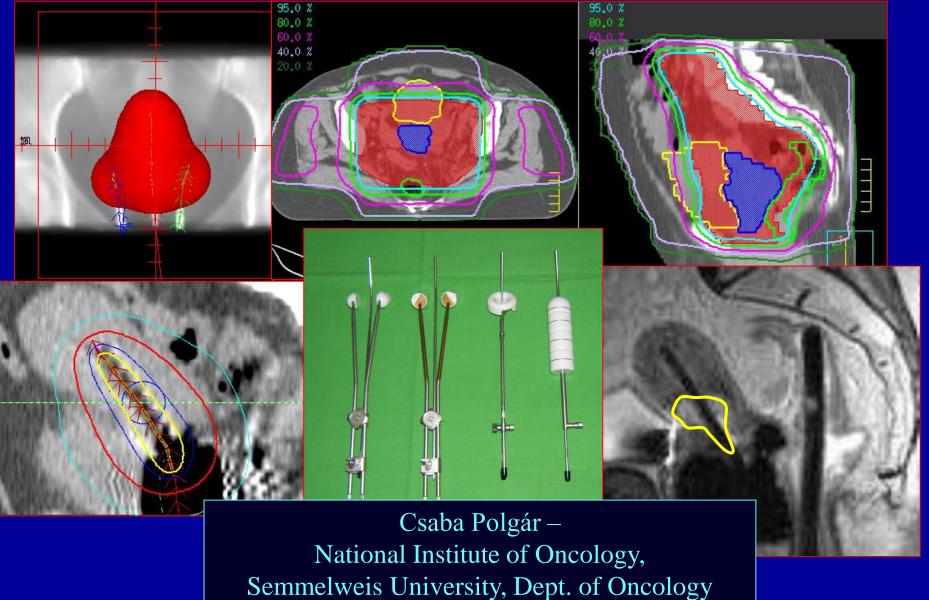


Management of gynaecological tumours





Incidence of malignant tumours (2007 és 2014) Females

	Localisation					Inc	cidence				
			2008	2009	2010	2011	2012	2013	2014	<u>2017</u>	
1	Skin (Non-melanoma; C	C44)	6673	6622	6258	7 993	7687	7936	9061		
2	Breast		6938	6861	6610	7 767	7733	7775	7880		
3	Colorectal		4582	4457	4373	4 942	4886	4793	4902		
4	Lung & Bronchus		4305	4103	3930	4 606	4404	4573	4675		
5	Lymphoproliferative dis	5.	1873	1951	1845	2 066	2229	2142	2177		
6	Uterine corpus (C54-C5	(5)	1365	1378	1299	1 648	1523	1548	1694	1640	+275
7	Ovarium (C56)		1261	1185	1104	1 410	1421	1402	1357	1383	+122
8	Skin melanoma		1085	1059	1031	1156	1239	1258	1234		
9	Stomach		1154	1062	1000	1 129	1089	1048	1000		
10	Cervix uteri (C53)		1076	981	932	1 159	1060	1121	1154	983	-93
		All:	41218	39874	38680	45681	45227	45778	48052	<u>2017</u> - Vul	va: 228
	All (wo C44):		34 544	33 252	32 404	37 688	37540	37842	38991	Vag	ina: 124

Annual mortality (2004-2013)

		Females										
	Lagalization	Mortality										
	Localisation	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	
1	Lung & Bronchus	2408	2235	2321	2566	2733	2766	2 907	2975	3133	3173	
2	Colorectal	2261	2095	2141	2158	2190	2187	2 261	2219	2274	2242	
3	Breast	2285	2085	2059	2045	2108	2169	2 011	2138	2096	2167	
4	Pancreas	828	803	873	909	895	940	985	908	1053	1033	
5	Lymphoproliferative	945	857	802	860	835	820	834	855	852	831	
6	Ovarium (C56)	666	612	610	660	687	687	675	700	700	739	+73
7	Stomach	857	738	744	720	744	822	694	746	732	677	
8	Gallbladder	560	467	465	439	428	457	420	428	434	418	
9	Uterine corpus (C54-C55)	402	375	385	357	334	377	386	436	429	417	+15

Cervix uteri (C53)

All:

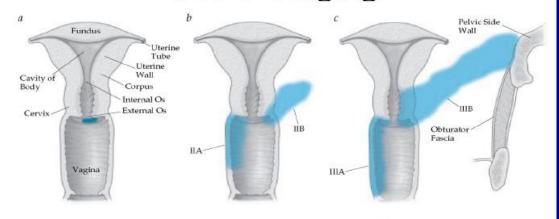
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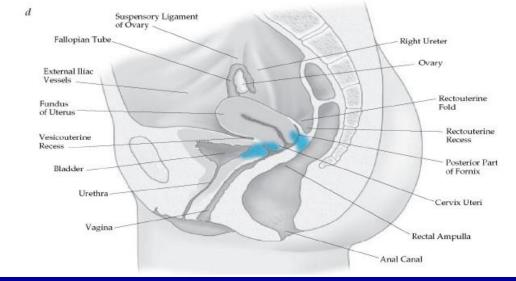
-88

