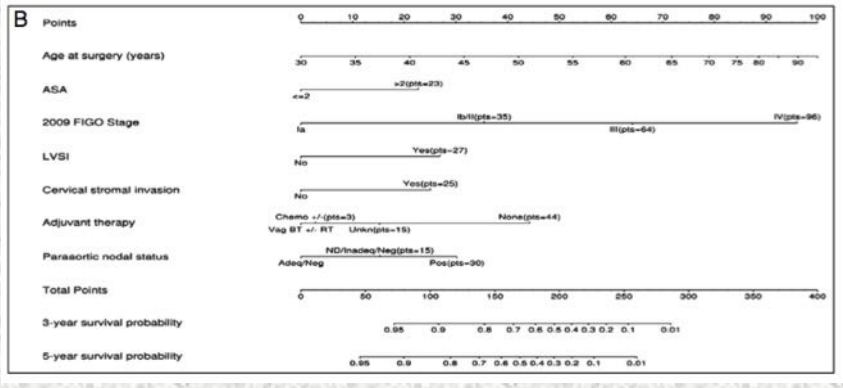
Risk-scoring models for individualized prediction of overall survival in low-grade and high-grade endometrial cancer

Mariam M. AlHilli [a], Andrea Mariani [a], Jamie N. Bakkum-Gamez [a], Sean C. Dowdy [a], Amy L. Weaver [b], Preema P. Peethambaram [c], Gary L. Keeney [d], William A. Cliby [a], Karl C. Podratz [a,*]

Low risk



High risk



Conclusion. Patients with low-grade and high-grade EC can be counseled regarding their predicted OS using the proposed risk-scoring models. This may facilitate institution of personalized treatment algorithms, surveillance strategies, and lifestyle interventions.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2016

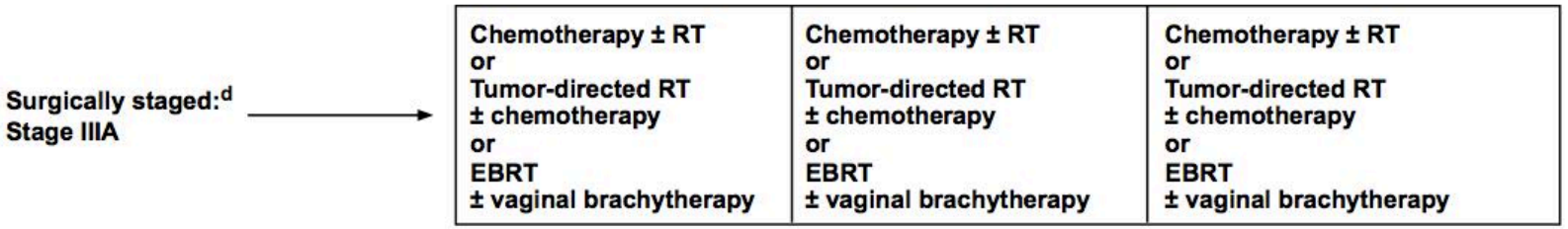
CLINICAL FINDINGS	ADVERSE RISK FACTORS[k]	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,l,m] G1	G2	G3
Surgically staged: Stage I[d] — Stage IA (<50% myometrial invasion)	Adverse risk factors not present	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
	Adverse risk factors present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or EBRT (category 2B for EBRT)	Observe or Vaginal brachytherapy and/or EBRT
Stage IB (≥50% myometrial invasion)	Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Vaginal brachytherapy and/or EBRT or Observe (category 2B for observation)
	Adverse risk factors present	Observe or Vaginal brachytherapy and/or external beam radiation therapy (EBRT)	Observe or Vaginal brachytherapy and/or EBRT	EBRT and/or Vaginal brachytherapy ± chemotherapy[g,n] (category 2B for chemotherapy)

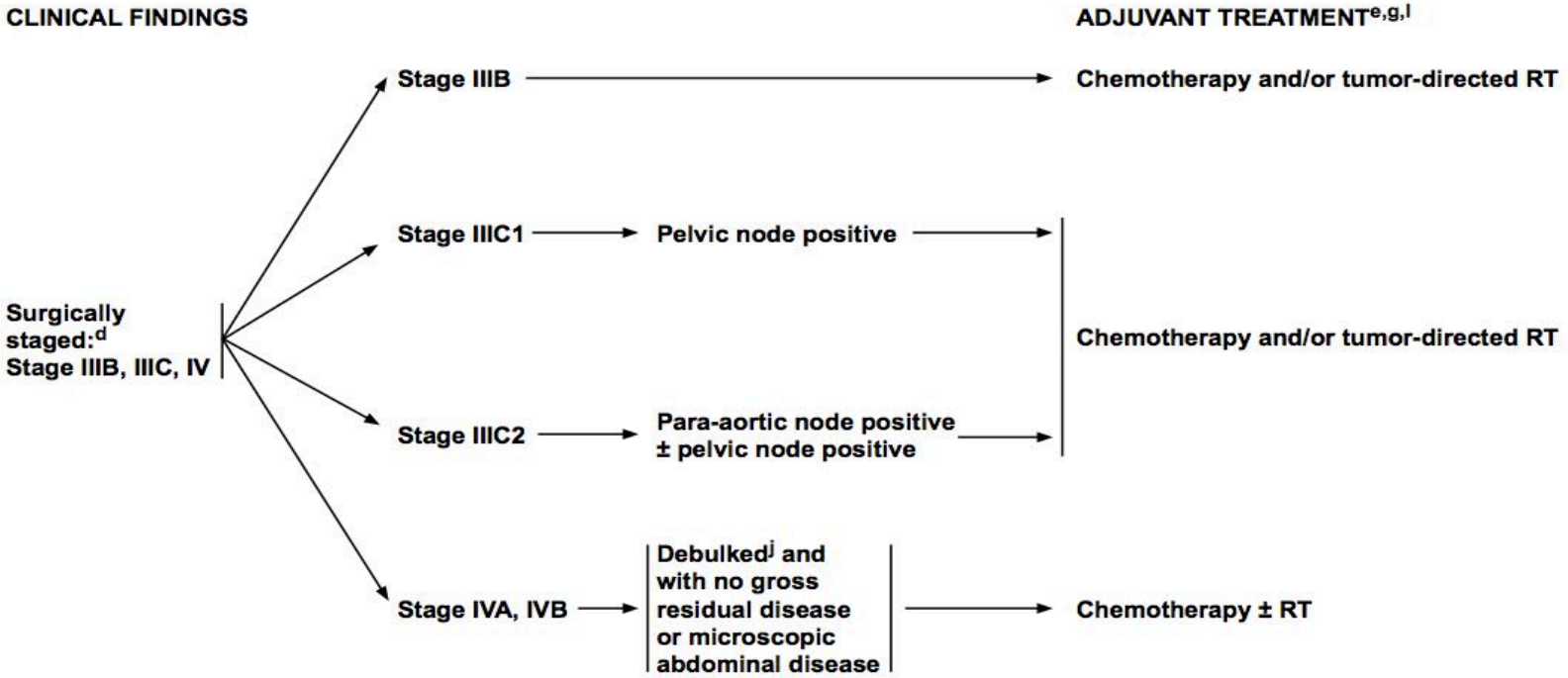
CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,g,l,m] G1	G2	G3
Surgically staged:[d] Stage II[o,p]	Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± chemotherapy[n] (category 2B for chemotherapy)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2016





