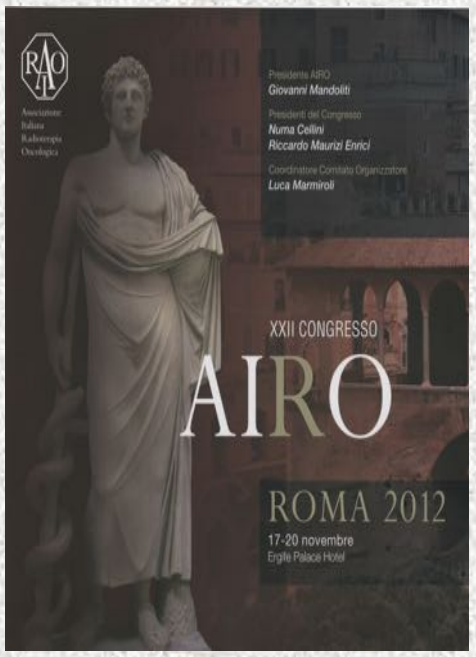
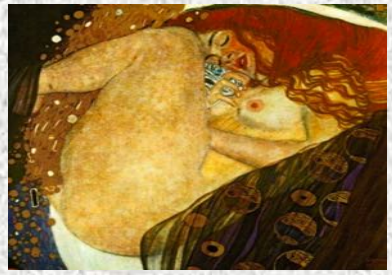
XXII CONGRESSO AIRO ROMA 2012 17-20 novembre Ergife Palace Hotel

Trattamenti integrati nel carcinoma della vulva



La radioterapia: Indicazione e risultati clinici

Vitaliana De Sanctis
Radioterapia Oncologica
Università "Sapienza"
Roma



the peak 70 and 79 years of age,

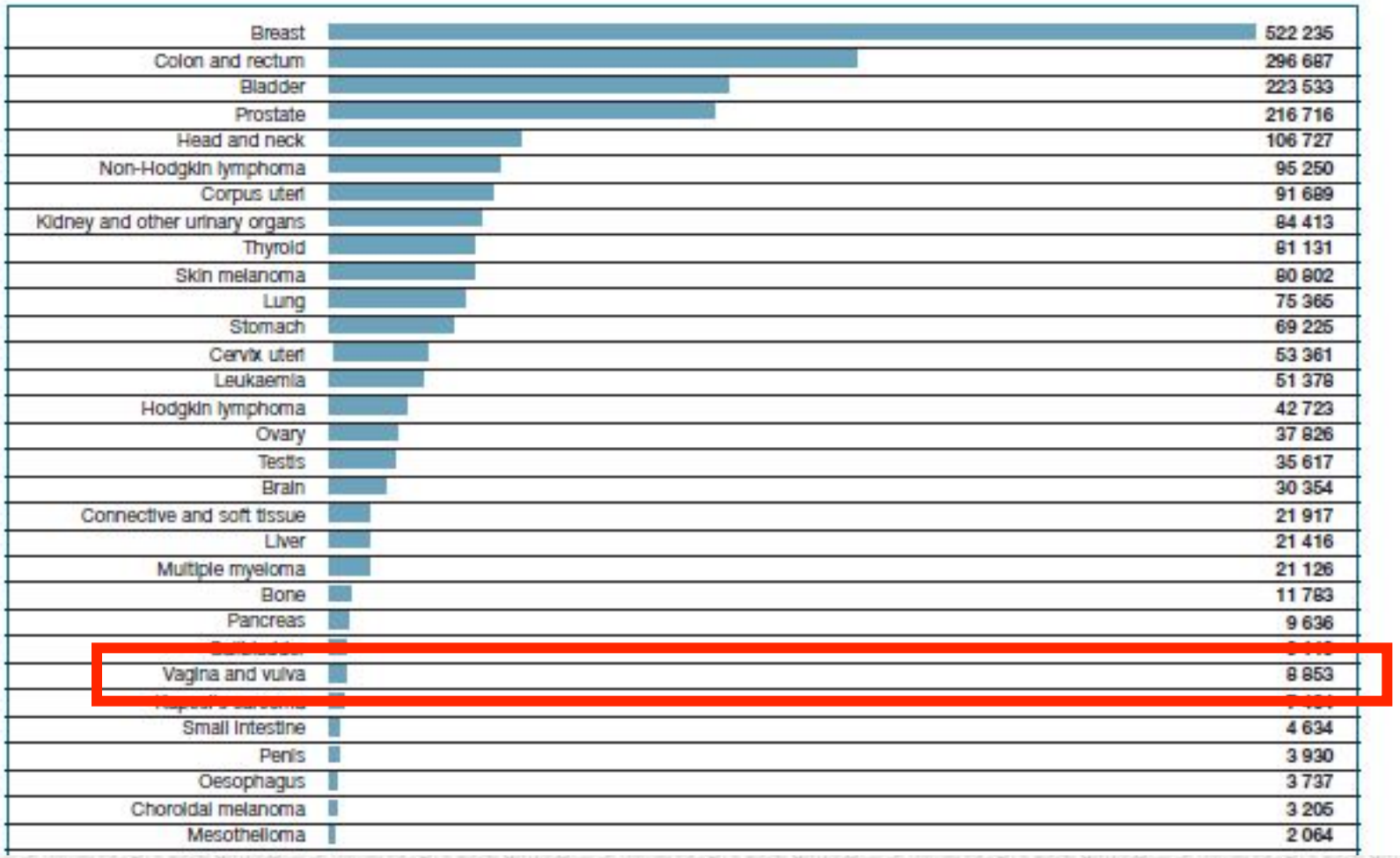
4–5% of the genital malignancies in women.

3,900 new cases and 920 deaths /year in the US

American Cancer Society (2010) Cancer Facts & Figures

88% of the patients, the symptoms had been present for about 6 months
28% longer than 5 years.

prevalenza 2006
9.953/2.243.953 (4.4%)



New aspects of vulvar cancer: Changes in localization and age of onset

Monika Hampl [a,*], Stella Deckers-Figiel [a], Juergen A. Hampl [b], Daniel Rein [a], Hans G. Bender [a]

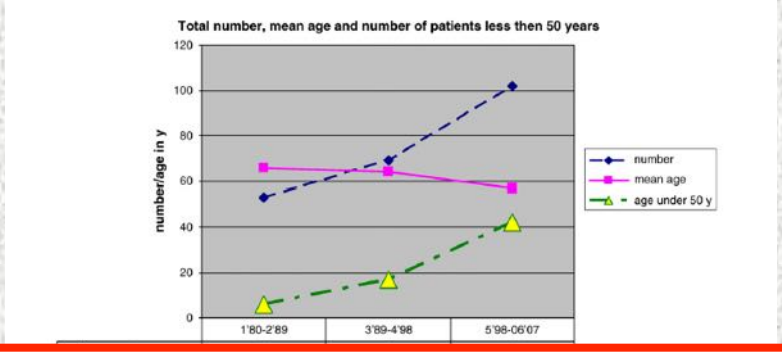
Gynecologic Oncology 109 (2008) 340–345

From 01/1980 until 06/2007 **224 pts**

I period
1980-1989
53 pts mean age 65.6

II period
1989-1998
69 pts mean age 63.9

III period
1998-2007
102 pts mean age 57



Total increase 192%

Two-third of the tumors women age <50 years were HPV-positive with a nearly 4-time increase in younger patients (+372%) due to HPV high risk infection.

Gynecologic Oncology Group risk groups for vulvar carcinoma: improvement in survival in the modern era

Landrum LM Gynecol Oncol 2007

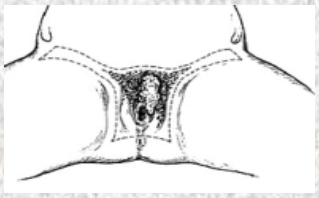
175 pts

Risk classification	Tumor size/lymph nodes		Survival rate	Historic group Survival rate
Minimal	Tumor ≤2 cm and negative lymph nodes	51%	100%	97.9%
Low	Tumor 2.1–8 cm and negative lymph nodes	40%	97%	87.4%
	Tumor ≤2 cm and one positive lymph node			
Intermediate	Tumor >8 cm and negative lymph nodes	6%	82%	74.8%
	Tumor >2 cm and one positive lymph node			
	Tumor ≤8 cm and two unilateral positive lymph nodes			
High	Tumor >8 cm and two unilateral positive lymph nodes	3%	100%	29%
	Three or more positive lymph nodes			
	Bilateral positive lymph nodes			

Survival among the minimal and low risk groups is preserved in spite of less radical surgery.

5-year survival rate for intermediate and high risk patients also appears to be improved. This is likely a result of advancement in adjuvant chemo-radiation and a younger patient population that presents with less advanced disease

SURGICAL CONCEPTS EVOLUTION



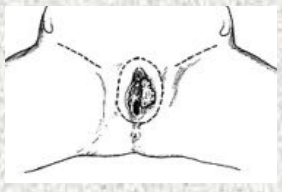
1950

Cancer of the vulva.

***Taussig FJ Am J Obstet Gynecol 1940;40:764*.**

The anatomy of the lymphatic drainage of the vulva and its influence on the radical operation for carcinoma.

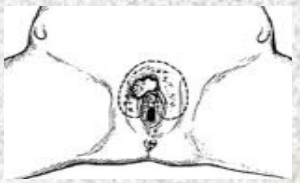
***Way S. Ann Coll Surg Eng 1948;3:187*.**



1980

Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions.

Hacker NF Obstet Gynecol 1981;58:574.



An alternative approach to early cancer of the vulva.

DiSaia PJ, *Am J Obstet Gynecol 1979;133:825*.

1990

Intraoperative lymphatic mapping for vulvar cancer.

Levenback C Obstet Gynecol 1994;84:163.