Staging of Cervical Cancer - FIGO 2009

FIGO stage classification of cervical cancers				
St. 0	Carcinoma in situ			
St. I	Tumour is confined to the cervix			
St. I/A1	Stromal invasion depth is <3 mm, horizontal spread is <7 mm			
St. I/A2	Invasion depth is 3-5 mm, horizontal spread is <7 mm			
St. I/B1	Macroscopic tumour, but ≤4 cm			
St. I/B2	"Bulky" tumour, >4 cm			
St.II.	Tumour invades past the uterus, but not past the pelvic wall or to the lowest 1/3 of the vagina			
St. II/A	Upper third of the vagina is involved			
St. II/A1	Macroscopic tumour, but ≤4 cm			
St. II/A2	"Bulky" tumour, >4 cm			
St. II/B	The tumour invades the parametria, but does not spread to the pelvic wall			
St. III/A	Lower two thirds of the vagina are involved			
St. III/B	The tumour invades the parametria to the pelvic wall; hydronephrosis is present			
St. IV/A	Tumour infiltrates the bladder and/or rectum			
St. IV/B	Distant metastases are present			

Cervix Cancer FIGO Staging





Cervical Cancer – Symptoms, Diagnosis, Staging

- Smptomps:
 - Early: vaginal discharge, contact bleeding
 - Late: bloody discharge, pain, weight loss, fatigue, anaemia
- Diagnostic work-up, staging:
 - Cytology, conisation, excisional biopsy
 - Physical exam (incl. RDE!) local extent
 - Pelvic MRI local/regional spread
 - PET/CT PAO & distant metastases
 - Cystoscopy/Rectoscopy
 suspicion of bladder/rectal invasion

Cervical Cancer – Prognostic Factors

- Stage
 - 5-year survival: St. 0-I/A1: 100%, St. I/A2: 95-100%, St. I/B: 82-90%,
 St. II/A: 75%, St. II/B: 60-65%, St. III: 25-50%, St. IV/A: 18-35%
- Lymph node status (pN)
 - PIL: St. I/A1: 0-1%, St. I/A2: 5-7%, St. I/B: 11-16%, St. II: 27-45%,
 St. III: 42-60%
 - PAO: St. I/B: 6%, St. II: 13-19%, St. III: 20-29%, St. IV: > 30%
- Histological type
 - (squamous cell cc., adenocc., adenosquamosus cc.)
- Histological Grade
- Lympho-Vascular Invasion (LVI)
- Surgical margin
- Hgb-level, anaemia
- Overall treatment time
 - Radiotherapy < 8 weeks

Cervical Cancer - Management:

- St. 0-I/A1:
 - Surgery alone (hysterectomy, trachelectomy, conisation)
 - Surgery contraindicated: definitive RT (brachytherapy)
- St. I/A2-I/B1:
 - Wertheim-operation ± postop. RT
 - Preop. RT + Wertheim-operation ± postop. RT
 - Surgery contraindicated: definitive, accelerated RT
- St. I/B2-II/A-II/B (early):
 - Definitive, simultaneous RCT
 - Wertheim-operation + postop. RT or RCT
 - Preop. RT + Wertheim-operation + postop. RT or RCT
 - Neoadjuvant CT + Wertheim-operation + postop. RT

St. II/B-III/A-B-IV/A:

- Definitive, simultaneous RCT
- St. IV/B:
 - Palliative RT + CT (cisplatin-paclitaxel-bevacuzimab)

St. 0-I/B1: Surgical treatment

St. I/B2-IV/A: Radiochemotherapy

> St. IV/B: Palliative RT & CT

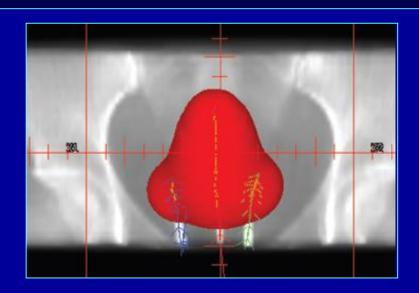
Cervical Cancer – Indications of Radiotherapy

- Curative:
 - Preoperative
 - Postoperative
 - Definitive (primary)
 - RT alone
 - Simultaneous RCT
- Palliative



Rationale for Preoperative Radiotherapy:

- Tumour down-sizeing, down-staging
- Devitalisation of malignant cells, decreasing the chance of tumour spread during surgery
- Pathological complete remission (pCR)
- In case of pCR postop. RT can be omitted, less posttreatment side-effects.