Endometrial cancer

Pelvic +-Lombo-Aortic lymph nodes

Volumes and techniques

Endometrial cancer

pelvic volume only

- pT high risk and pN0 both pelvic and LA
- pN+ pelvic and pN0 LA

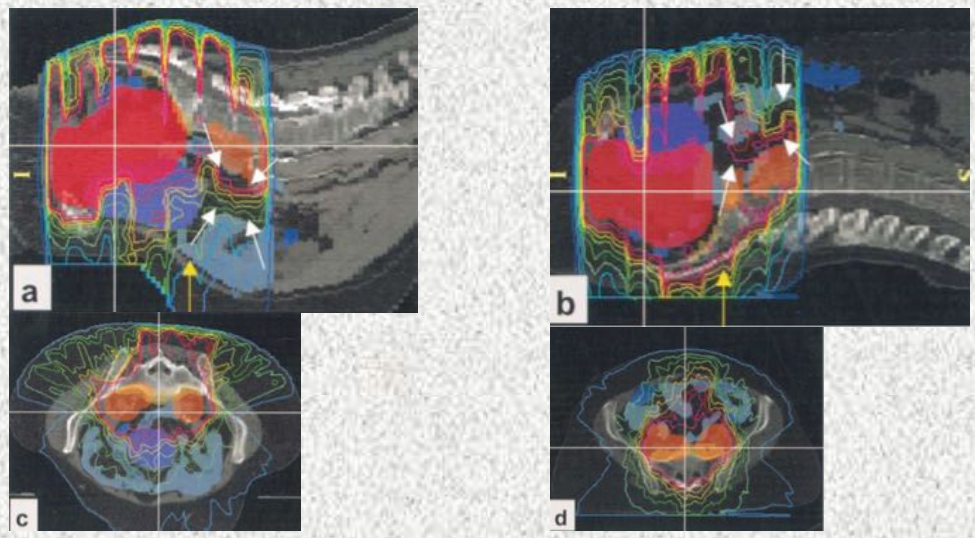
Pelvic and lombo aortic volume

- pT high risk and pN+ pelvic and/or pN+ LA
- pN+ pelvic without pLA

DOES PRONE POSITIONING REDUCE SMALL BOWEL DOSE IN PELVIC RADIATION WITH INTENSITY-MODULATED RADIOTHERAPY FOR GYNECOLOGIC CANCER?

MUSTAFA ADLI, M.D.,* NINA A. MAYR, M.D.,* HEATHER S. KAISER, M.D.,†
MARK W. SKWARCHUK, PH.D.,† SANFORD L. MEEKS, PH.D.,† GEORGE MARDIROSSIAN, PH.D.,*
ARNOLD C. PAULINO, M.D.,‡ JOSEPH F. MONTEBELLO, M.D.,* ROBERT C. GASTON, D.O.,*
JOEL I. SOROSKY, M.D.,§ AND JOHN M. BUATTI, M.D.†

Int. J. Radiation Oncology Biol. Phys,2003



Conclusion: These preliminary data suggest that prone positioning on a belly board can reduce the small bowel dose further in gynecology patients treated with pelvic RT, and that the dose reduction depends on the IMRT technique used.

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY IN POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

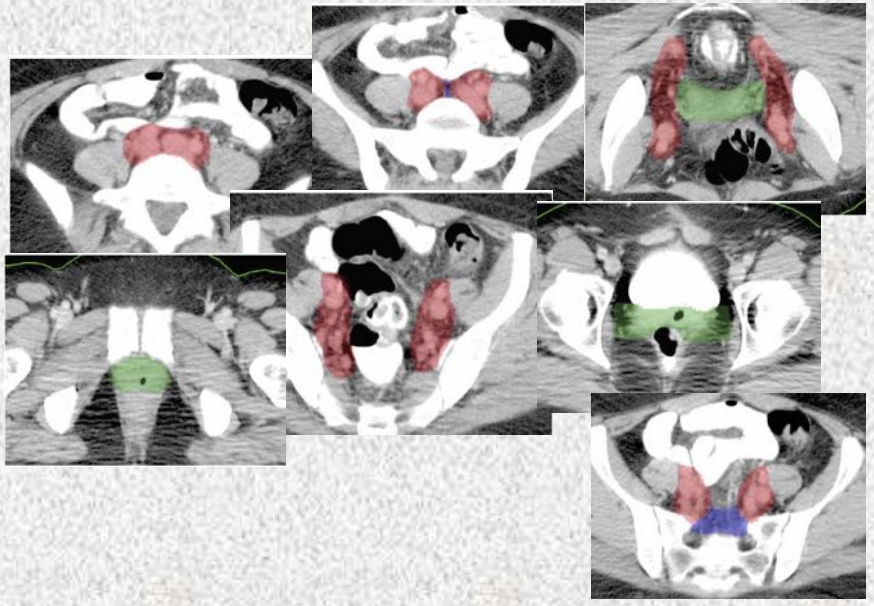
WILLIAM SMALL, JR., M.D.,* LOREN K. MELL, M.D.,† PENNY ANDERSON, M.D.,‡ CARIEN CREUTZBERG, M.D.,§ JENNIFER DE LOS SANTOS, M.D.,¶ DAVID GAFFNEY, M.D., PH.D.,‖ ANUJA JHINGRAN, M.D.,# LORRAINE PORTELANCE, M.D.,** TRACEY SCHEFTER, M.D.,†† REVATHY IYER, M.D.,‡‡ MAHESH VARIA, M.D.,§§ KATHRYN WINTER, M.S.,¶¶ AND ARNO J. MUNDT, M.D.‖‖