1969 FIGO Clinical staging

1988 FIGO Surgical staging

2000 FIGO Surgical staging revised

stage	FIGO staging 1969	FIGO staging 1988	FIGO staging 2000
	Clinical staging	Surgical staging	Surgical staging
0	Carcinoma in situ	Carcinoma in situ	carcinoma in situ
I	Tumour confined to vulva, 2cm or less in largest diameter, and no suspicious groin nodes	Tumour confined to vulva or perineum, < 2cm in greatest dimension, nodes are negative	Ia: Tumour confined to vulva or vulva and perineum, 2cm or less in greatest dimension and with stroma invasion no greater than 1.0mm. Nodes are negative. Ib: Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion greater than 1.0 mm. Nodes are negative
II	Tumour confined to vulva, more than 2 cm in diameter, and no suspicious groin nodes	Tumour confined to vulva or perineum, > 2cm in greatest dimension, nodes are negative	Tumour confined to vulva or vulva and perineum, more than 2 cm in greatest dimension. Nodes are negative
III	Tumour of any size with: (1) Adjacent spread to the urethra and/or vagina, perineum, and anus, and/or (2) Clinically suspicious lymph nodes in either groin	Tumour of any size with: (1) Adjacent spread to the lower urethra or anus, and/or (2) Unilateral regional lymph nodes metastases	(1) Tumour invades any of the following: lower urethra, vagina, anus. (2) Unilateral regional lymph nodes metastases
IVa	IV: Tumour of any size : (1) infiltrating the bladder mucosa, or the rectal mucosa, or both, including the upper part of the urethral mucosa, and/or (2) fixed to the bone, and/or (3) other distant metastases		
IVb		Any distant metastasis, including pelvic	Any distant metastasis, including pelvic

International Journal of Gynecology and Obstetrics 105 (2009) 105–106

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

www.figo.org

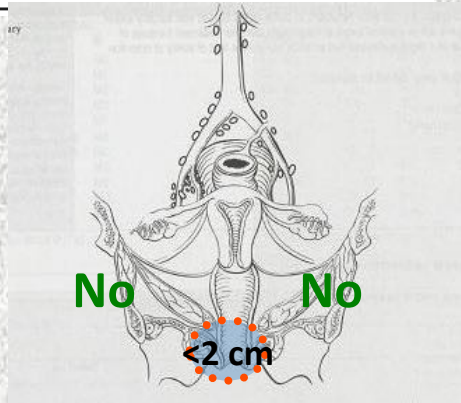
SPECIAL COMMUNICATION

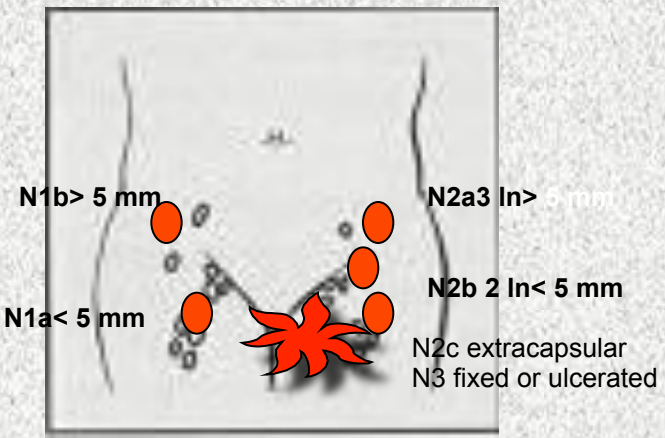
Revised FIGO staging for carcinoma of the vulva

Neville F. Hacker

Royal Hospital for Women and University of New South Wales, Sydney, Australia

1) Stage IA will remain unchanged because this is the only group of patients with a negligible risk of lymph node metastases, but
2) Stage I and II have been combined.
3) The number and morphology of the involved nodes have been taken into account,
4) bilaterality of positive nodes has been discounted.





To decrease the incidence of locoregional failures after wide local excision in patients with stage I and II tumors

To serve as an alternative to inguinal or pelvic lymph node dissection in patients with clinically negative nodes

The role of Radiation therapy

To treat patients before surgery for locally extensive tumors that may be considered inoperable initially

To reduce the incidence of postsurgical failure in patients with stage III and IV disease;

Patients with T1a disease have no risk of groin metastases and do not need lymphadenectomy

Hacker, Cancer 93; Homesley, Cancer 95; Benedet, Int J Gynecol Oncol 2000; Magrina Int J Gynecol Oncol 2000

Omission of groin irradiation seems to be justified in low risk patients T1, N0-1 stage, no central location, no vessel invasion, tumor thickness ≤ 2 mm and G1-G2 tumors

Manavi, Int J Radiat Biol Phys 97

c T1- 2 **cN0** M0

radical excision of the tumour and bilateral inguinal and femoral lymph node dissection

tumour recurrences in the groin after surgery is often reported as less than 2% .

Petereit 1993, Stehman 1992; Van der Velden 1996

Wound healing

Morley 76, 50%
Homeseley 86, 49%
Podtraz 83,85%
Stehman 93, 48%
Hallak, 2007, 19%
Petereit 93, 72%

Lymphedema

Homeseley 86, 27%
Podtraz 83, 69%
Stehman 93, 25%
Hallak, 2007 7%

2011

Primary groin irradiation versus primary groin surgery for early vulvar cancer (Review)

van der Velden J, Foss G, Lawrie TA

THE COCHRANE COLLABORATION®

Background

Despite changes in technique, morbidity after surgery for vulvar cancer is high and Mainly related to the groin dissections. Primary radiotherapy to the groin is expected to result in lower morbidity. However, studies on the efficacy of primary radiotherapy to the groin in term of groin recurrences and survival show conflicting results

Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group Study.

Stehman FB Int J Radiat Oncol Biol Phys 1992;

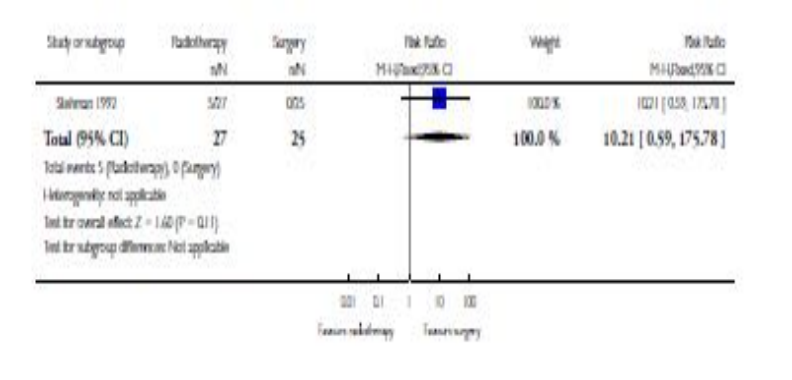
300 pts T1-3 cN0

STOPPED EARLY

52 pts

Radiotherapy 50 Gy

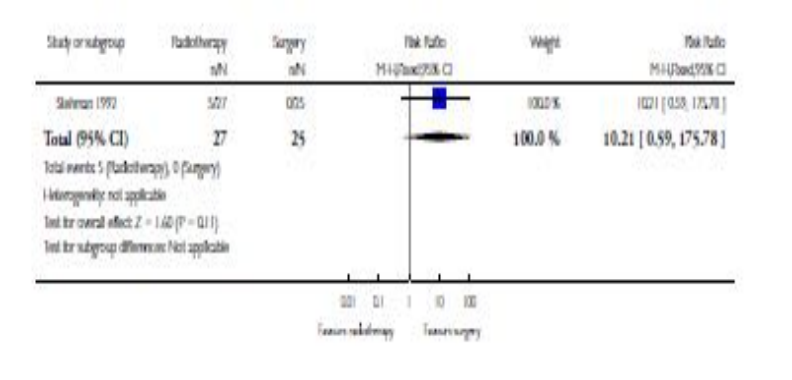
Inguinal-femoral lymphadenectomy



5/27 (18.5%) **P=0.02** **0/25 (100%)**

Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group Study.

Stehman FB Int J Radiat Oncol Biol Phys 1992;



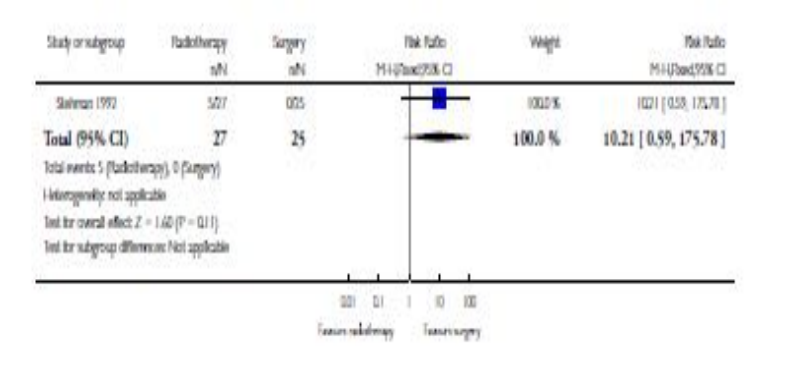
Statistical bias

1) **The patients were not identically distributed in both study group**

2) **not used important prognostic factors indicating the Involvement of the lymph nodes such as tumor thickness and vascular infiltration**

Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group Study.

Stehman FB Int J Radiat Oncol Biol Phys 1992;



Radiotherapic bias

50 Gy prescription at 3 cm below the anterior skin surface, with 50% of the dose with electron beam 12-13 MeV whereas the primary site and the pelvic nodes were not treated

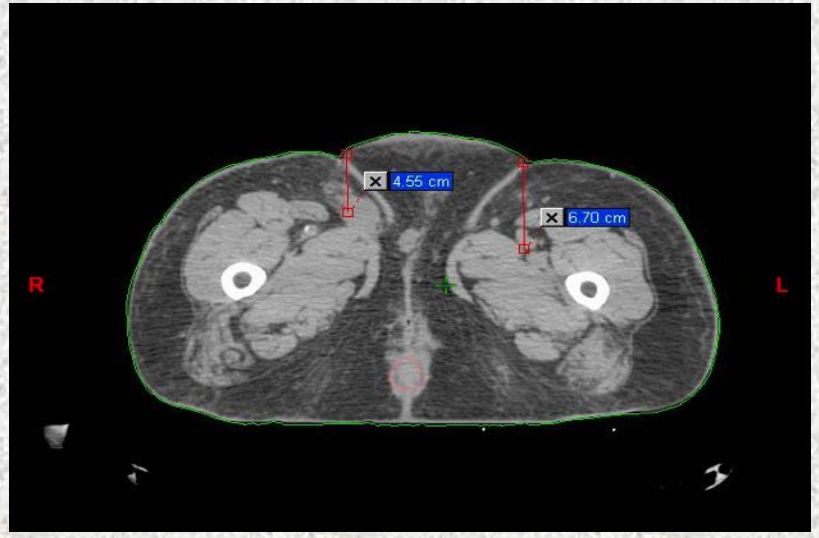
Lymp nodes deeper than 4 cm could have been undertreated

Femoral vessel depth and the implications for groin node radiation.
Koh, WJ

Int J Radiat Oncol Biol Phys 93

Reanalysis
substantial underdosage of the target volume

the three failure treated with electrons received estimated dose of
21.8-33.05 Gy



GROIN NODE IRRADIATION FOR VULVAR CANCER: TREATMENT PLANNING MUST DO MORE THAN SCRATCH THE SURFACE

Lanciano Int J Radiat Oncol Biol Phys 93

Accurate target definition: " if the target is not properly defined, ..tumor control is impossible

Definition of the target with CT or MRI is crucial

The simplicity and accuracy of parallel opposed photon field for most nodal depths make this tecnique most appealing for a cooperative trial…

Inguinofemoral radiation of N0.N1 vulvar cancer may be equivalent to Lymphadenectomy if proper radiation technique is used

Petereit Int J Radiat Oncol Biol Phys 93

49 pts T1-4, N0-1

retrospective

	25 lymphadenectomy		**23 RT 50 Gy**
Nodal control	**100%**	**P=0.14**	**91%**
3-year cause specific survival	**96%**		**90%**

Prophylactic inguinal-femoral irradiation as an alternative to primary lymphadenectomy in treatment of vulvar carcinoma

SORANA HALLAK[1], LUZ LADI[2] and BENGT SORBE[1]