Postoperative RT according to risk groups:

Low-risk group:

➤ Positive surgical margins (R1/R2) and/or



POSTOP. RCT

- Positive LN status (pN1) and/or
- Histologically proved parametral involvement

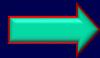
Intermediate-risk group:

- \triangleright Close surgical margins (≤ 3 mm) and/or
- Stromal invasion $\geq 10 \text{ mm and/or}$
- Primary tumour size > 4 cm and/or
- ► LVI and/or
- Grade III tumour and/or
- Adenocarcinoma

POSTOP. RT

High-risk group:

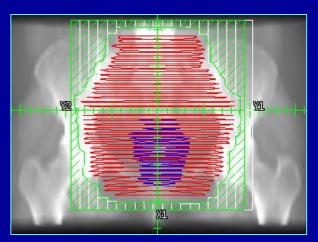
- Lack of above risk factors
- Tumour free specimen (pCR & pN0)

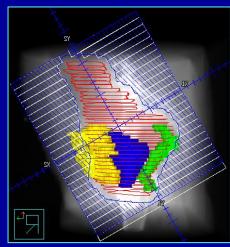


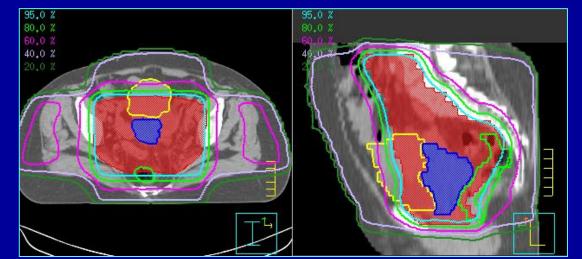
OBSERVATION

Pelvic external beam RT - 3D conformal radiotherapy (3D-CRT), 4-field box technique

Field arrangement





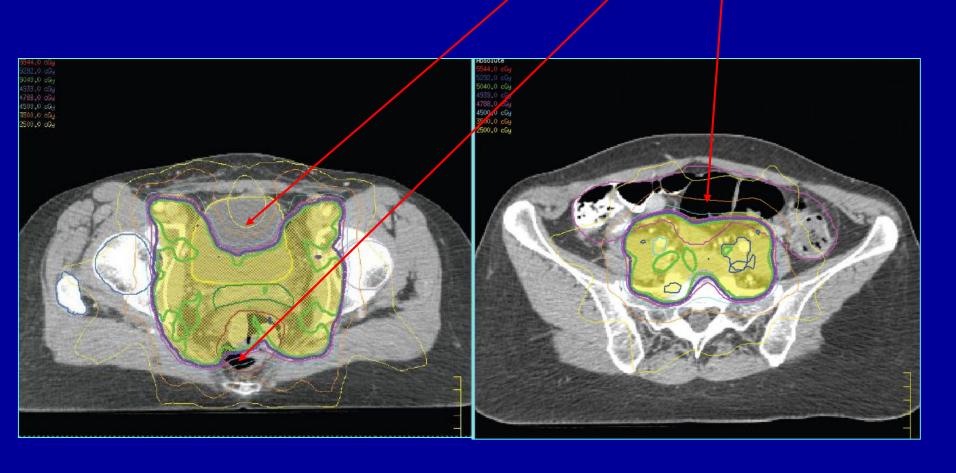


Dose distribution

Blue: uterus; green: rectum; yellow: bladder; red: PTV

Pelvic external beam RT Intensity-modulated radiotherapy (IMRT)

Significantly lower dose to bladder, rectum and bowels!



Indication and doses of primary radiotherapy and radiochemotherapy according to clinical stage – NIO protocol

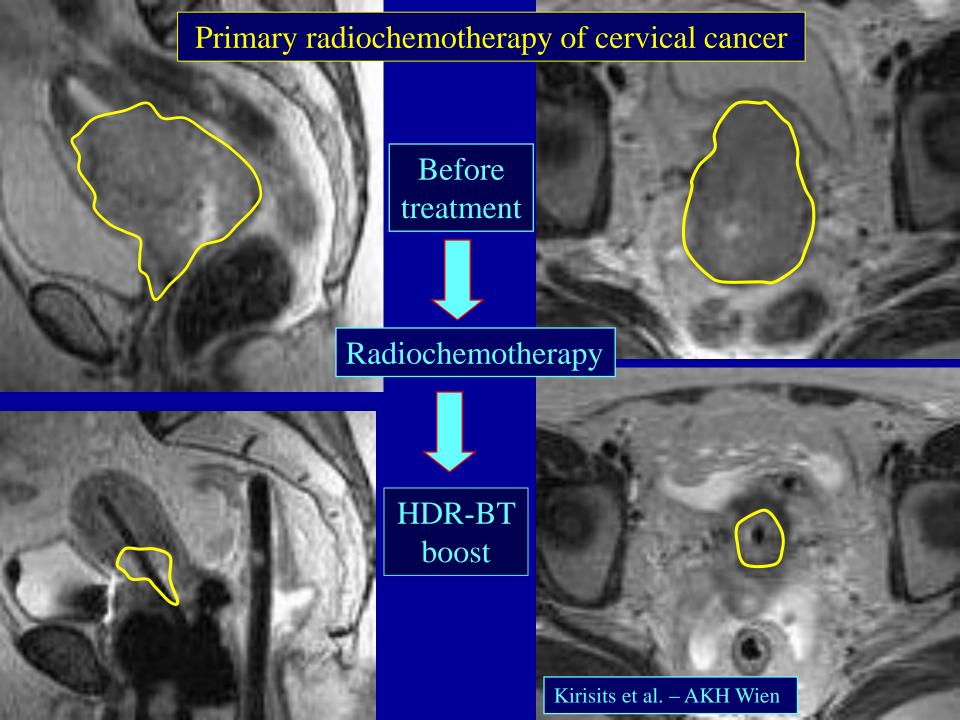
Stage	Treatment	Teletherapy dose	Brachytherapy dose
St. I/A1	RT: brachytherapy alone	_	6 x 7 Gy HDR AL (1 fraction/week)
St. I/A2- I/B1	RT: combined, accelerated RT (brachy- + teletherapy)	45 Gy (accelerated treatment, 4 fractions/week)	6 x 7 Gy HDR AL (acelerated treatment, 1 fraction/week)
St. I/B2-IV/A	RKT: weekly 40 mg/m ² cisplatin + teletherapy + boost brachytherapy	45-50.4 Gy ± 10 Gy boost to parametria	3-4 x 7 Gy HDR AL boost (after teletherapy)