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 2, pp. 428–434, 2008

Table 1. Consensus clinical target volume for adjuvant (postoperative) radiotherapy for cervical and endometrial cancer

Target site	Definition
Common iliac lymph nodes	From 7 mm below L4–L5 interspace to level of bifurcation of common iliac arteries into external and internal iliac arteries
External iliac lymph nodes	From level of bifurcation of common iliac artery into external artery to level of superior aspect of femoral head where it becomes femoral artery
Internal iliac lymph nodes	From level of bifurcation of common iliac artery into internal artery, along its branches (obturator, hypogastric) terminating in paravaginal tissues at level of vaginal cuff
Upper vagina	Vaginal cuff and 3 cm of vagina inferior to cuff
Parametrial/paravaginal tissue	From vaginal cuff to medial edge of internal obturator muscle/ischial ramus on each side
Presacral lymph nodes*	Lymph node region anterior to S1and S2 region

* If patient has cervical cancer or endometrial cancer with cervical stromal invasion.



CTV
superior border :
7 mm below
the L4-L5 interspace

inferior border :
3.0 cm below the upper
extent of the vagina or to 1.0 cm above
the inferior extent of the obturator foramen
have to include any adjacent or suspicious
lymph nodes, lymphoceles and
pertinent surgical clips

The pelvic CTV also included
the presacral nodes in patients cervical involvement.

The PTVs were 7 mm around the vaginal and nodal CTVs

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY IN POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

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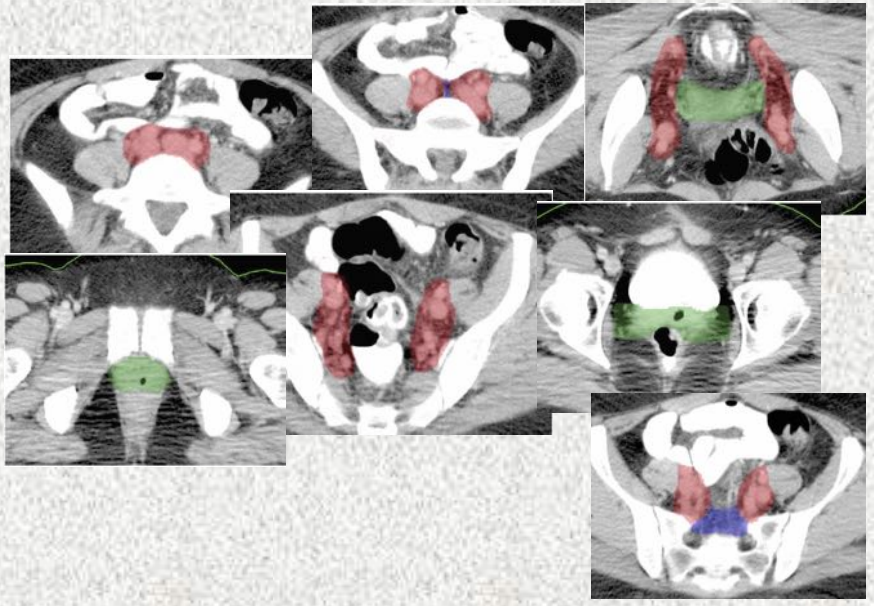

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The pelvic CTV also included
the presacral nodes in patients cervical involvement.

The PTVs were 7 mm around the vaginal and nodal CTVs

ITV vagina

small radiopaque
marker seeds be inserted into the vaginal apex before simulation to help identify the vaginal apex on the computed tomography (CT) scan.

Markers or devices that distended or otherwise altered the vaginal anatomy were strongly discouraged.

bladder

Two separate treatment planning CT scans (full bladder and empty bladder) were required.
.
After acquisition of the full-bladder CT scan, the patient was asked to empty her bladder, and a second scan was obtained with the bladder empty

The full-bladder and empty-bladder CT scans were fused, and a vaginal-parametrial clinical target volume (vaginal CTV) was defined that included the positions of the vagina and paravaginal tissues on both scans.

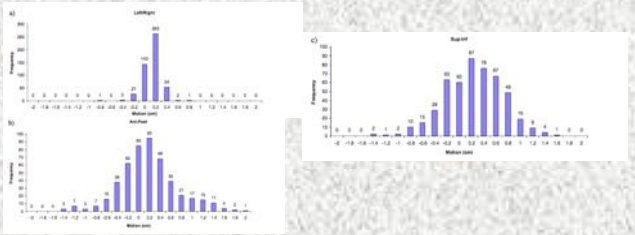
Patients were to be treated with a full bladder

ASSESSMENT OF ORGAN MOTION IN POSTOPERATIVE ENDOMETRIAL AND CERVICAL CANCER PATIENTS TREATED WITH INTENSITY-MODULATED RADIATION THERAPY

ELEANOR E. R. HARRIS, M.D., KUJTIM LATIFI, M.S., CHAD RUSTHOVEN, B.S., KEN JAVEDAN, PH.D., AND KENNETH FORSTER, PH.D.

Int. J. Radiation Oncology Biol. Phys, 2011

Vaginal organ motion

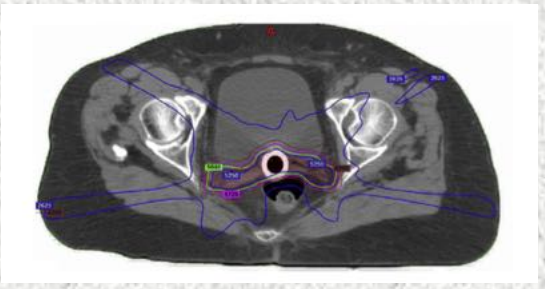


majority of motion occurs in the anterior–posterior and superior–inferior directions, with mean interfraction movements of 4–7 mm

the implementation of IGRT to help evaluate movement on a routine and patient specific basis is the most accurate method to accurately account for interfraction motion.