INTERNATIONAL JOURNAL OF ONCOLOGY 31: 1077-1085, 2007

pts stage

297 T1-4

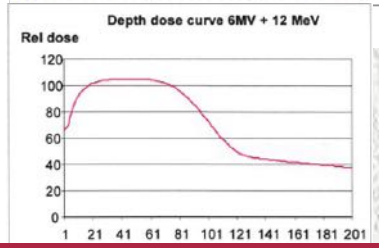
RT 267
S 27

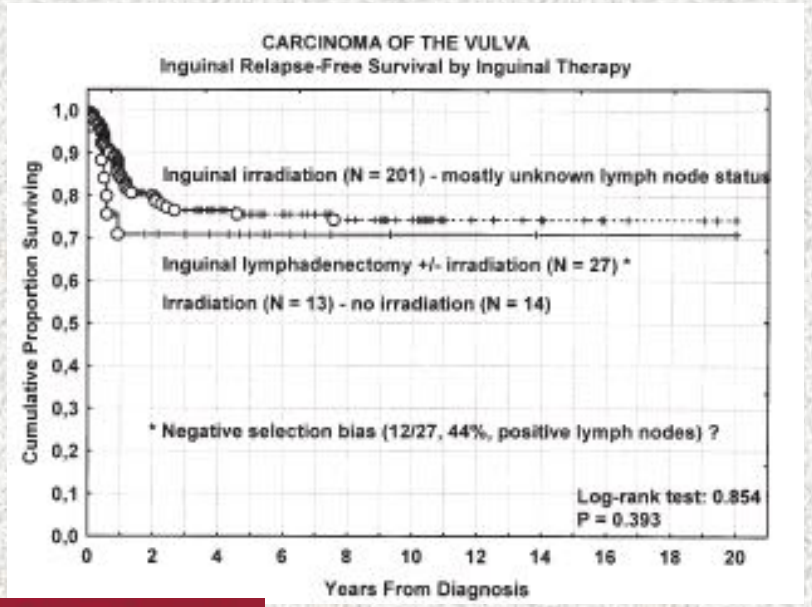
RELAPSE FREE SURVIVAL

75%
75%

PHOTON/ ELECTRON 50:50

Type of radiotherapy		
Adjuvant	186	63.3
Curative	28	9.5
Palliative	16	5.4
None	64	21.8
Target		
Inguinal lymph nodes	199	67.7
Vulva	23	7.8
Pelvis	8	2.7
None	64	21.8
Schedule		
2 x 2.64 Gy x 9[a]	96	41.7
1 x 3.0 Gy x 18	46	20.0
1 x 2.0 Gy x 25	88	38.3





Primary groin irradiation versus primary groin surgery for early vulvar cancer (Review)

van der Velden J, Foss G, Lawrie TA

THE COCHRANE COLLABORATION®

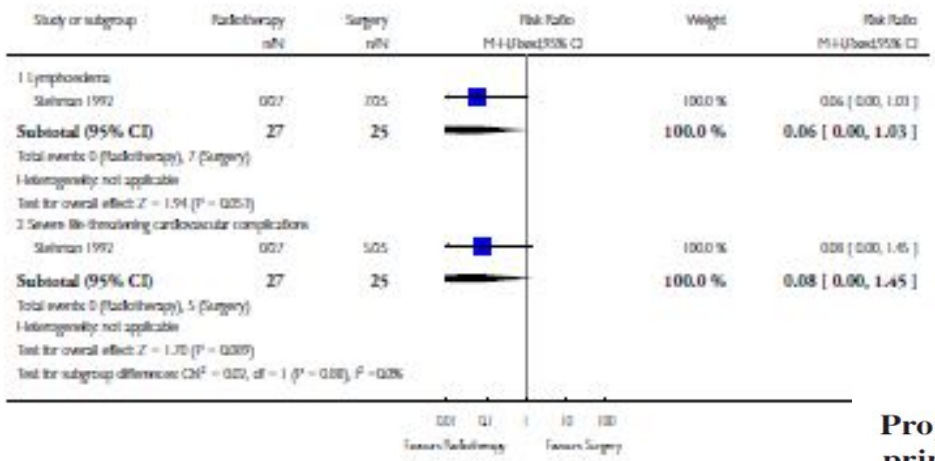
Daly 1974	Non-randomised study. Insufficient numbers.
Edsmyr 1961	Non-randomised study. Incidence of groin recurrences cannot be analysed separately
Hallak S 2007	Retrospective observational study. 294 cases of vulvar cancer were given post-operative radiotherapy after standar surgery which included inguinal lymphadenectomy in only 27 cases. 110 patients had Stage I disease Two separate inguinal fields were irradiated with combined photon (6MeV) and electron (12 MeV) beams. Dos 47.5 Gy to 54 Gy; depth: relative depth dose > 100 from 2 till 7 cm. Three different fraction schedules were use Follow-up was for a minimum of 10 years. Overall, 127 recurrences were recorded (43%) - 15/110 patients wit Stage 1 disease (14%). The 5-year survival of the Stage I group was 69% and relapse free survival (RFS) wa 60%. RFS rate was not associated with the type of surgery performed (total/partial vulvectomy or local tumou excision) The inguinal relapse free rate was 75% both for patients treated with adjuvant inguinal irradiatio without lymphadenectomy (n=201) and patients treated with primary lymphadenectomy ± inguinal irradiatio (n=27). It was not possible to identify the inguinal relapse free rate for the stage I/II patients who had radiotherap as sole treatment for the groins separately. Post-op complications were significantly more frequent in the subgrou
Leiserowitz 1997	Non-randomised study. Incidence of groin recurrences cannot be analysed separately
Manavi 1997	Case-control study of T1 N0-1 M0 patients. Control – 'wait and see'. 65 patients received radiotherapy to inguinofemoral nodes, 70 received no treatment to nodes. 5 patients had non-squamous cell carcinoma. No significant difference in relapse rates and survival. Radiotherapy dose: 60Gy; type: telecobalt; depth: 45 Gy at 5cm. Groin recurrence – 3/65 (4.6%) versus 7/70 (10%). "Low" morbidity: 5/65 (vaginal stenosis: 2, inguinal pain, recto-vaginal fistula, infection) versus 2/70 (vaginal stenosis). Survival overall – 91% (? disease specific: ? disease free)
Perez 1998	Observational study of 87 women with T1-2 N0-1 M0 vulvar cancer (7 with non-squamous cell carcinoma): 19/87 women received radiotherapy to inguinofemoral lymph nodes. Dose: 50-70Gy; type: photons (electron boost); depth: at 4cm. Groin recurrence occurred in 2/19 cases (10.5%). No survival data
Petereit 1993	Non-randomised study. Incidence of groin recurrences cannot be analysed separately in relation to early stage disease
Pirtoli 1982	Non- entioned.

(inguinal) lymph node dissection performed. This is a sub-optimal procedure and makes comparison difficult

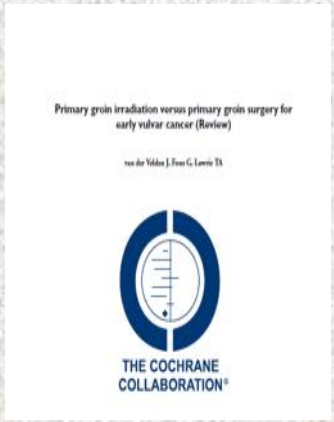
Bias statistici

Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group Study.

Stehman FB Int J Radiat Oncol Biol Phys 1992;



morbidity



INTERNATIONAL JOURNAL OF ONCOLOGY 31: 1077-1085, 2007

Prophylactic inguinal-femoral irradiation as an alternative to primary lymphadenectomy in treatment of vulvar carcinoma

SORANA HALLAK[1], LUZ LADI[2] and BENGT SORBE[1]

[1]Department of Gynecological Oncology, and [2]Department of Obstetrics and Gynecology, Örebro University Hospital, S-701 85 Örebro, Sweden

Received January 8, 2007; Accepted June 7, 2007

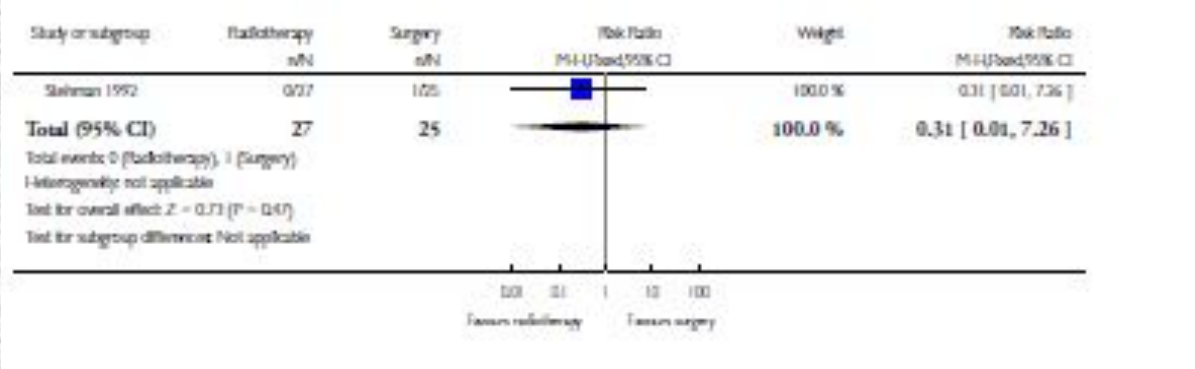
therapy.[a]

Factor	Odds ratio	95% C.I.	P-value
Radiotherapy (D/F)	1.00	0.50-2.00	0.990
Lymphadenectomy	4.63	1.11-19.21	0.033

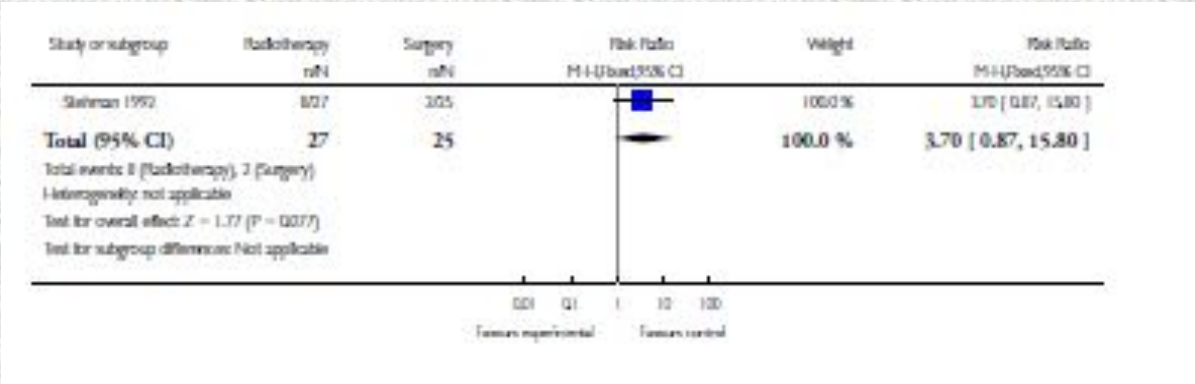
[a]Logistic regression analysis. D/F, dose per fraction (2.0 Gy versus 3.0 or 2.64 Gy).

Groin dissection versus groin radiation in carcinoma of the vulva: a Gynecologic Oncology Group Study.