Indications of radiochemotherapy:

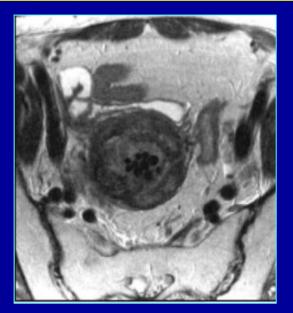
- (Preoperative)
- Definitive (primary)
- Postoperative

Standard radiochemotherapy protocols:

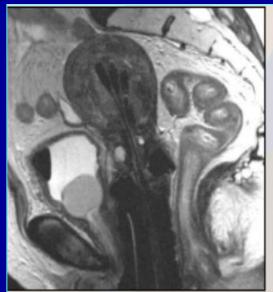
- Radiotherapy:
 - 45-50.4 Gy (25-28x 1.8 Gy/die) pelvic RT (5-5.5 hét)
- Weekly cisplatin:
 - 40 mg/m² CDDP weekly (5-6 cycles)
- Cisplatin-5-FU:
 - 70 mg/m² CDDP (Day 1) + 1000 mg/m² 5-FU (Days 1-4)
 (2 cycles during 1^{st.} and 5^{th.} weeks of RT)



Endometrial cancer FIGO & TNM staging – FIGO 2009



70%





TNM	FIGO	
Tx		No evidence of primary tumour
0		No primary tumour
Tis	0	Carcinoma in situ (preinvasive cancer)
T1	I	Tumour is confined to the endometrium
T1a	IA	Tumour infiltrates less than half of the myometrium
T1b	IB	Tumour infiltrates at least half of the myometrium
T2	II	Tumour infiltrates cervical stroma, but is confined to the uterus
Т3	III	Local and/or regional tumour invasion
ТЗа	IIIA	Tumour infiltrates the peritoneal surface of the uterus and/or appendices
T3b	IIIB	Vaginal and/or parametrial involvement
N1	IIIC	Tumour has metastasised to the pelvic and/or the paraaortic lymph nodes
	IIIC1	Tumour has metastasised to the pelvic lymph nodes
	IIIC2	Tumour has metastasised to the paraaortic lymph nodes
	IV	Tumour infiltrates bladder and/or rectal mucosa and/or tumour has metastasised to distant organs
T4	IVA	Tumour infiltrates bladder and/or rectal mucosa
M1	IVB	TDistant metastases are present (abdominal cavity and/or inguinal lymph node metastases)

Endometrial cancer – Symptoms, Diagnosis, and Staging

- Symptoms:
 - Postmenopausal vaginal bleeding
- Diagnostic work-up, staging
 - Hysteroscopy, fracionated abrasion histological diagnosis
 - Physical exam. (incl. RDE!) local extent
 - Pelvic MRI local/regional spread
 - CT, PET/CT PAO & distant metastases
 - Cystoscopy/Rectoscopy
 suspicion of bladder/rectal invasion

Management of Endometrial Cancer

Primary treatment = Surgery

- Early stage:
 - -TAH + BSO + /- LAD*
 - Peritoneal revision
 - Advanced stages:
 - Debulking surgery

*TAH = Total Abdominal Hysterectomy

BSO = Bilateral Slapingo-Oophorectomy

LAD = Lymphadenectomy

- +/ Adjuvant RT/CT according to final histology report

Management of Endometrial Cancer:

• St. I-II:

- TAH + BSO +/- LAD +/- postop. RT
- Preop. RT + TAH + BSO +/- LAD +/- postop. RT
- If surgery contraindicated: primary RT

St. III:

- Surgery + postop. RT + systemic therapy (chemo- or hormone therapy)
- If surgery contraindicated: primary RT/RCT

• St. IV/A:

- Primary RT + systemic therapy
- Exenteration

St. IV/B:

- Palliative RT + systemic therapy (CT + HT)

Indications of radiotherapy for endometrial cancer:

- Curative:
 - (Preoperative)
 - Postoperative
 - Definitive (primary)
 - RT alone
 - Simultaneous RCT

Palliative

Histological types

• Type 1 histology: endometrioid adenocc.