			fiducial			
Jhingran et al.[53]	24	yes	Vaginal apex fiducial (16/24)	7.3	2.5	7.0
Haripotepornkul et al.[52]	10	intact	Cervical fiducials	4.2	1.9	4.1

vaginal ITV



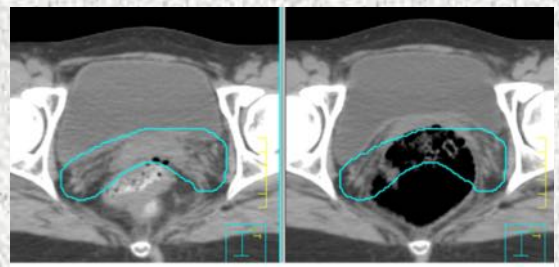
Whitout vaginal ITV

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY IN POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

William Small, Jr., M.D.,* Loren K. Mell, M.D.,† Penny Anderson, M.D.,‡ Carien Creutzberg, M.D.,§ Jennifer De Los Santos, M.D.,¶ David Gaffney, M.D., Ph.D.,‖ Anuja Jhingran, M.D.,# Lorraine Portelance, M.D.,** Tracey Schefter, M.D.,†† Revathy Iyer, M.D.,‡‡ Mahesh Varia, M.D.,§§ Kathryn Winter, M.S.,¶¶ and Arno J. Mundt, M.D.‖‖

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 2, pp. 428–434, 2008

changes to the above recommendations are currently underway,



effect of rectal filling on movement of the vaginal apex is of great clinical concern,

accurate depiction of para-aortic and presacral lymph nodes have been raised

inguinal nodes was not addressed, and treatment of these nodes can be considered if there is low vaginal involvement

Circumferential margins around femoral vessels required to adequately cover this nodal region were >2 cm in most directions

Kim, 2012

clinical efficacy and toxicity when utilizing IMRT

Retrospective studies

	Histology	Postoperative	# patients	Time interval	OS (%)	DFS (%)	Locoregional failure (%)	Acute grade ≥3 toxicity (%)	Chronic grade ≥3 toxicity (%)
Chen MF et al. [25]	cervical	yes	54	3 yr	98	78	7	6	2
Shih et al. [26]	endometrial	yes	46	5 yr	97	88	9	13 (mostly hematologic)	2
Folkert et al.[27]	cervical	yes	34	3 yr	94	91	6	35 (mostly hematologic)	0
Beriwal et al.[30]	endometrial	yes	47	3 yr actuarial	90	84	0	0	2
RTOG 0418 [34,36,37](**abstract**)	both	yes	Cervical - 40 Endometrial - 43	Cervical - 2 yr Endometrial - 3 yr	Cervical - 95 Endometrial - 92	Cervical - 87 Endometrial - 91	Cervical - 11 Endometrial - 7	Cervical - 25 (hematologic)	–
Hasselle et al.[31]	cervical	mixed	111	3 yr	78	69	14	2	7
Kidd et al.[32]	cervical	intact	135 (receiving IMRT)	mean f/u 22 months	95	67	13	–	6
Chen CC et al.[29]	cervical	intact	109	3 yr	78	68	14	27 (mostly hematologic)	11
Beriwal et al.[28]	cervical	intact	36	2 yr actuarial	65	51	20	33 (mostly hematologic)	10

however, to test this rigorously a phase III trial is needed.

RTOG and GOG
phase III randomized trial comparing 3D versus IMRT in posthysterectomy patients. RTOG/GOG 1203, the TIME-C trial, is currently open to accrual. The primary endpoint is a patient reported outcome evaluating bowel function. Secondary endpoints include overall survival and local control

Phase II trial

Impact of post operative intensity modulated radiotherapy on acute gastro-intestinal toxicity for patients with endometrial cancer: Results of the phase II RTCMIENDOMETRE French multicentre trial ☆

Isabelle Barillot [a,b,*], Elsa Tavernier [c], Karine Peignaux [d], Danièle Williaume [e], Philippe Nickers [f], Magali Leblanc-Onfroy [g], Delphine Lerouge [h]

Radiotherapy and Oncology 2014

Table 1
Dose constraints to organs at risk.

Rectum, sigmoïd	Maximal dose 45 Gy Median dose <40 Gy V40 Gy ⩽40%
Bladder	Maximal dose 45 Gy Median dose <40 Gy V40 Gy ⩽40%
Femoral heads	V50 Gy <10%
Peritoneal cavity	V30 Gy ⩽500 cc or V40 Gy ⩽300 cc

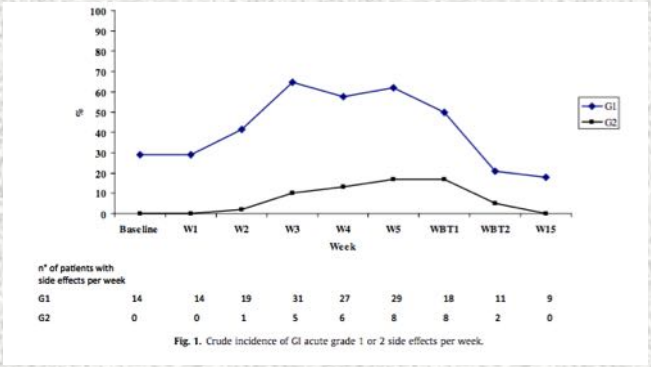


Fig. 1. Crude incidence of GI acute grade 1 or 2 side effects per week.

Table 3
Mean and median doses delivered to the CTV and organs at risk (n = 48 patients).

Volumes	Maximum dose (Gy)	Mean dose (Gy)	Median dose (Gy)
CTV	48.2 ± 2.1	45.8 ± 1.2	45.3 ± 0.7
Rectum	46.3 ± 1.6	33.2 ± 5	34.3 ± 5.1
Sigmoïd	46.7 ± 2.6	36 ± 4.1	37.5 ± 4.9
Bowel	48.4 ± 1.8	19.7 ± 7.1	19.1 ± 6.7
Bladder	46.8 ± 1.7	32.8 ± 3.4	31.8 ± 4.9

Conclusion: In accordance with our hypothesis, post-operative IMRT resulted in a low rate (less than 30%) of acute GI grade 2 toxicity, in patients with endometrial carcinomas. At W15, no patient demonstrated a grade 2 adverse event, and the prevalence of remaining grade 1 events was less than 20%.