Stehman FB Int J Radiat Oncol Biol Phys 1992;



Mortality related to treatment



Mortality disease specific


Primary groin irradiation versus primary groin surgery for early vulvar cancer (Review)

van der Velden J, Feun G, Lawrie TA

until a clear equivalence between groin Irradiation and dissection is demonstrated in a well-designed prospective randomized trial with QA of radiotherapy,

lymphoadenectomy still represents the standard approach to the groin

sentinel node' studies

Author	Year	Number of patients	Blue dye (D)	Tracer (T)	Preoperative lymphoscintigraphy	Success rate (%)	False negative
Levenback et al. [49]	1995	21	Y	N	N	66	0
Decesare et al. [50]	1997	10	N	Y	N	100	0
De Cicco et al. [51]	1997	15	N	Y	Y	100	0
de Hullu et al. [52]	1998	10	Y	Y	Y	100	0
Ansink et al. [53]	1999	51	Y	N	/	56	2
Tavares et al. [54]	2001					100	0
Molpus et al. [55]	2001					100	0
Makar et al. [56]	2001					100	0
De Cicco et al. [57]	2000					100	0
de Hullu et al. [58]	2000					100	0
Levenback et al. [59]	2001					88	0
Sliutz et al. [60]	2002					100	0
Moore et al. [61]	2003					100/61[b]	0
Puig-Tintoré et al. [62]	2003					96	0
Louis-Sylvestre et al. [63]	2005					100	0
Merisio et al. [64]	20	20	Y[a]	Y	Y	100	1
Rob et al. [65]		59	Y[d]	Y	Y	100 (D/T)[g]	0 (D/T)
						68.8 (D)	1 (D)
Haupy et al. [66]	007	42	Y[h]	Y	N	95	0
	2008	36	Y	Y		100	
Van der Zee et al. [68]	2008						
Levenback et al. [69]	2009						
Lindell et al. [70]	10						

Negative SN
T< 4 cm
Groin surgery omitted
Relapse 6/259 (2.3%)
3-trs survival 97%

Sensitivity 89.9%
Negative predictive value 95.6%
False-negative predictive value 4.4%

Toxicity of surgery

sentinel node studies

Author	Year	Number of patients	Blue dye (D)	Tracer (T)	Preoperative lymphoscintigraphy	Success rate (%)	False negative
Levenback et al. [49]	1995	21	Y	N	N	66	0
Decesare et al. [50]	1997	10	N	Y	N	100	0
Rob et al. [65]	2007	59	Y[d]	Y	Y	100 (D/T)[g] 68.8 (D)	0 (D/T) 1 (D)
Hauspy et al. [66]	2007	42	Y[h]	Y	N	95	0
Moore et al. [67]	2008	36	Y	Y		100	
Van der Zee et al. [68]	2008	403[i]	Y	Y			
Levenback et al. [69]	2009	515	Y	Y	Y[l]	96.2 (D/T) 78.8 (D)	
Lindell et al. [70]	2010	77	Y	Y	Y	98 (D/T)[k] 94 (D)	2

Groningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V II)
Observational study
Sentinel node negative: no lymphoadenectomy
Sentinel node positive: radiotherapy

To decrease the incidence of locoregional failures after wide local excision in patients with stage I and II tumors

To serve as an alternative to inguinal or pelvic lymph node dissection in patients with clinically negative nodes

The role of Radiation therapy

To treat patients before surgery for locally extensive tumors that may be considered inoperable initially

To reduce the incidence of postsurgical failure in patients with stage III and IV disease;

Surgical–pathologic factors associated with a higher risk of local recurrence:

deep invasion (>5mm) and lymphovascular space invasion

Boyce J, Gynecol Oncol 1985;20:364,
Binder SW, Gynecol Oncol 1990;37:9.

Positive margins

Heaps JM et al Obstet Gynecol 1990;38:309–314

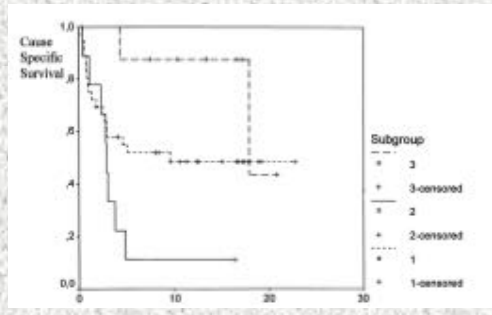
Close surgical margin

Heaps JM, Fu Gynecol Oncol 1990;38:309.
Chan JK, Gynecol Oncol 2007;104:636–41.

LONG-TERM IMPACT OF POSTOPERATIVE RADIOTHERAPY IN CARCINOMA OF THE VULVA FIGO I/II

MARTIN BUSCH, PD DR. MED.,* BIRGIT WAGENER,† MOSHE SCHAFFER, DR. MED.,* AND ECKHART DÜHMKE, PROF. DR. MED.*

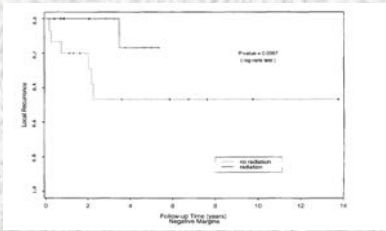
Int. J. Radiation Oncology Biol. Phys., Vol. 48, No. 1, pp. 213–218, 2000



10 pts adjuvant 60 Gy
9 pts adjuvant 40 Gy
51pts observation

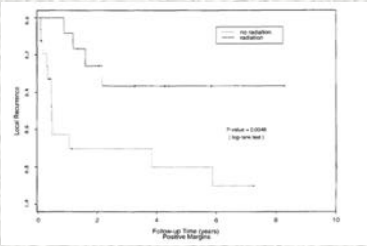
T1-2 No

No prospective trial has succesfully tested this hypothesis



31 pts adjuvant RT local recurrence 16%
31 pts observation local recurrence 58%

Positive margin



To decrease the incidence of locoregional failures after wide local excision in patients with stage I and II tumors

To serve as an alternative to inguinal or pelvic lymph node dissection in patients with clinically negative nodes

The role of Radiation therapy

To treat patients before surgery for locally extensive tumors that may be considered inoperable initially

To reduce the incidence of postsurgical failure in patients with stage III and IV disease;

Management of pelvic lymph nodes

Pelvic lymphadenectomy revealed positive pelvic nodes in approximately 5% of all the cases,
15–20% of the patients with positive groin nodes and nearly 0% of those wit

Since the clinical benefit of pelvic lymphadenectomy is limited, this procedure is rarely carried out today

Ro
free by pelvic lymphadenectomy

Franklin III EW, Obstet Gynecol 1971; Podratz KC, Am J Obstet Gynecol 1982;

Therefore, the potential survival benefit of pelvic lymphadenectomy appears to be 1% (20% of 5% who have pelvic nodal disease) for all patients or 4% (20% of 20% who have pelvic nodal disease) for those with positive groin nodes

Thomas GM, Gynecol Oncol 1991;

Management of pelvic lymph nodes

Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes.

Homesley HD, Obstet Gynecol 1986;68:733

114 pts

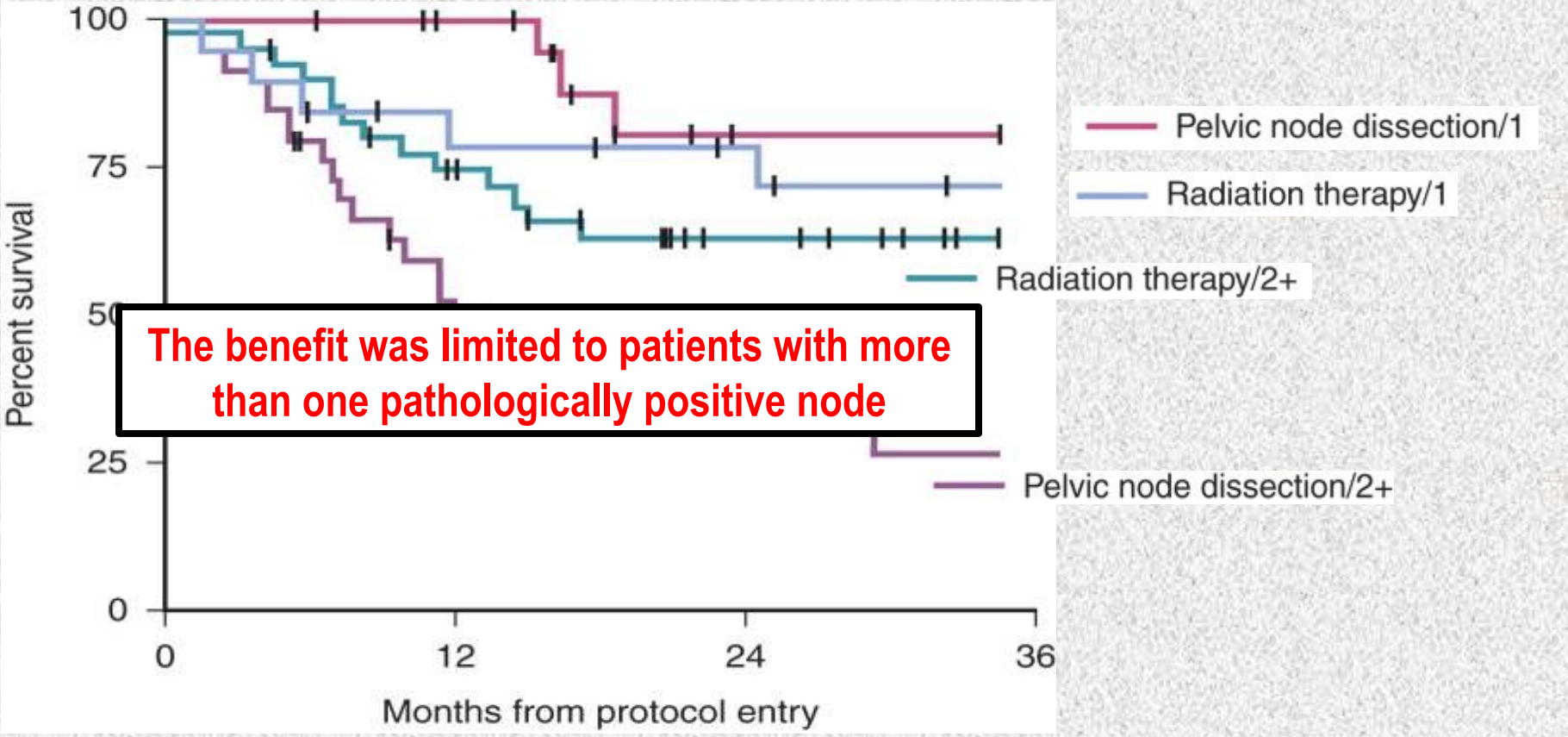
Radical vulvectomy and bilateral inguinal femoral lymphoadenectomy

Groin pN+

	Radiotherapy Groin and pelvic nodes 45-50 Gy		**Pelvic lymph node dissection**
	2-yrs OS 68%	**P=0.03**	**2-yrs OS 54%**
Clinically pos nodes	**2-yrs OS 59%**		**2-yrs OS 31%**
≥2 pos nodes	**2-yrs OS 63%**		**2-yrs OS 37%**

Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes.

Homesley HD, Obstet Gynecol 1986;68:733



The benefit was limited to patients with more than one pathologically positive node

Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study).

Am J Obstet Gynecol 1991;164(4):997–1004.