• Type 2 histology: clear cell carcinoma

papillary/serous cc.

carcinosarcoma

Risk groups

<u>Low risk</u>	Intermediate risk	<u>High risk</u>
- G1/2 endometrioid cc and ≤ 50% myometrial invasion	 G1/2 endometrioid cc and 50% myometrial inv. G3 endometrioid cc and ≤ 50% myom. invasion 	G3 endometrioid cc. and50% myometrial inv.All Type 2 histology

Postoperative RT of endometrial cancer— NIO protocol

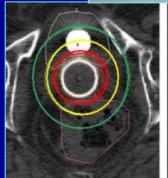
Postoperative radiotherapy	Postoperative radiotherapy of endometrial tumours, according to stage				
Characteristics	Postoperative treatment				
I/A, G1-2	NOT REQUIRED!				
I/A, G3	Vaginal brachytherapy				
I/B, G1-2	AD was performed and is negative: Vaginal brachytherapy				
	LAD was not performed: Vaginal + pelvic radiotherapy				
I/B, G3, II, any G	Vaginal + pelvic radiotherapy				
III/A	Vaginal + pelvic radiotherapy Systemic treatment (hormone or chemotherapy)				
III/B, III/C, IV/A, IV/B	Vaginal + pelvic radiotherapy (if stage III/C2 + PAO radiotherapy) Systemic treatment (hormone or chemotherapy)				
G: grade; PAO: paraaortic lymph node region					

Papillary/serous and clear-cell cc: Vaginal + pelvic RT in each case!

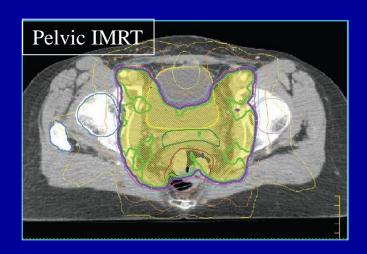
Postoperative RT of endometrial cancer— NIO protocol

Radiotherapy types and dosage for patients who	Radiotherapy types and dosage for patients who did not receive preoperative radiotherapy				
Vaginal brachytherapy only	3x7 Gy at a depth of 0.5 cm, usually at an active length of 5 cm from the closing line				
Combined pelvic EBRT + vaginal brachytherapy	3x5 Gy at a depth of 0.5 cm, usually at an active length of 5 cm from the closing line, followed by 45-50.4 Gy (1,8-2 Gy/day) EBRT				
Paraaortic + pelvic radiotherapy (if PAO lymph nodes are positive)	Pelvic + PAO region radiotherapy with 3-D conformal planning or IMRT, with a total dose of 45-50.4 Gy (1.8 Gy/day)				



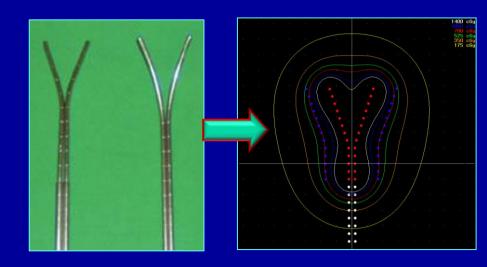


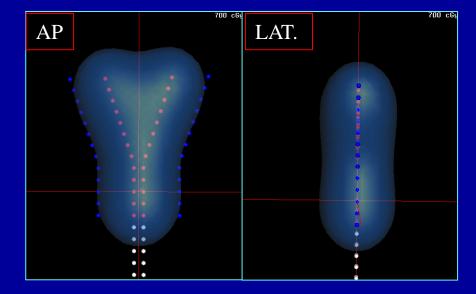




Primary radiotherapy of endometrial cancer – Only in case of contraindicated surgery!

The definitive radiotherapy of endometrial tumours						
Accelerat	Accelerated treatment: 1x IC weekly, on other days, 4 x EXT.					
ICBT	5x7 Gy calculated for the endometrial surface					
EBRT	RT 46 Gy with 4-field box technique; after 30 Gy, half-beam block technique or IMRT					
Single int	racavitary radiotherapy					
ICBT 6x7 Gy calculated for the endometrial surface						
ICBT: intracavitary brachytherapy; EBRT: external beam radiotherapy						





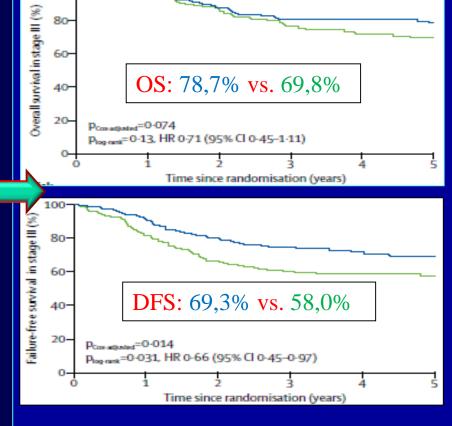
Drug treatment of endometrial cancer:

• Chemotherapy (St. III-IV):

- CAP (Cyclophosphamid-Adriamycin-Platina)
- Carboplatin-Paclitaxel
- Postop. Radiochemotherapy (St. III):
 - Simultaneous Cisplatin during RT (Week 1 & 4)
 - + 4 cycles of adjuvant Carboplatin-Paclitaxel

• Hormone therapy:

- Gestagenes (Megace)
- Anti-estrogenes (Tamoxifen)



Staging of ovarian cancer



Symptoms, diagnosis, and staging

Symptoms:

- Early: none!
- Late: bloating, ascites, abdominal discomfort
- Most commonly recognized in advanced stage III/C!