A Phase II Study of Intensity Modulated Radiation Therapy to the Pelvis for Postoperative Patients With Endometrial Carcinoma: Radiation Therapy Oncology Group Trial 0418

Anuja Jhingran, MD,* Kathryn Winter, MS,† Lorraine Portelance, MD,‡ Brigitte Miller, MD,§ Mohammad Salehpour, PhD,* Rakesh Gaur, MD,¶ Luis Souhami, MD,‖ William Small, Jr., MD,** Lawrence Berk, MD,†† and David Gaffney, MD, PhD‡‡

Int J Radiation Oncol Biol Phys, 2012

Fifty-eight patients were accrued by 25 institutions; 43 were eligible for analysis.

Forty- two patients (98%) had an acceptable IMRT plan;
1 had an unacceptable variation from the prescribed dose to the nodal planning target volume.

Table 2 Review of doses to the vaginal and nodal PTVs

	Nodal PTV dose score, n (%)			
Vaginal PTV dose score	Per protocol	Acceptable variation	Unacceptable deviation	Total
Per protocol	11 (26.2)	3 (7.1)	0 (0.0)	14 (33.3)
Acceptable variation	18 (42.9)	9 (21.4)	1 (2.4)	28 (66.7)
Total	29 (69.1)	12 (28.6)	1 (2.4)	42 (100.0)

Abbreviation: PTV = planning target volume.

Table 3 Review of doses to the organs at risk

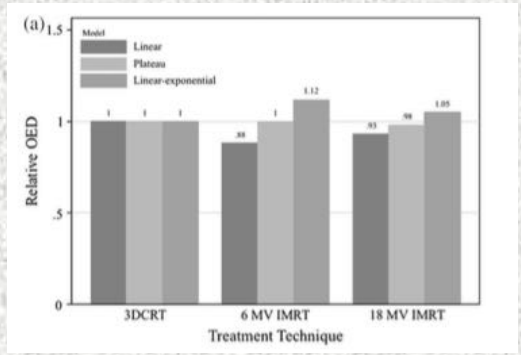
		Dose met criteria		Dose did not meet criteria	
Critical structure	Criteria	n	%	n	%
Normal tissue	≤ 1% or ≤ 1 mL receives > 110% prescribed dose	42	100.0	0	0.0
Bladder	< 35% receives ≥ 45 Gy	14	33.3	28	66.7
Rectum	< 60% receives ≥ 45 Gy	10	22.8	32	76.2
Small bowel	< 30% receives ≥ 40 Gy	35	83.3	7	16.7
Femoral heads	< 15% receives ≥ 30 Gy	28	66.7	14	33.3

Conclusions: Pelvic IMRT for endometrial cancer is feasible across multiple institutions with use of a detailed protocol and centralized quality assurance (QA). For future trials, contouring of vaginal and nodal tissue will need continued monitoring with good QA and better definitions will be needed for organs at risk.

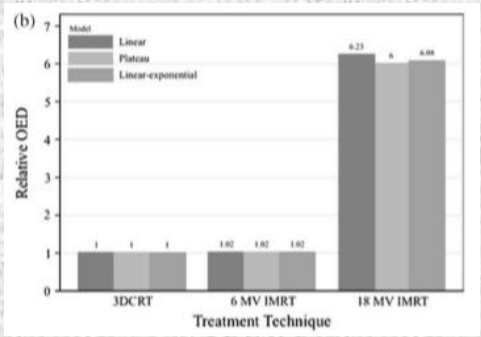
EFFECT OF INTENSITY-MODULATED PELVIC RADIOTHERAPY ON SECOND CANCER RISK IN THE POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

DANIEL R. ZWAHLEN, M.D.,*† JEREMY D. RUBEN, F.C.RAD.ONC., F.R.A.N.Z.C.R.,*
PHILLIP JONES, B.APP.SCI.,* FRANK GAGLIARDI, M.SC.,* JEREMY L. MILLAR, F.R.A.N.Z.C.R.,*
AND UWE SCHNEIDER, PH.D.‡

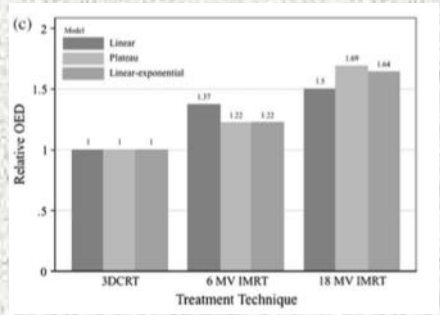
bladder



breast



skin



Conclusion: Cancer risk after IMRT for cervical and endometrial cancer is dependent on treatment energy. 6-MV pelvic IMRT represents a safe alternative with respect to SCR relative to 3DCRT, independently of the dose–response model. 18-MV IMRT produces second neutrons that modestly increase the SCR.

Endometrial cancer

pelvic volume only

- pT high risk and pN0 both pelvic and LA
- pN+ pelvic and pN0 LA

Pelvic and lombo aortic volume

- pT high risk and
- pN+ pelvic and/or pN+ LA
- pN+ pelvic without pLA

Paraaortic lymph node metastasis

A chronological review of the endometrial cancer literature documenting paraaortic lymph node metastasis and their location in various subgroups of patients.

Study		Overall "at risk" population[a]		Limited to patients with PA LNM		Limited to patients with pelvic LNM		Limited to patients with PA LNM and negative pelvic nodes
Author year	n[d]	PA LNM	PA LNM[b] with negative pelvic nodes	High PA LNM	High PA LNM with negative low PA	PA LNM	High PA LNM with negative low PA	High PA LNM with negative low PA
Hiratake 1997 [5]	200	18/200 (9%)	2/160 (1%)	7/11 (64%)	2/11 (18%)	16/40 (40%)	n.a.	n.a.
Matsumoto 2002 [6]	106	20/106 (19%)	2/81 (2%)	16/20 (80%)	5/20 (25%)	18/25 (72%)	n.a.	n.a.
Fotopoulou 2010 [7]	62	10/62 (16%)	2/51 (4%)	7/10 (70%)	n.a.	11/18 (61%)	n.a.	n.a.
Turan 2011 [8]	78	12/78 (15%)	3/64 (5%)	11/12 (92%)	7/12 (58%)	9/17 (53%)	4/17 (24%)	3/3 (100%)
Dogan 2012 [9]	161	7/161 (4%)	2/144 (1%)	6/7 (86%)	4/7 (57%)	5/16 (31%)	2/16 (13%)	2/2 (100%)
Kumar 2013[c]	425	49/425 (12%)	11/351 (3%)	30/34 (88%)	12/34 (35%)	37/73 (51%)	6/50 (12%)	6/9 (67%)
Total	1032	116/1032 (11%)[a]	22/851 (3%)[a]	77/94 (82%)	30/84 (36%)	96/189 (51%)	12/83 (14%)	11/14 (79%)