	5-year survival
negative nodes	90.9%,
1–2 positive nodes	75.2%
3–4 positive nodes	36.1%,
5–6 positive nodes	24.0%
7 or more positive nodes	0%

Prognostic value of pathological patterns of lymph node positivity in squamous cell carcinoma of the vulva stage III and IVA FIGO.

Origoni M, Gynecol Oncol 1992;45(3):313–6.

		5-year survivals
nodal metastases less than	5 mm	90.0%,
	5–15 mm	41.6%
	>15 mm	20.6%

extracapsular spread had a poor prognosis (25%) compared with patients with disease confined to the node (85.7%) ; P=0.001).

Extracapsular Growth of Lymph Node Metastases in Squamous Cell Carcinoma of the Vulva

The Impact on Recurrence and Survival

Jacobus van der Velden, M.D., Arnold C. M. van Lindert, Ph.D.,† Frits B. Lammes, Ph.D.,* Fiebo J. W. ten Kate, Ph.D.,‡ Daisy M. D. S. Sie-Go, Ph.D.,§ Hans Oosting, Ph.D.,‖ and A. Peter M. Heintz, Ph.D.†*

CANCER *June 15, 1995*, Volume 75, No. 12

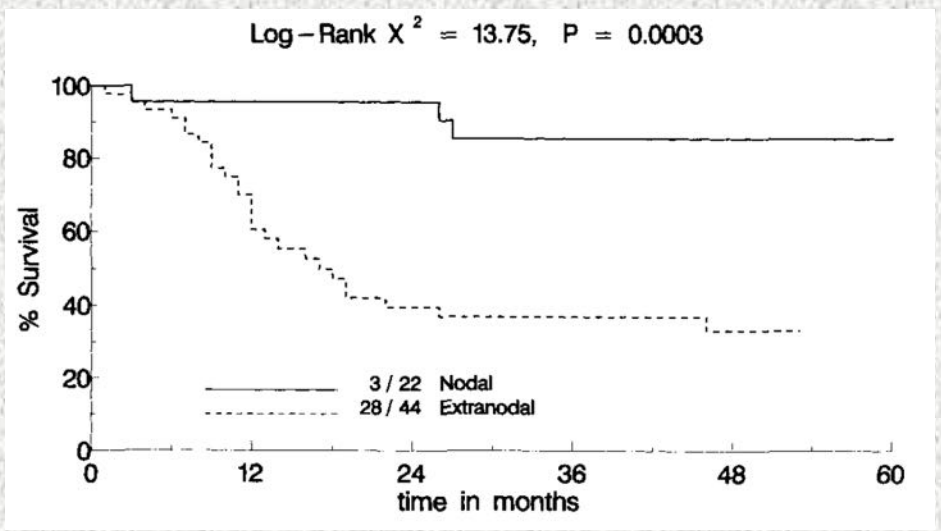


Table 2. Effect on Survival of Various Clinicopathologic Variables Additional to Extranodal Spread

Variable	Chi-square	*P* value
Extranodal spread	16.22	0.00
Size	2.00	0.16
No. of nodes	1.39	0.24
FIGO stage	0.54	0.46
Metastasis size	0.23	0.63
Nodal replacement	0.06	0.80
Laterality	0.03	0.87

FIGO: International Federation of Gynecology and Obstetrics.

Gynecologic Oncology 114 (2009) 343–345

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial

G. Fons [a,*], S.M.A. Groenen [b], M.H.M. Oonk [c], A.C. Ansink [c], A.G.J. van der Zee [c], M.P.M. Burger [a], L.J.A. Stalpers [d], J. van der Velden [a]

Number of recurrences per site of recurrence.

Site of recurrence	Intra capsular metastasis	
	Without RT[a]	With RT
None	30 (68)[b]	19 (62)
Local (vulva)	7 (16)	7 (23)
Groin	1 (2)	0 (0)
Pelvis	1 (2)	2 (6)
Distant	2 (5)	2 (6)
Unknown	3 (7)	1 (3)
Total	44 (100)	31 (100)

[a] Radiotherapy.
[b] Percentage.

Prognostic Role of Lymph Node Metastases in Vulvar Cancer and Implications for Adjuvant Treatment

Linn Woelber, MD, Christine Eulenburg, PhD,† Matthias Choschzick, MD,‡ Andreas Kruell, MD,§ Cordula Petersen, MD,§ Friederike Gieseking, MD,* Fritz Jaenicke, MD,* and Sven Mahner, MD**

International Journal of Gynecological Cancer • Volume 22, Number 3, March 2012

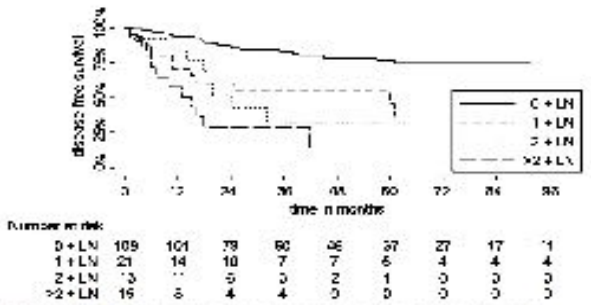


FIGURE 2. Impact of the number of positive lymph nodes on disease-free survival (n = 157, $P < 0.001$ node positive vs. node negative; $P = 0.080 > 2$ vs. 1 positive node; $P = 0.189$ 2 vs. 1 positive node).

TABLE 3. Multivariate analysis of the prognostic impact of the number of positive lymph nodes as a continuous variable on disease recurrence under consideration of the interaction between number of positive nodes and adjuvant radiotherapy (n = 157)

	P	HR	95% CI	
No. affected nodes (no adjuvant radiotherapy groins/pelvis)	**<0.001**	1.752	1.380	2.225
No. affected nodes (adjuvant radiotherapy groins/pelvis)	0.828	0.972	0.749	1.261
Interaction between no. positive nodes and adjuvant radiotherapy	**0.001**	0.555	0.394	0.781
pT2 vs pT 1a/b	0.721	1.143	0.549	2.383
pT3/4 vs pT 1a/b	0.336	1.634	0.601	4.446
G2 vs G1	0.533	0.731	0.272	1.961
G3 vs G1	0.858	1.098	0.395	3.047
Age per year	**0.003**	1.036	1.012	1.061
Depth of invasion per mm	0.333	1.026	0.974	1.080

Bold values indicate significant results.
CI, confidence interval; HR, hazard ratio.

Conclusions: The negative impact of lymph node metastases is already evident in patients with only 1 affected lymph node. In patients receiving adjuvant radiotherapy, the negative effect of additional lymph node metastases is reduced; adjuvant treatment might therefore be beneficial in patients with only 1 positive node.

Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study

Maaike H Oonk, Bettien M van Hemel, Harry Hollema, Joanne A de Hullu, Anca C Ansink, Ignace Vergote, René H Verheijen, Angelo Maggioni, Katja N Gaarenstroom, Peter J Baldwin, Eleonora B van Dorst, Jacobus van der Velden, Ralph H Hermans, Hans W van der Putten, Pierre Drouin, Ingo B Runnebaum, Wim J Sluiter, Ate G van der Zee

Lancet Oncology 2010;11:646

Our data show that the risk of non-sentinel node metastases Increases with size of sentinel-node metastasis.
No size cutoff seems to exist below which chances of non-sentinel-node metastases are close to zero.

Therefore all patients with sentinel-node metastases should have additional groin treatment

C

To decrease the incidence of locoregional failures after wide local excision in patients with stage I and II tumors

To serve as an alternative to inguinal or pelvic lymph node dissection in patients with clinically negative nodes

The role of Radiation therapy

To treat patients before surgery for locally extensive tumors that may be considered inoperable initially

To reduce the incidence of postsurgical failure in patients with stage III and IV disease;

Cervical cancer
1990

Anal cancer
1974

VULVAR CANCER
1987

Combined therapy as an alternative to exenteration for locally advanced vulvovaginal cancer. II. Results, complications, and dosimetric and surgical considerations.

A.Boronow RC, J Clin Oncol 1987;10:171–81.

37 pts
brachytherapy ± external beam RT
local control 86%

No patients required a pelvic exenteration

Radiochemotherapy

Why ?

Women undergoing exenterative procedures have higher surgical complications rates, including a mortality rate of 2% to 10%

To avoid exenterative procedures

Such r… erly due to s…

Andersen 1985; Moore 1998; Maggioni 2009

Such radical surgery is also inappropriate for young women as it causes severe psychosessual problem

Gadducci 2006

CHEMORADIATION AS PRIMARY OR ADJUVANT TREATMENT FOR LOCALLY ADVANCED CARCINOMA OF THE VULVA

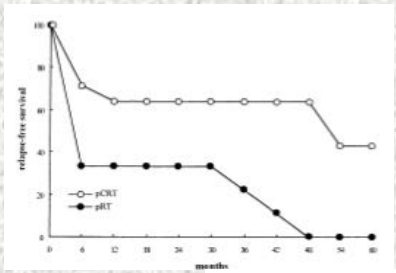
STEPHANIE C. HAN, M.D.,* DAVID H. KIM, M.D.,* SUSAN A. HIGGINS, M.D.,*
MARIA-LUISA CARCANGIU, M.D.,‡ AND BARRY M. KACINSKI, M.D., PH.D.*†

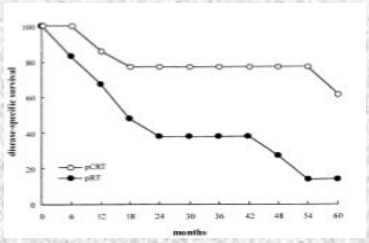
Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 5, pp. 1235–1244, 2000

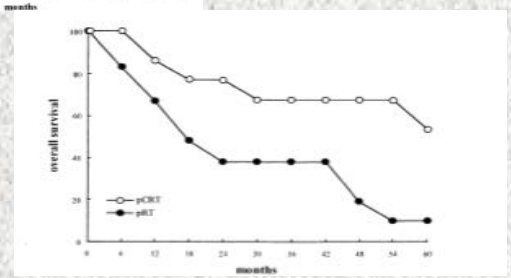
Table 1. Clinical features of patients treated with primary chemoradiation and doses of radiation therapy

Patient	Age (years)	Clinical stage	EBRT dose (Gy)
Primary chemoradiation			
1	65	T3N0	48
2	73	T3N1	57
3	73	T3N0	54
4	52	T3N0	62
5	54	T3N0	52
6	76	T4N1	62
7	64	T3N0	54
8	49	T3N1	40
9	81	T3N2	40
10	58	T3N0	45
Chemoradiation for recurrent disease			
11	79	T2N0	44
12	66	T1N0	45
13	69	T1N0	54
14	67	T2N1	45

EBRT = external beam radiation therapy.







Conclusion: Concurrent radiation therapy and chemotherapy decreases local relapse rate, improves disease-specific and overall survival over RT alone as primary treatment for locally advanced vulvar cancer. © 2000

WHICH CHEMOTHERAPY SCHEDULE?

bleomycin

Irradiation and bleomycin in the treatment of inoperable vulval carcinoma.

Iversen T Acta Obstet Gynecol Scand 1982

Combined bleomycin and irradiation in preoperative treatment of advanced Squamous cell carcinoma of the vulva.