Diagnostic work-up, and staging:

- CA-125 tumour marker
- Physical exam. (RDE: Douglas's pouch!)
- Vaginal US
- Pelvic CT/MRI
- Irresectable tumour: core-biopsy

St. I	The tumour is confined to the ovaries
IA	Tumour is limited to one ovary, capsule intact
IB	Tumour is present in both ovaries, capsule intact
IC	Tumour is present in one or both ovaries, and
IC1	Surgical-artificial spill is present
IC2	Capsule has ruptured before surgery
IC3	Ascites or positive intraperitoneal cytology are present
St. II	Tumour is present in one or both ovaries, extension includes other pelvic structures
IIA	Tumour has spread to the uterus or the fallopian tubes
IIB	Tumour has spread to intraperitoneal pelvic structures
St. III	Tumour is present in one or both ovaries, with extension to extrapelvic peritoneal and/or retroperitoneal lymph nodes
III/A1	Positive retroperitoneal lymph nodes (III/A1 (i) < 10 mm III/A1 (ii) > 10 mm
III/A2	Microscopic extrapelvic peritoneal metastases + positive lymph node status
III/B	Macroscopic <2 cm extrapelvic peritoneal metastasis (liver/spleen) and/or positive retroperitoneal lymph nodes
III/C	Macroscopic (> 2 cm) extrapelvic peritoneal metastasis (liver/spleen) and/or positive retroperitoneal lymph nodes
St. IV	Distant metastases present beyond the peritoneal area
IV/A	Pleural effusion contains tumour cells
IV/B	Distant metastasis (liver, lung, spleen; inguinal or extra-abdominal lymph node metastases)

Management of ovarian cancer

<u>Primary treatment = Surgery + Chemotherapy</u>

- Staging laparotomy:
 - -TAH + BSO + ROM + LAD*
 - Peritoneal revision
 - Cytology of peritoneal washing fluid
 - Optimal surgery: Rate of R0 resestion >66%
 - Suboptimal surgery: 3-4 cycles of CT interval laparotomy
- Adjuvant CT:
 - Carboplatin-Paclitaxel (Taxol)
 - 2^{nd.} & 3^{rd.} line:
 - Platinum resistant: Bevacizumab (Avastin)
 - Platinum sensitive: Platina reinduction, Docetaxel (Taxotere), Topotecan (Hycamtin), liposomal Doxorubicin (Caelyx), PARP-inhibitors (Olaparib, Rucaparib),

*TAH = Total Abdominal Hysterectomy BSO = Bilateral Slapingo-Oophorectomy ROM = Resection of Omentum Majoris LAD = Lymphadenectomy

Indications of radiotherapy for ovarian cancer

- Adjuvant
- Salvage/consolidating
- Palliative

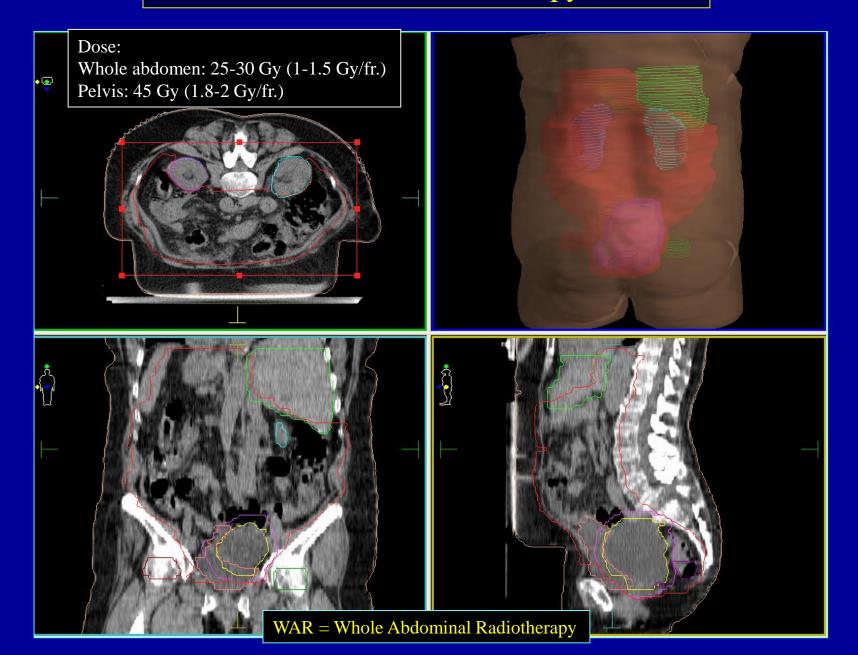
- Lack of level 1-2 evidencies
- Previous clinical studies used CT without platinum/taxanes
- No definitive guidelines



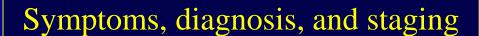
• <u>Indication:</u> individual decision limited to cases with contraindication of chemotherapy

- Distant metastases (e.g. supraclavicular met.)
- Persistant or recurrent pelvic tumour mass
- Paraaortic LN metastases
- Whole abdominal RT: only in good general condition (ECOG: 0-1)