Diagnostic Performance of Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography Imaging for Detection of Primary Lesion and Staging of Endometrial Cancer Patients

Systematic Review and Meta-Analysis of the Literature

Vahid Reza Dabbagh Kakhki, MD, Sara Shahriari, MD,† Giorgio Treglia, MD,‡*

Int J Gynecol Cancer 2013

Sixteen studies (807 patients in total)

Primary lesion : Sensitivity 81.8% specificity 89.8%

lymph node staging Sensitivity 72.3% specificity 92.9%

distant metastasis detection Sensitivity 95.7% specificity 95.4

TABLE 2. Diagnostic performance (including sensitivity, specificity, LR^+ and LR^-, and DOR) of 18-F-FDG PET imaging for lymph node staging of endometrial cancer

	Sensitivity, %	Specificity, %	LR^+	LR^-	DOR
Lymph nodes overall: patient basis	72.3 (63.8–79.8)	92.9 (90.6–94.8)	8.36 (5.9–11.8)	0.36 (0.25–0.5)	27.75 (15.82–48.65)
Lymph nodes overall: region basis	64.6 (56.6–72)	97 (96.3–97.7)	20.1 (9.2–43.7)	0.39 (0.21–0.72)	58.8 (20.5–169)
Pelvic lymph nodes: patient basis	60.9 (47.9–72.9)	97.3 (95–98.7)	15.42 (8.63–27.55)	0.43 (0.21–0.86)	41.97 (18.81–93.61)
Pelvic lymph nodes: region basis	68.3 (57.1–78.1)	97.5 (96.6–98.3)	24.2 (14.38–40.9)	0.33 (0.17–0.64)	93.2 (30.8–282)
Para-aortic lymph nodes: patient basis	87 (66.4–97.2)	99.1 (97.3–99.8)	46.6 (18.41–117.92)	0.14 (0.05–0.38)	309 (70.6–1352)
Para-aortic lymph nodes: region basis	79.3 (60.3–92)	97 (95.2–98.2)	16.8 (3.4–82.1)	0.26 (0.1–0.7)	73 (6.6–809)

Data are stratified according to location (pelvic or para-aortic) and units of calculation (patient or lesion basis).

CONCLUSIONS:

Because of low sensitivity, diagnostic utility of (18)F-FDG PET imaging is limited in primary tumor detection and lymph node staging of endometrial cancer patients. However, high specificities ensure high positive predictive values in these 2 indications. Diagnostic performance of (18)F-FDG PET imaging is much better in detection of distant metastases. Larger studies with better design are needed to draw any more definite conclusion.

Accuracy of integrated FDG-PET/ contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer

Kazuhiro Kitajima Eur Radiol (2009)

Table 2 Overall patient- and node-based diagnostic accuracy of PET/CT

	Sensitivity	Specificity	PPV	NPV	Accuracy
All patients	50.0%	90.9%	66.7%	83.3%	80.0%
(n=45)	6/12	30/33	6/9	30/36	36/45
All lymph nodes	51.1%	99.8%	85.2%	98.9%	98.7%
(n=1,976)	23/45	1,927/1,931	23/27	1,927/1,949	1,950/1,976
Pelvic lymph nodes	52.2%	99.8%	85.7%	99.1%	98.9%
(n=1,223)	12/23	1,198/1,200	12/14	1,198/1,209	1,210/1,223
Paraaortic lymph nodes	50.0%	99.7%	84.6%	98.5%	98.3%
(n=753)	11/22	729/731	11/13	729/740	740/753

The overall patient-based sensitivity (50%) specificity, (90.9%) positive predictive value ((PPV) 66.7% , negative predictive value (NPV) (83.3%) and accuracy (80%)

Integrated FI **PET negative IS NOT = pN0** **al imaging, but only moderately sensitive in predicting lymph node metastasis preoperatively in patients with uterine cancer.**

The Role of Positron Emission Tomography/Computed Tomography in Planning Radiotherapy in Endometrial Cancer

Bryony Simcock, MBBS, BSc, CGO, Kailash Narayan, MD,* Elizabeth Drummond, BAppSc, MSc,* David Bernshaw, MD,* Elizabeth Wells,† and Rodney J. Hicks**

Int J Gynecol Cancer 2015;

TABLE 1. Demographics of 48 patients who had PET/CT postoperative before adjuvant treatment planning and 25 patients who had a PET/CT before commencing radiotherapy for recurrent disease

Characteristic	n (high risk)	n (recurrent)
Age range, 32–85 y		
Mean age, 61.7 y		
FIGO stage		
1A	1	5
1B	6	6
1C	7	2
2A	3	2
2B	6	2
3A	7	2
3B	1	0
3C	17	3
4B	0	2
Unknown	0	1
Tumor grade		
1	14	14
2	13	7
3	18	2
Unknown	3	2
Lymph node status		
Negative	8	15
Positive	15	8
Not done	25	2

TABLE 2. Distribution of disease pre-PET/CT and post-PET/CT in high-risk postoperative women

	Unknown	Negative	Pelvic Nodes	Extensive Nodal	Systemic Disease
Pre-PET/CT distribution	25	7	15	0	1
Post-PET/CT distribution	0	29	10	7	2

TABLE 3. Distribution of disease pre-PET/CT and post-PET/CT in women with possible recurrent disease

	Equivocal/Negative	Vaginal Vault	Vault and Nodal	Nodal Only	Systemic Disease
Pre-PET/CT distribution	3	13	0	6	3
Post-PET/CT distribution	3	7	4	4	7

Results: PET/CT found additional disease in 35% of postoperative patients, changing planned treatment in 31%. In the group with known recurrence, additional disease was found in 72%, changing management in 36%.

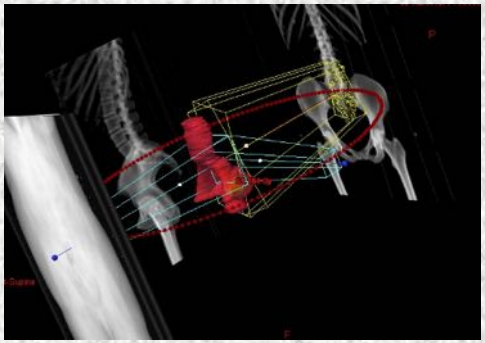
Conclusions: PET/CT is a valuable tool for planning radiotherapy in endometrial cancer.