Scheistroen M Acta Oncol 1993

Worse outcome
Lung toxicity

5-FU with or without MMC

authors	pts	chemotherapy	Radiation dose	Response to chemoradiation
Levin *Gyn Oncol 1986*	6	5-FU+MMC	20-25 Gy	OR= 6 (100%) Surgery 4pts
Thomas *Gyn Oncol 1989*	24	5-Fu±MMC	45-51Gy	CR=14 (58.3%) Surgery 5 pts
Sebag-Montefiore *Int J Gyn C 1994*	32	5-FU+MMC	45-50 Gy	CR=15 (46%) OR=26 (81.2%)
Wahlen *Cancer 1995*	19	5-FU+MMC	45-50 Gy	CR=10 (53%), OR=17 (89%)
Lupi *Cancer 1996*	31	5-FU+MMC	54 Gy	OR 29 (93%)
Landoni *Gyn Oncol 1996*	58	5-FU+MMC	54GY	pCR=13 (31%)

5-FU with or without MMC

authors	pts	CHT	Radiation dose	Response to chemoradiation
Levin	6 primary	5-FU+MMC	20-25 Gy	OR= 6 (100%) Surgery 4pts
Thomas	9 primary 15 recurrence	5-FU±MMC	45-51Gy	CR=14 (58.3%) Surgery 5 pts
Sebag-montefiore	32 primary	5-FU+MMC	45-50 Gy	CR=15 (46%) OR=26 (81.2%)
Wahlen	19 primary	5-FU+MMC	45-50 Gy	CR=10 (53%), OR=17 (89%)
Lupi	24 primary 7 recurrent	5-FU+MMC	54 Gy	OR 29 (93%)
Landoni	41 primary 17 recurrent	5-FU+MMC	54GY	pCR=13 (31%)

5-FU with or without MMC

authors	pts	chemotherapy	
Levin	6	5-FU+MMC	5-FU 1000 mg/m2/day ic 1-4, MMC 10 mg/m2 d1
Thomas	24	5-fu±MMC	5-FU 1000 mg/m2/day ic 1-4 ± MMC 6 mg/m2 d1
Sebag-Montefiore	32	5-FU+MMC	5-FU 750-1000 mg/m2/day ic 1-5, MMC 10-15 mg/m2 d1
Wahlen	19	5-FU+MMC	5-FU 1000 mg/m2/day ic 1-4, MMC 10 mg/m2 d1
Lupi	31	5-FU+MMC	5-FU 750 mg/m2/day ic 1-5, MMC 15 mg/m2 d1
Landoni	58	5-FU+MMC	5-FU 750 mg/m2/day ic 1-5, MMC 15 mg/m2 d1

5-FU with or without MMC

authors	pts	CHT	Radiation dose	
Levin	6	5-FU+MMC	20-25 Gy	2.0-2.5 Gy x 10
Thomas	24	5-fu±MMC	45-51Gy	45 Gy to the pelvis 51 to the vulva with e-
Sebag-Montefiore	32	5-FU+MMC	45-50 Gy	25 Gy SPLIT 1 mth 25 Gy 45 Gy continous
Wahlen	19	5-FU+MMC	45-50 Gy	45-50 Gy continous
Lupi	31	5-FU+MMC	54 Gy	36 Gy SPLIT 2 wks 18 Gy to the vulva
Landoni	58	5-FU+MMC	54GY	36 Gy SPLIT 2 wks 18 Gy to the vulva

5-FU with or without MMC

authors	pts	chemotherapy	Radiation dose	Response to chemoradiation
Levin	6	5-FU+MMC	20-25 Gy	CR 31%-100%
Thomas	24	5-fu±MMC	45-51Gy	
Sebag-Montefiore	32	5-FU+MMC	45-50 Gy	
Wahlen	19	5-FU+MMC	45-50 Gy	
Lupi	31	5-FU+MMC	54 Gy	
Landoni	58	5-FU+MMC	54Gy	

5-FU with or without CDDP

authors	pts	chemotherapy	Radiation dose	Response to chemoradiation
Berek *Gyn Oncol 1991*	12	CDDP+5-FU	44-54	CR 8 (66.7%), OR=11 (91.7%)
Russell *Gyn Oncol 1992*	23	CDDP+5-FU	36-54	CR 20 (80%)
Eifel *Gyn Oncol 1995*	12	CDDP+5-FU	40-50	PCR=4 (33.3%), OR=11(91.7%)
Cunningham *Gyn Oncol 1997*	14	CDDP+5-FU	50-65	CR=9 (64.3%), OR 13 (92.8%)
Moore *Int J Oncol Biol Phi 98*	71	CDDP+5-FU	47.6	CR=33 (46.5%)
Gerszten *Gyn Oncol 2005*	18	CDDP+5-FU	44.6	CR= 13 (72.2%), OR=18 (100%)

5-FU with or without CDDP

authors	pts	CHT	Radiation dose	Response to chemoradiation
Berek	12 primary	CDDP+5-FU	44-54	CR 8 (66.7%), OR=11 (91.7%)
Russell	18 primary 7 recurrence	CDDP+5-FU	36-54	CR 20 (80%)
Eifel	12 primary	CDDP+5-FU	40-50	PCR=4 (33.3%), OR=11(91.7%)
Cunningham	14 primary	CDDP+5-FU	50-65	CR=9 (64.3%), OR 13 (92.8%)
Moore	71 primary	CDDP+5-FU	47.6	CR=33 (46.5%)
Gerszten	18 primary	CDDP+5-FU	44.6	CR= 13 (72.2%), OR=18 (100%)

5-FU with or without CDDP

authors	pts	chemotherapy	
Berek	12	CDDP+5-FU	5-FU 1000 mg/m2/day ic 1-4 CDDP 50-100 mg/m2/day 1-2,
Russell	23	CDDP+5-FU	5-FU 750-1000 mg/m2/day ic 1-4 CDDP 100 mg/m2/day 1
Eifel	12	CDDP+5-FU	5-FU 250 mg/m2/day ic 1-4, weekly CDDP 4 mg/m2/day 1-4, weekly
Cunningham	14	CDDP+5-FU	5-FU 1000 mg/m2/day ic 1-4 CDDP 50 mg/m2/day 1
Moore	71	CDDP+5-FU	5-FU 1000 mg/m2/day ic 1-4 CDDP 50 mg/m2/day 1
Gerszten	18	CDDP+5-FU	5-FU 1000 mg/m2/day ic 1-4 CDDP 50 mg/m2/day 1

5-FU with or without CDDP

authors	pts	chemotherapy	Radiation dose	
Berek	12	CDDP+5-FU	44-54	44-54 Gy continous
Russell	23	CDDP+5-FU	36-54	36-54 Gy continous
Eifel	12	CDDP+5-FU	40-50	40-50 Gy continous
Cunningham	14	CDDP+5-FU	50-65	vulva 50 to 65 Gy pelvi of 45 to 50 Gy.
Moore	71	CDDP+5-FU	47.6	1.7 Gy BID to 4.760 SPLIT COURSE
Gerszten	18	CDDP+5-FU	44.6	1.6 Gy BID to 44.6 SPLIT COURSE

5-FU with or without CDDP

authors	pts	chemotherapy	Radiation dose	Response to chemoradiation
Berek	12	CDDP+5-FU	44-54	CR 33%-80%
Russell	23	CDDP+5-FU	36-54	
Eifel	12	CDDP+5-FU	40-50	
Cunningham	14	CDDP+5-FU	50-65	
Moore	71	CDDP+5-FU	47.6	
Gerszten	18	CDDP+5-FU	44.6	

Outcomes after radiation therapy with concurrent weekly platinum-based chemotherapy or every-3–4-week 5-fluorouracil-containing regimens for squamous cell carcinoma of the vulva

Raymond H. Mak [a], Lia M. Halasz [a], Cynthia K. Tanaka [b], Marek Ancukiewicz [c], Delray J. Schultz [d], Anthony H. Russell [c], Akila N. Viswanathan [b,*]

Gynecologic Oncology 120 (2011) 301–107

	All patients (n=44)	Every-3–4-week 5-FU-based chemotherapy (n=28)	Weekly platinum-based chemotherapy (n=16)	p-Value
Median (range) follow-up (months)	31.5 (3.8–165.7)	25.9 (3.8–165.7)	54.6 (7.6–130.1)	p=0.04
Actuarial 2-year OS	71.3%	70.0%	74.5%	p=0.65
Actuarial 2-year DFS	58.1%	56.0%	61.9%	p=0.85
Actuarial 2-year FFR	62.6%	58.7%	68.9%	p=0.65
Actuarial 2-year LRR	32.2%	32.9%	31.3%	p=0.93
Actuarial 2-year DM	8.6%	10.6%	6.3%	p=0.81
pCR[a]	53.8% (14/26)	50.0% (9/18)	62.5% (5/8)	p=0.68
Clinical complete response	58.8% (20/34)	58.3% (14/24)	60.0% (6/10)	p=1.0

	Weekly CDDP	5F-U	
acute skin toxicity G3	**62.5%**	**32%**	**p=0.26**
acute non-skin toxicities G4 **Dehydration, diarrhea, mucositis**	**0**	**11.5%**	**p=0.07**
treatment breaks Median day	**0.5**	**12**	**p=0.01**

Concurrent radiochemotherapy

Author	pts	CHT	RT (Gy)	Local disese persistence or recurence after RTCHT ± surgery	Follow-up months
Levin, 86	6	5-FU+MMC	18-60	1 (17%)	1-25
Evans,88	4	5-FU+MMC	25.7	2 (50%)	20-29
Thomas,89	24	5-FU± MMC	44-60	9 (37%)	5-45
Whalen, 95	19	5-FU+MMC	45-50	1(5%)	3-70
Eifel, 95	12	5-FU+CDDP	40-50	5 (42%)	17-30
Cunningham, 97	14	5-FU+CDDP	45-50	4 (29%)	7-80
Gerszten, 2005	18	5-FU+CDDP	44.6	3 (17%)	1-55

Local disease persistence or recurrence after chemoRT± surgery

23% (0%-54%)

Impressive response and local control

Patterns of Care for Radiotherapy in Vulvar Cancer: A Gynecologic Cancer Intergroup Study

David K. Gaffney, MD, Andreas Du Bois, MD,† Kailash Narayan, MD,‡ Nick Reed, MD,§ Takafumi Toita, MD,|| Sandro Pignata, MD,¶ Peter Blake, MD,# Lorraine Portelance, MD,** Azmat Sadoyze, MD,†† Richard Potter, MD,‡‡ Alessandro Colombo, MD,§§ Marcus Randall, MD,|||| Mansoor R. Mirza, MD,¶¶ and Edward L. Trimble, MD##*

(*Int J Gynecol Cancer* 2009;19: 163–167)

12 cooperative groups: 2/3 neoadjuvant Radiochemotherapy
unresectable or >III stage
48.2±5 Gy
different indications, RT fields, CHT

THE COCHRANE COLLABORATION®

2011, Issue 4

Chemoradiation for advanced primary vulval cancer (Review)

Background

Vulval cancer is a rare gynaecological cancer. There is no standard approach for treating locally advanced primary vulval cancer (FIGO stage III and IV). Combined treatment modalities have been developed using radiotherapy, chemotherapy and surgery. The advantages and disadvantages of such treatment is not well evaluated.