Whole Abdominal Radiotherapy = WAR



Staging of vulvar cancer



Symptoms:

- Exophytic or exulcerated tumours of labia minora or majora
- Skin discharge, itching, bleeding

Diagnostic work-up and staging:

- Physical exam. (inguinal lymphatic region + rectovaginal exam.)
- Inguinal US
- Pelvic CT/MRI
- Incisional biopsy

Histological diagnosis



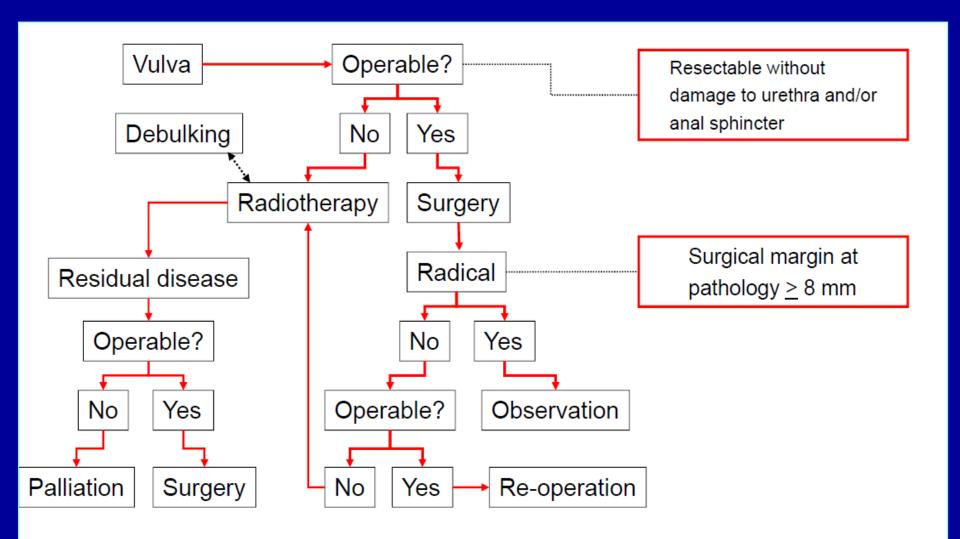
	St.					
Frimary tumour						
Tis	0	Carcinoma in situ				
Γ1	la	Tumour diameter is <2 cm, depth of invasion does not exceed 1 mm (microinvasive cancer)				
	lb	Tumour diameter is <2 cm, depth of invasion is >1 mm				
Т2	II	Tumour diameter is >2 cm				
Т3	III	Tumour invades the urethra, and/or the vagina, perineum, anus; unilateral inguinal metastasis				
Т4	IVa	Tumour invades rectal and/or bladder mucosa, the mucosa of the upper urethral segment, and/or metastasises to the pelvic bone; bilateral inguinal metastasis				
	IVb	distant metastases, abdominal lymph node positivity				
N Lymp	h node st	tatus				
NX		Lymph node status cannot be assessed				
NO		No lymph node metastases				
N1		Unilateral inguinal lymph node metastases				
N2		Bilateral inguinal lymph node metastases				
M Dista	ant metas	tases				
MX		Distant metastases cannot be assessed				
M0		No distant metastases				
M1		Distant metastases are present (pelvic lymph node metastases are also considered M1)				

Management of vulvar cancer

Primary treatment = Surgery

- Stage I/A:
 - Local wide excision
- Stage I/B:
 - Radical vulvectomy + bilateral inguinal dissection
- +/- Adjuvant RT

Management of vulvar cancer



Radiotherapy of vulvar cancer

- Postoperative
- Primary RT/RKT
- Palliative



Postoperative radiotherapy of vulvar cancer

NCCN guideline for local and inguinal RT

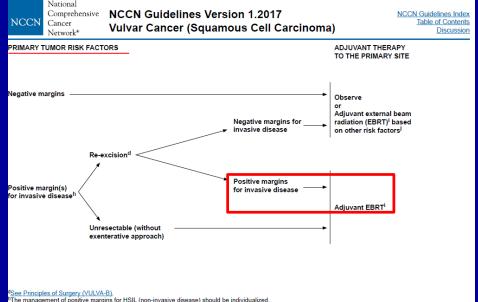
Surveillance

(VULVA-8) VIJI VA-3



EBRTⁱ ± concurrent chemotherapy^l (especially if ≥2 LNs positive or 1 LN positive with >2 mm metastasis) (category 1 for radiation)

Surveillance



Nationa NCCN Guidelines Version 1.2017 Comprehensive NCCN Guidelines Index **NCCN** Table of Contents Cancer Vulvar Cancer (Squamous Cell Carcinoma) Discussion Network⁶ NODAL EVALUATION ADJUVANT THERAPY TO THE NODES LNs-negative sentinel node(s) or Observe nguinofemoral nodes) EBRTi ± concurrent chemotherapy (category 1 for radiation) SLN(s) positive^k Completion inguinofemoral node dissection EBRTi ± concurrent chemotherapy (especially if ≥2 LNs positive or 1 LN positive wit >2 mm metastasis) (category 1 for radiation) Inguinofemoral node dissection with positive LN(s)

ee Principles of Radiation Therapy (VULVA-C).