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY IN POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

William Small, Jr., M.D.,* Loren K. Mell, M.D.,† Penny Anderson, M.D.,‡ Carien Creutzberg, M.D.,§ Jennifer De Los Santos, M.D.,¶ David Gaffney, M.D., Ph.D.,‖ Anuja Jhingran, M.D.,# Lorraine Portelance, M.D.,** Tracey Schefter, M.D.,†† Revathy Iyer, M.D.,‡‡ Mahesh Varia, M.D.,§§ Kathryn Winter, M.S.,¶¶ and Arno J. Mundt, M.D.‖‖

The para-aortic portion of the planning target volume (PTV) was contiguous with the pelvic portion and encompassed the aorta and inferior vena cava with an initial 7-mm margin to the CTV and a 1-cm margin to the PTV.

the superior para-aortic PTV border started at the level of the T12-L1 interspace,was contiguous with the pelvic portion



PRELIMINARY OUTCOME AND TOXICITY REPORT OF EXTENDED-FIELD, INTENSITY-MODULATED RADIATION THERAPY FOR GYNECOLOGIC MALIGNANCIES

JOSEPH K. SALAMA, M.D.,* ARNO J. MUNDT, M.D.,*† JOHN ROESKE, PH.D.,*† AND NEIL MEHTA, M.D.*

Int. J. Radiation Oncology Biol. Phys, 2006

The prescription dose for the EF- IMRT plans was 45 Gy, delivered in 1.8-Gy daily fractions. Patients with clinically evident gross disease in the para-aortic chain or pelvis received an additional 9-Gy boost to gross disease delivered in 1.8-Gy daily fractions.

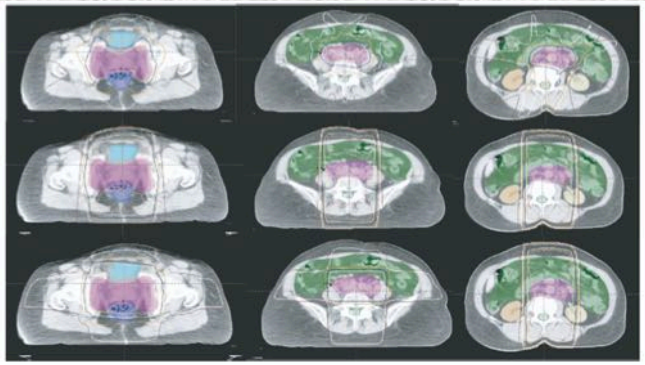


Fig. 1. Intensity-modulated radiation therapy (IMRT), four-field, and anterior-posterior/posterior-anterior (AP-PA) isodose distributions are presented for a representative patient in the low pelvis, upper pelvis, and kidney region. The 30%, 50%, 70%, 90%, and 100% isodose curves are presented for each of these plans.

Table 2. Acute toxicity in patients studied

Toxicity	Total	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic					
Blood leukopenia	7	2	3	1	1
Neutropenia/granulocytopenia	2	0	1	0	1
Anemia	12	5	7	0	0
Gastrointestinal					
Large intestine	13	2	11	0	0
Nausea	5	2	2	1	0
Genitourinary					
Dysuria	3	2	1	0	0

Conclusions: Extended-field IMRT is safe and effective with a low incidence of acute toxicity. Longer follow-up is needed to assess chronic toxicity, although early results are promising.

Dose to organs at risk in the upper abdomen in patients treated with extended fields by helical tomotherapy: a dosimetric and clinical preliminary study

Sara Bresciani[1*], Elisabetta Garibaldi[2], Gabriella Cattari[2], Angelo Maggio[1], Amalia Di Dia[1], Elena Delmastro[2], Domenico Gabriele[3], Michele Stasi[1] and Pietro Gabriele[2]

Radiation Oncology 2013,

The dose prescription for the EF-IMRT plans was 51– 54 Gy (1.7-1.8 Gy/fraction) for prophylactic lymph nodes and 60/66 Gy (2–2.2 Gy/fraction) to PTV N + in the para-aortic or pelvis chain, with a simultaneous integrated boost (SMART technique irradiation).

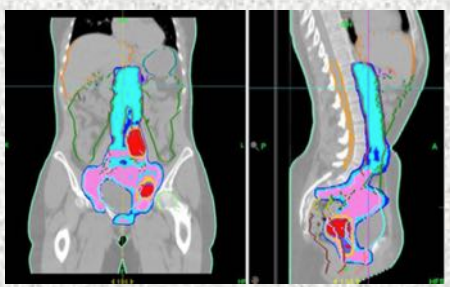


Table 1 Normal tissue tolerance

Critical structure	Volume	Dose/volume	Toxicity rate	Toxicity endpoint
Liver	Mean	<30-32 Gy	<5%	RILD (in normal liver function)
Kidney, bilateral	Mean	<15-18 Gy	<5%	Clinical dysfunction
Kidney, bilateral	Mean	<28 Gy	<50%	Clinical dysfunction
Kidney, bilateral	V12	<55%	<5%	Clinical dysfunction
Kidney, bilateral	V20	<32%	<5%	Clinical dysfunction
Kidney, bilateral	V23	<30%	<5%	Clinical dysfunction
Kidney, bilateral	V28	<20%	<5%	Clinical dysfunction
Stomach	D100	<45 Gy	<7%	Ulceration
Small bowel (peritoneal cavity)	V45	<195 cc	<10%	Grade 3+ toxicity

Table 3 Mean doses and standard deviations to organs at risk for patients with toxicity