Objectives

To evaluate the effectiveness and safety of neoadjuvant and primary chemoradiation for women with locally advanced primary vulval cancer compared to other primary modalities of treatment such as primary surgery or primary radiation.

Primary chemoradiation vs primary surgery

Landrum, 2008
Mulayim, 2004
retrospective

no statistically significant difference in survival
HR= 1.09, 95% CI 0.37- 3.17

THE COCHRANE COLLABORATION®

Neoadjuvant chemoradiation vs primary surgery

Maneo, 2003
RCT

did not appear to offer longer survival compared to primary surgery in advanced vulval tumours
RR = 1.29, 95%CI 0.87- 1.91

Neoadjuvant chemoradiation for advanced primary vulvar cancer.
Van Doorn HC,
Cochrane Database Syst Rev 2006

THE COCHRANE COLLABORATION®

1) **Patients with an inoperable primary tumor or lymph nodes benefit from chemoradiation if an operation of lesser scope can ultimately be performed**

2) **Neoadjuvant therapy is not justified in patients with tumors that can be adequately treated with radical vulvectomy and bilateral groin node dissection**

Neoadjuvant RTCHT

authors	pts	CHT	Radiation dose	Response to RTCHT	Planned surgery (Response)

Response rate after RTCHT ranged from 46% to 91%

Dose of radiation are usually ~ 50 Gy

Surgery not actually delivered to all cCR patients

pCR rate ~ 30%

Definitive RTCHT

authors	pts	CHT	Radiation dose	Response to RTCHT	Salvage surgery

Overall response rate ranged 81%-100%

Dose of radiation are usually about 50 Gy but better

OS with dose > 50 Gy

Surgery is kept as a reserve treatment for the salvage of the residual disease

PREOPERATIVE CHEMORADIATION FOR ADVANCED VULVAR CANCER: A PHASE II STUDY OF THE GYNECOLOGIC ONCOLOGY GROUP

DAVID H. MOORE, M.D.,* GILLIAN M. THOMAS, M.D.,† GUSTAVO S. MONTANA, M.D.,‡ ANGELIKA SAXER, C.C.R.A.,§ DONALD G. GALLUP, M.D.,‖ AND GEORGE OLT, M.D.¶

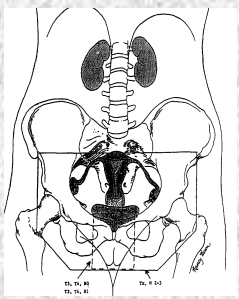
Int. J. Radiation Oncology Biol. Phys., Vol. 42, No. 1, pp. 79–85, 1998

GOG 101

104 pts T3-4 N2-3
8/89 to 2/94

Treatment regimen	Day of treatment 1	2	3	4	5	8	9	10	11	12
Radiation therapy*	XX	XX	XX	XX	X	X	X	X	X	X
Cisplatin, 50 mg/m²	X									
5-FU, 1000 mg/m²	X	X	X	X						
1½ to 2½ weeks split course	29	30	31	32	33	36	37	38	39	40
Radiation therapy*	XX	XX	XX	XX	X	X	X	X	X	X
Cisplatin, 50 mg/m²	X									
5-FU, 1000 mg/m²	X	X	X	X						

5-FU = 5-fluorouracil.
*Radiation therapy delivered 170 cGy twice daily (fractions separated by 6 hours) during 5-FU infusion and 170 cGy once daily for remainder of treatment course. Each split course delivered 2380 cGy.



47.6 Gy BID
SPLIT COURSE

Table 3. Acute adverse effects

Acute adverse effect	Grade 0	1	2	3	4
Hematologic	47	16	7	3	0
Emesis	44	13	16	0	0
Diarrhea	57	8	6	1	1
Other gastrointestinal	49	8	14	0	2
Urinary	54	12	6	1	0
Hepatic	71	1	1	0	0
Pulmonary	67	5	1	0	0
Infection	64	1	5	1	2
Neurologic	66	3	2	2	0
Cutaneous	10	8	16	19	20
Cardiovascular	69	0	1	2	1
Lymphatics	47	9	13	4	0
Fever	63	3	6	1	0
Wound breakdown	64	3	2	2	2

PREOPERATIVE CHEMORADIATION FOR ADVANCED VULVAR CANCER: A PHASE II STUDY OF THE GYNECOLOGIC ONCOLOGY GROUP

DAVID H. MOORE, M.D.,* GILLIAN M. THOMAS, M.D.,† GUSTAVO S. MONTANA, M.D.,‡ ANGELIKA SAXER, C.C.R.A.,§ DONALD G. GALLUP, M.D.,‖ AND GEORGE OLT, M.D.¶

Table 4. Surgical management of primary tumor versus anticipated surgical management prior to chemoradiotherapy

	Actual procedure							
Anticipated procedure	Biopsy	Wide local excision	Vulva	Other	Vagina	Anterior exenteration	Posterior exenteration	None
Vagina	3	7[1]	3	0	0	0	0	2[2,4]
Urethra	0	1	1	0	0	0	0	1[4]
Bone	0	1	2	0	0	0	0	0
Anterior exenteration	2[5]	1	2	3[6,6,6]	0	0	0	3[3,7,7]
Posterior exenteration	2	12	15[5,9]	1[1]	1	0	1	1[2]
Posterior exenteration + Urethra	0	0	1	0	0	0	0	0
Total exenteration	1	2	0	1[8]	0	0	1	0

Among the 50 patients initially presenting with vulvar cancers requiring exenterative surgery, only one patient required exenterative surgery and two patients required colostomy to resect residual disease.

at the time of planned surgery
33/71 (46.5%): no visible vulval cancer
38/71 (53.5%): gross residual cancer
2/71 (2.8%) residual unresectable disease

PREOPERATIVE CHEMO-RADIATION FOR CARCINOMA OF THE VULVA WITH N2/N3 NODES: A GYNECOLOGIC ONCOLOGY GROUP STUDY

GUSTAVO S. MONTANA, M.D., F.A.C.R.,* GILLIAN M. THOMAS, M.D.,† DAVID H. MOORE, M.D.,‡ ANGELIKA SAXER, C.C.R.A.,§ CHARLES E. MANGAN, M.D.,‖ SAMUEL S. LENTZ, M.D.,¶ AND HERVY E. AVERETTE, M.D.#

GOG 101

Int. J. Radiation Oncology Biol. Phys., Vol. 48, No. 4, pp. 1007–1013, 2000

unresectable, N2/N3 groin lymph node

Table 3. Protocol summary

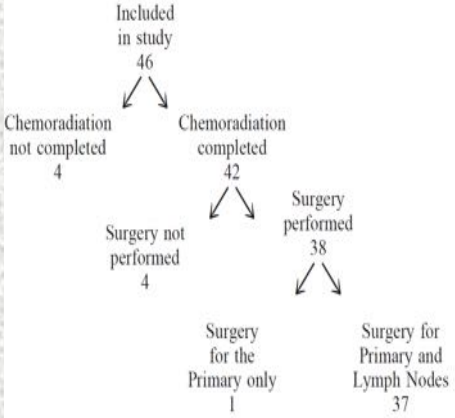


Table 5. Treatment outcome after surgery (n = 38)

Outcome	Number
No evidence of disease	12
Dead of intercurrent disease	5
Dead with complications	2
Recurrence, primary only	9
Recurrence, primary only and distant metastasis	1
Recurrence, inguinal nodes only	1
Distant metastasis only	8

resectability rate, 95%,
lymph nodes negative in 15/37 (41%)

A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: A gynecologic oncology group study

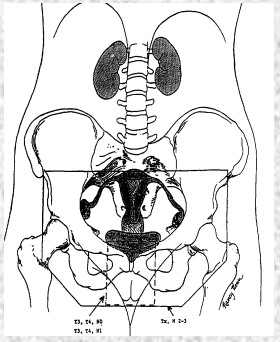
David H. Moore [a,*], Shamshad Ali [b], Wui-Jin Koh [c], Helen Michael [d], Mack N. Barnes [e], Carolyn K. McCourt [f], Howard D. Homesley [g], Joan L. Walker [h]

Gynecologic Oncology 124 (2012) 529–533

GOG-205

58 T3 or T4 N0-3, M0 primary 1/2005 to 9/2009
not amenable to surgical resection by standard radical vulvectomy.

N0 underwent pretreatment inguinal-femoral lymph node dissection and If pN0, radiation therapy to only the primary tumor



c CR → incisional biopsy of the primary tumor site

c RP → surgical excision of gross residual disease in the vulva and/or inguinal-femoral lymph nodes

45 Gy (1.8 Gy) and 57.6 Gy to gross disease
no scheduled radiation break
CDDP weekly (40 mg/m2)

A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: A gynecologic oncology group study

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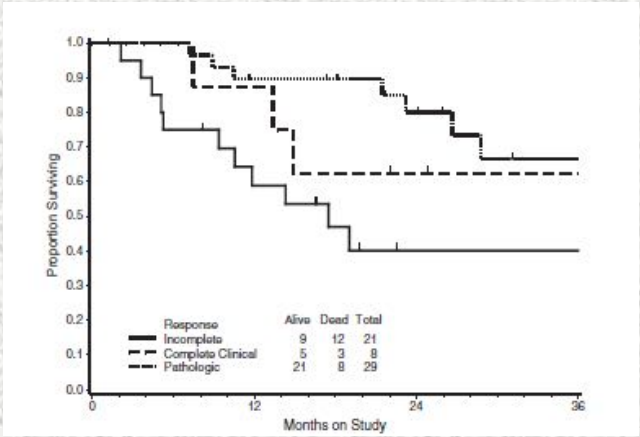
40 (69%) women who completed the planned study treatment

among all evaluable patients
pCR at the vulvar primary 50% (29/58)

among patients with cCR
pCR at the vulvar primary 78% (29/37),



Adverse event[a]	Grade				
	0	1	2	3	4
Leukopenia	16	11	13	18	0
Anemia[b]	7	22	25	3	1
Thrombocytopenia	28	22	5	3	0
Neutropenia	30	7	10	8	3
Other hematologic	45	0	0	12	1
Allergy/immunology	54	1	3	0	0
Auditory/hearing	55	0	3	0	0
Cardiovascular	48	3	3	3	1
Fatigue	13	20	20	5	0
Other constitutional symptoms	45	7	6	0	0
Alopecia	45	8	3	2	0
Radiation dermatitis	47	1	4	6	0
Rash desquamation	29	7	12	8	2
Other dermatologic/skin	46	6	4	2	0
Endocrine	50	7	1	0	0
Nausea	15	25	17	1	0
Vomiting	30	19	8	1	0
Diarrhea	20	22	10	6	0
Other gastrointestinal	24	14	11	9	0
Creatinine	47	7	4	0	0
Other renal/genitourinary	37	10	8	3	0
Hemorrhage	54	3	0	1	0
Hepatic	52	4	2	0	0
Infection	44	1	5	7	1
Lymphatics	56	2	0	0	0
Metabolic/laboratory	33	12	3	6	4
Musculoskeletal	54	2	2	0	0
Neuropathy, motor	56	0	2	0	0
Neuropathy, sensory	48	7	3	0	0
Other neurologic	45	7	4	1	1
Ocular/visual	57	1	0	0	0
Pain	23	10	15	10	0
Pulmonary	53	0	4	1	0
Sexual/reproductive	52	4	1	1	0

A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: A gynecologic oncology group study

David H. Moore [a,*], Shamshad Ali [b], Wui-Jin Koh [c], Helen Michael [d], Mack N. Barnes [e], Carolyn K. McCourt [f], Howard D. Homesley [g], Joan L. Walker [h]

GOG studies of preoperative chemo-radiation: locally-advanced vulva carcinoma.