See Principles of Surgery: Inquinofemoral Sentinel Lymph Node Procedure (VULVA-B 3 of 4) See Systemic Therapy (VULVA-D)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged

The management of positive margins for HSIL (non-invasive disease) should be individualized.

ee Principles of Radiation Therapy (VULVA-C)

Other primary risk factors include: lymphovascular invasion, negative but close tumor margins (<8 mm), tumor size, depth of invasion, and pattern of invasion (spray or diffuse). Nodal involvement (as an indicator of lymphovascular space invasion) may also impact selection of adjuvant therapy to the primary site.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged

Primary radiotherapy of vulvar cancer

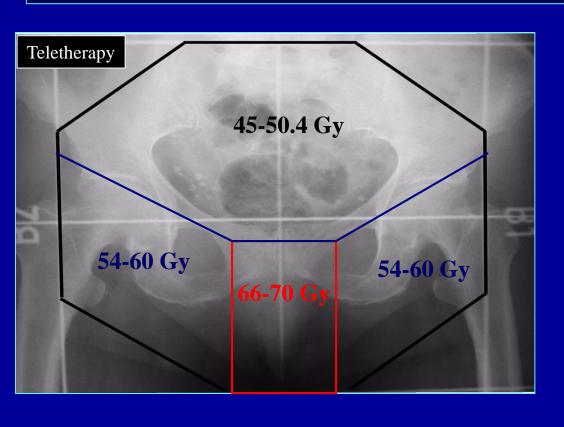
Radiochemoterapy – only for young pts. In good general condition!

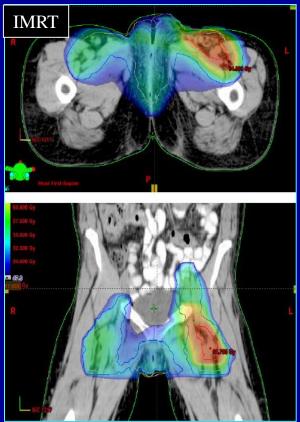
Phase II clinical studies:

Cisplatin-5-FU – CR: 33-89%

5-FU-Mitomycin C – CR: 42-100%







Staging of vaginal cancer



Symptoms, diagnosis, and staging

Symptoms:

- Vaginal discharge, bleeding

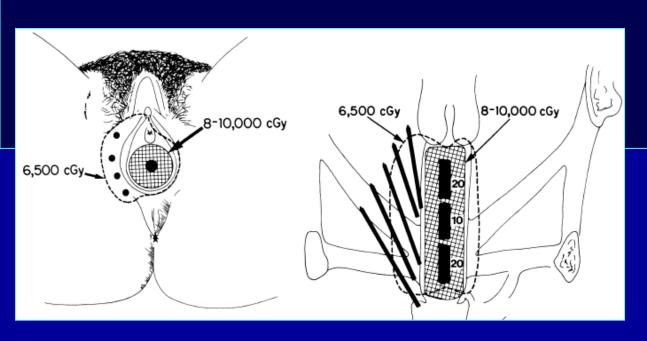
Diagnostic work-up & staging:

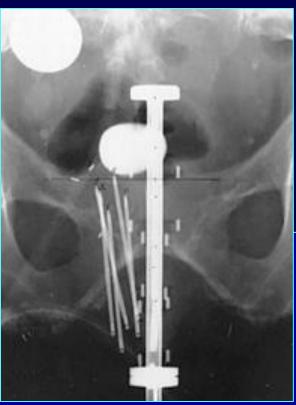
- Physical exam. (inguinal LNs + rectovaginal exam.)
- Inguinal US
- Pelvic CT/MRI
- Incisional biopsy **Szövettan**

TNM	FIGO	
Tis	0	In situ cc.
T1	I	Tumour limited to the vagina
T2	II	Paracolpium invaded
T3	III	Paracolpium ivaded, pelvic wall
T4	IVA	Bladder/Rectal involvement
N0		No LN met.
N1	III	Regional LN met. (inguinal, pelvic)
M 0		No distant met.
M1	IVB	Distant met.

Radiotherapy of vaginal cancer

- Usually primary RT good results + function preservation!
 - St. I: BT alone $-5-6 \times 7$ Gy
 - St. II-IV/A: 45-50.4 Gy external beam RT + 3-5 x 7 Gy BT
 - Local control: St I: 77-88%; St II: 58-68%; St III: 40-60%; St. IV/A: 20-30%
 - Simultaneous radiochemotherapy limited evidence:
 - Squamous cell. cc: 5-FU-MMC, cisplatin
 - Adenocc + clear-cell cc: 5-FU-VBL





Palliative RT of GYN tumours

- Indivudualized treatment according to the volume of the disease and the general condition of the patient
- Lower total dose: 20-50 Gy
- Hypofracionated short RT courses: 10 x 3 Gy, 5 x 4 Gy
- Less sophisticated techniques: two opposed fields
- Vaginal bleeding 1-2 x 8-10 Gy HDR brachytherapy
- RT of distant metastases:
 - Distant LN mets. (PAO, supraclavicular)
 - Hematogene mets. (bone, brain)





Thank you for your kind attention!