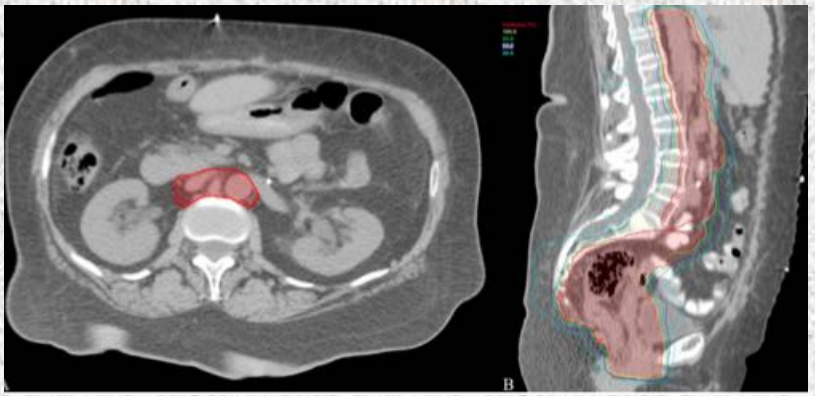
Organs at risk		G1 acute/subacute	G2 acute/subacute	G3 acute/subacute
Pancreas	D_{mean} (Gy)	32.0 ± 8.2/37.8	/	
	D_{max} (Gy)	61.7 ± 8.6/67.1		/
Liver	D_{mean} (Gy)	10.8 ± 3.1/11.6 ± 2.2	/	
	D_{max}(Gy)	45.8 ± 12.5/54.4 ± 2.1		/
Small bowel	V_{45}(cc)	168 ± 59	130 ± 84	158

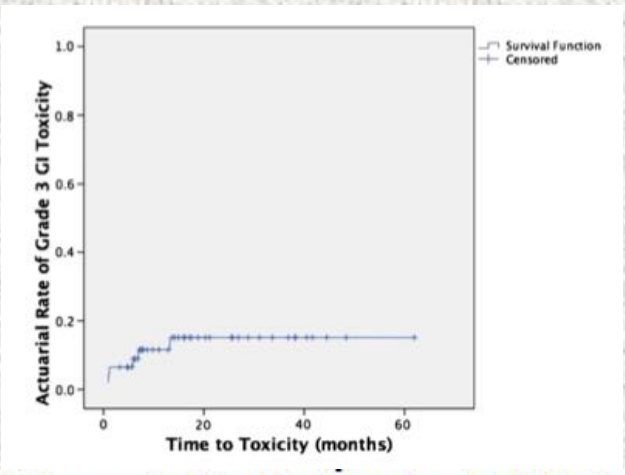
Duodenal and Other Gastrointestinal Toxicity in Cervical and Endometrial Cancer Treated With Extended-Field Intensity Modulated Radiation Therapy to Paraaortic Lymph Nodes

Philip D. Poorvu, MD,* Cheryl A. Sadow, MD,† Kanokpis Townamchai, MD,* Antonio L. Damato, PhD,* and Akila N. Viswanathan, MD, MPH*

Int J Radiation Oncol Biol Phys,2013

median prescribed dose to the paraaortic nodes was 54 Gy (range, 41.4-65 Gy) **sequential dose escalation**





Conclusions: Treatment of paraaortic nodes with IMRT is associated with low rates of GI toxicities and no duodenal-specific toxicity, including patients treated with concurrent chemotherapy. This technique may allow sufficient dose sparing of the bowel to enable safe dose escalation to at least 65 Gy. © 2013 Elsevier Inc.

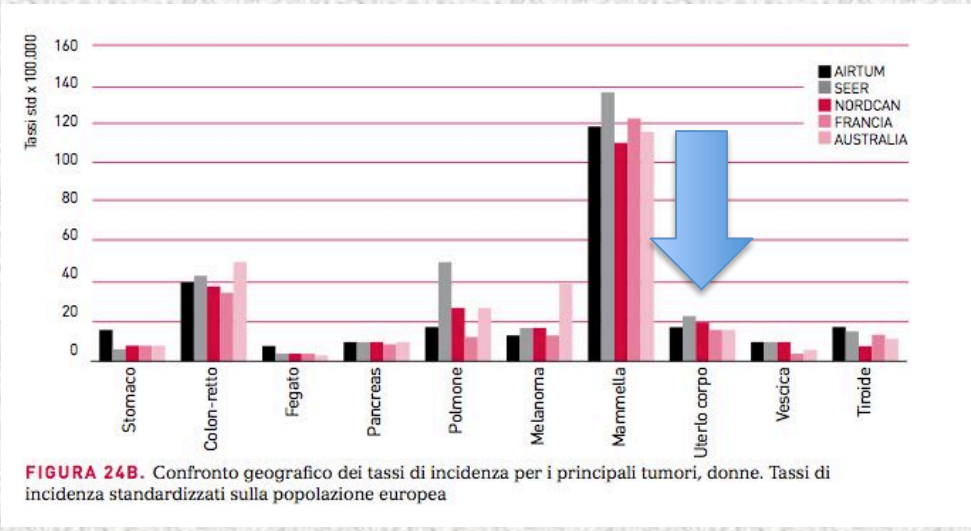


FIGURA 24B. Confronto geografico dei tassi di incidenza per i principali tumori, donne. Tassi di incidenza standardizzati sulla popolazione europea

Despite being the most common gynecological cancer in developed countries, there is evidence for many differences and discrepancies in the clinical management

Greggi, 2014

Grazie per l'attenzione

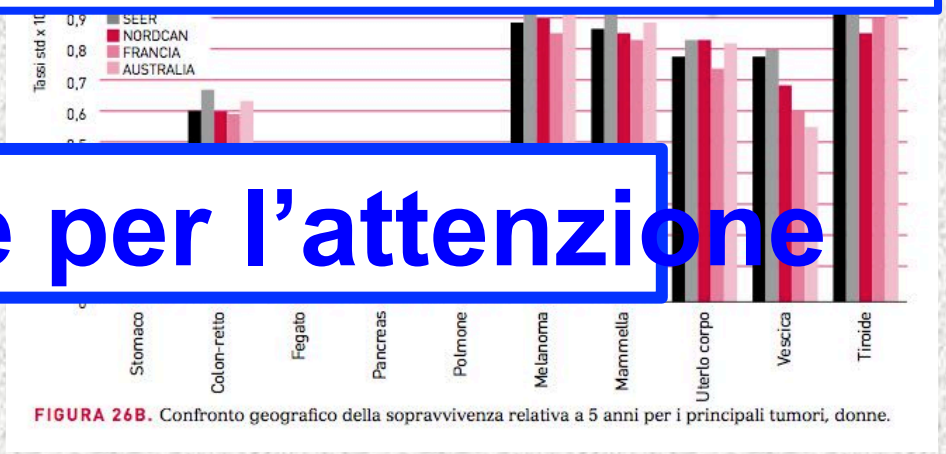


FIGURA 26B. Confronto geografico della sopravvivenza relativa a 5 anni per i principali tumori, donne.