	GOG 101	GOG 205
Evaluable	71	58
CCR	34 (48%)	37 (64%)
PCR	22 (31%)	29 (50%)
PCR/CCR	22/34 (65%)	29/37 (78%)

CCR = Clinical Complete Response.
PCR = Pathological Complete Response.

Conclusions. This combination of radiation therapy plus weekly cisplatin successfully yielded high complete clinical and pathologic response rates with acceptable toxicity.

Radiochemotherapy

Patients with advanced stage disease not suitable for surgery due to technical unresectability or medical comorbidities

Patients with early stage disease involving midline structures

definitive

Definition of " overtly inoperable"

Higher dose=Higher CR??

Which CHT?

neoadjuvant

Definition of "potentially operable"

Dose 50 Gy is enought?

Which CHT??

Which Chemotherapy? studies ongoing

TAX ± irradiation produce a clear additive cytotoxic effect in several vulvar squamous carcinoma cell lines

Combination of TAX and CDDP had a clear additive or synergistic cytotoxic effect on different vulvar squamous carcinoma cell lines

Jaakkola Cancer 1996, Jaakkola M, Anticancer Res 1997;
Raitanen M, Int J Cancer 2002;97:853–7

TAX in patients with recurrent, metastatic, or locally advanced vulvar cancer
EORTC phase II trial 55985 ongoing

Gefitinib in mice transplanted with the human vulvar tumour A431 expressing high levels of epidermal growth factor receptor [EGFR], significantly increased the growth inhibitory action of CDDP and TAX

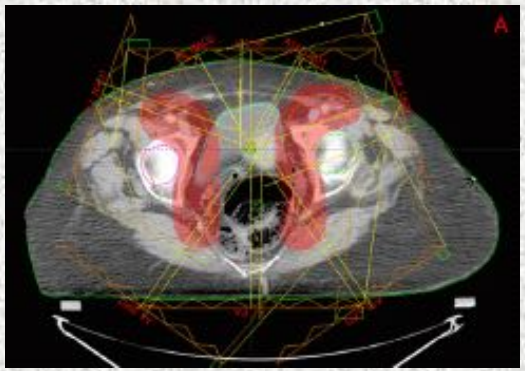
Sirotnak FM, Clin Cancer Res 2000

Which radiotherapy?
Studies ongoing

Preoperative intensity-modulated radiotherapy and chemotherapy for locally advanced vulvar carcinoma

Sushil Beriwal [a,*], Devin Coon [a], Dwight E. Heron [a], Joseph L. Kelley [b], Robert P. Edwards [b], Paniti Sukumvanich [b], Kristin K. Zorn [b], Thomas C. Krivak [b]

Gynecologic Oncology 109 (2008) 291 – 295



cCR of 74%
pCR of 64%

TOXICITY
acute skin reactions in all patients.
No patient had moist desquamation in the groin region.
Most patients had radiation induced diarrhea.
One patient died of a MI
Three/ 14 patients who had surgery had prolonged wound complications
No patient had grade 3 or above radiation related acute or late morbidity.
Six patients had measurable lymphedema

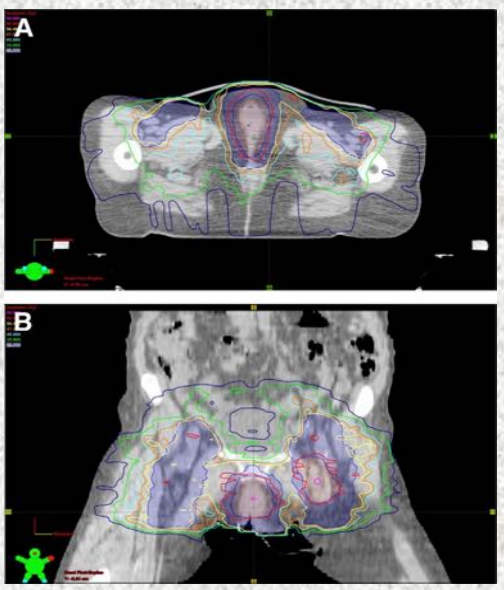
1.6 Gy twice a day for 10 fractions,
1.8 Gy once a day for 7–8 fractions, planned break of 10 to 14 days
1.6 Gy twice a day for 10 more fractions.
CDDP 40 mg/m2 on Day 1 and 5-FU 750 to 1000 mg/m2 on Days 1 to 5.
Surgery of residual tumor or biopsy of the tumor region if the patient had a complete clinical response was planned for 6–8 weeks after treatment.

Which radiotherapy?
Studies ongoing

A dosimetric evaluation of dose escalation for the radical treatment of locally advanced vulvar cancer by intensity-modulated radiation therapy

Monique C.W.M. Bloemers, M.D.,*† Lorraine Portelance, M.D.,† Russell Ruo, M.Sc.,‡ William Parker, Ph.D.,‡ and Luis Souhami, M.D.†

Medical Dosimetry 37 (2012) 310-313



sequential IMRT boost (seq-IMRT) 56.4 Gy simultaneous integrated boost (SIB-IMRT) 67.2 Gy.

IMRT reduces the dose to the OAR compared with 3D-CRT IMRT for vulvar cancer is feasible and an attractive option for dose escalation studies

New trials Focused on

Age and comorbidity

Effect of age and comorbidity on the treatment and survival of older patients with vulvar cancer

Rahel G. Ghebre [a,*], Rebecca Posthuma [a], Rachel Isaksson Vogel [b], Melissa A. Geller [a], Linda F. Carson [a]

Gynecologic Oncology 121 (2011) 595–599

Quality of life

Long-term sexual function in survivors of vulvar cancer: a cross-sectional study. Hazewinkel MH, Laan ET,

Gynecol Oncol. 2012 Jul;126(1):87-92.

No pelvic lymph node dissection

Yes inguinal lymph nodes

Dissection in patients with clinically negative nodes

LN sentinel??

The role of Radiation therapy

deep invasion (>5mm) and lymphovascular space invasion
Positive margins
Close surgical margin

No pelvic lymph node dissection
Yes inguinal lymph nodes
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The role of Radiation therapy

deep invasion (>5mm) and lymphovascular space invasion
Positive margins
Close surgical margin

No pelvic lymph node dissection
Yes inguinal lymph nodes dissection
in patients with clinically negative nodes

The role of Radiation therapy

More than 1 positive LN
and/or

Extracapsular disease

deep invasion (>5mm) and lymphovascular space invasion
Positive margins
Close surgical margin

No pelvic lymph node dissection
Yes inguinal lymph nodes dissection
in patients with clinically negative nodes

The role of Radiation therapy

RTCHT
definitive or neoadjuvant

STANDARD?
in unresectable disease

young patients

More than 1 positive LN
and/or

Extracapsular disease

deep invasion (>5mm) and lymphovascular space invasion
Positive margins
Close surgical margin

No pelvic lymph node dissection
Yes inguinal lymph nodes dissection
in patients with clinically negative nodes

Multi-disciplinary approach

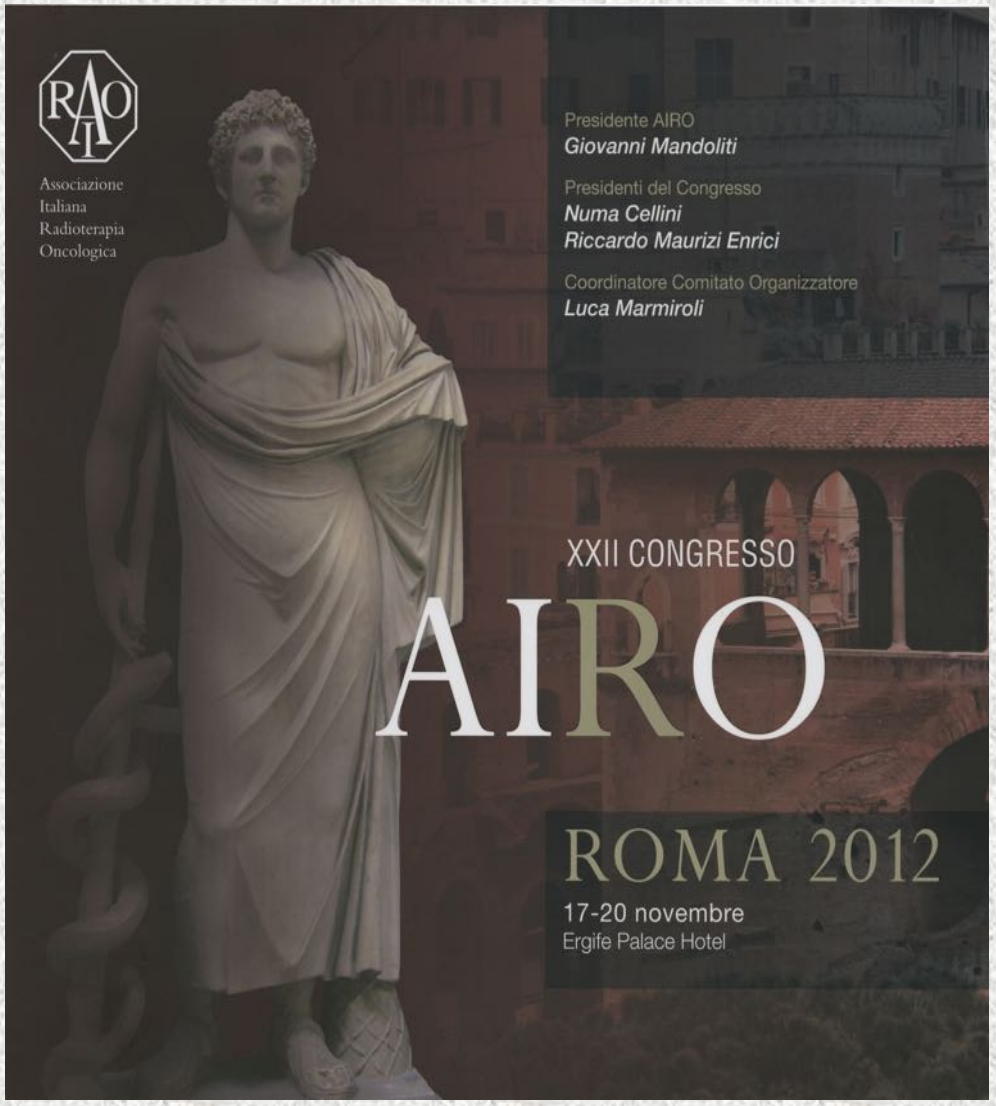
RTCHT
definitive or neoadjuvant

STANDARD?
in unresectable disease

young patients

More than 1 positive LN
and/or

Extracapsular disease



Grazie per l' attenzione