

Current Concepts in Endometrial Cancer

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Rising Death Rate for Endometrial Cancer

- In 2003: 40,100 new cases, with a total of 6,300 deaths
- In 1987: 2,900 deaths
- Stable incidence of endometrial cancer

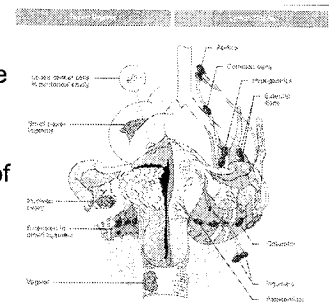
American Cancer Society (2002)

Issues

- Importance of Staging
- The Role of Laparoscopy
- The Role of Gynecologic Oncologist

Why Stage?

- Identification of extrauterine disease
- Separation into risk groups
- Therapeutic effect of lymphadenectomy



Who to Stage?

- Stage- No One
- Stage- All
- Stage selectively- based on risk

Depth of Invasion	Grade		
	G1 (N=180)	G2 (N= 288)	G3 (N= 153)
Endo Only (N= 86)			0
Inner 1/3 (N= 281)			
Mid 1/3 (N=115)			
Outer 1/3 (N= 139)			

GOG 33- Nodal Distribution In Node (+) Patients

	PALN (+)	PALN (-)
PELVIC (+)	22 (38%)	36 (51%)
PELVIC (-)	12 (17%)	XXXXX

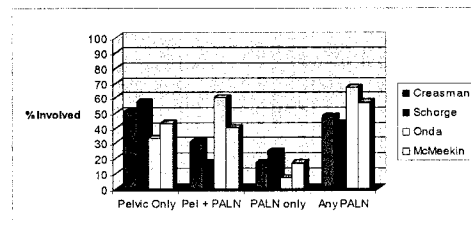
Creasman Cancer 60:2035,1987

Nodal Distribution in Node (+) Patients

	PALN (+)	PALN (-)	
PELVIC (+)	19 (40%)	20 (43%)	39/47 (83%)
PELVIC (-)	8 (17%)	XXXXX	
			27/47 (57%)

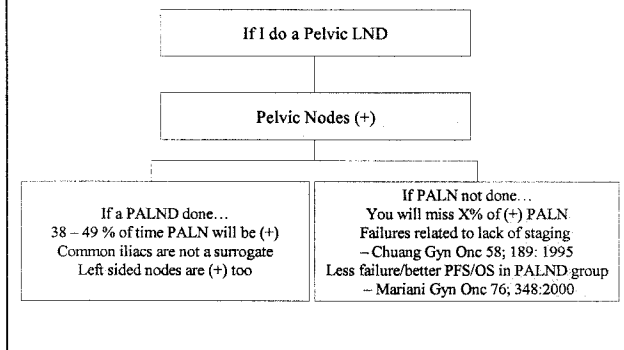
McMeekin Gyn Onc 82;375:2001

Distribution of Nodal Disease in Node (+) Endo CA

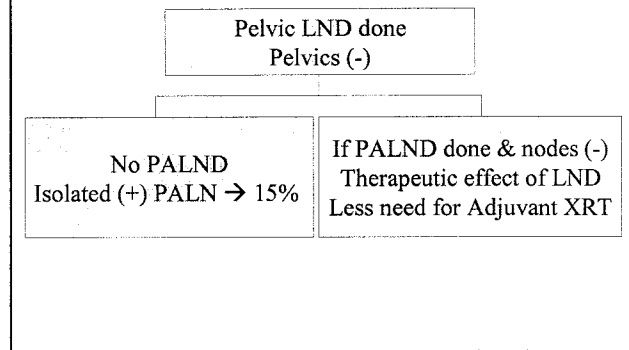


Cancer 1987, Gyn Onc 1996, Br J Ca 1997, Gyn Onc 2001

Decisions on Staging



Staging Decisions



Advantages of LND/Staging even when the nodes are (-)

- Therapeutic Effect of the LND itself
 - Kilgore-Significant survival advantage for pts having multiple-site node sampling (Gyn Onc 56;29:1995)
- Less use of post-op XRT
 - Mohan- 159 pts with pelvic lymphadenectomy + Cuff brachy --> 4% recurred (Gyn Onc 70:165:1998)
 - Straughn- 321 surgically staged IB pts, No XRT --> 5% recurred (Gyn Onc 84;191:2002)
 - Straughn- 220 surgically staged IC pts (45% rec'd XRT, 55% no XRT) No difference in 5 yr OS (92% vs 90%) (SGO Abstr 16, 2002)

Recurrence after Lymphadenectomy in Moderate and High-Risk Node-Negative Disease Not Receiving Whole-Pelvic RT

	No. of patients	Mean No. of nodes	Postop brachy therapy	Mean F/U time (months)	No. of recurrences	Recurrence site
Fanning <i>et al.</i>	22	28	Yes	34	1	Lung
Orr <i>et al.</i>	115	24	Yes	39	6	Liver 3 Lung 3
Larson <i>et al.</i>	105		No	43	8	Vagina 4 Lung 4
Mohan <i>et al.</i>	63	33	Yes	96	5	Abdomen 2 Clitoris 1 Lung 1 Unknown 1
Total	305				20 (6.6%)	Distant 15 (4.9%) Vaginal 4 (1.3%) Unknown 1 (0.3%)

Down Side to Staging

- You have to be there
 - Increased cost/time?
 - Increased operative complications
- | Study | N | Hem | Injury | DVT/PE | Lymph | Other |
|---------------|-----|-----|--------|--------|-------|------------|
| Morrow- 1991 | 883 | 2% | 2% | 2% | 1% | |
| Orr- 1991 | 149 | 4% | --- | 1% | 1% | |
| Homesley-1992 | 196 | 6% | --- | 4% | --- | Serious 6% |
- Staging followed by XRT --> Increased complications
 - Lewandowski 1990 --> 10.8% complications
 - Corn 1994 --> LND --> 7-11% complications

Surgically staged, Stage IIIc Endo CA

Study	N	Rx	PFS (%)	OS (%)
Greven 1993	32	XRT	—	56 ^{5yr}
Schorge 1995	35	XRT, chemo	37 ^{5yr}	52 ^{5yr}
Onda 1997	30	XRT +/- chemo	—	84 ^{5yr} (100% +PLN, 75% +PALN)
Nelson 1999	17	XRT	81 ^{5yr}	72 ^{5yr}
McMeekin 2001	47	XRT, chemo	—	87 ^{3yr} (+PLN), 70 ^{3yr} (+PALN)

Adjuvant Therapy in Early Stage: To Treat or Not to Treat

- XRT
 - WPRT
 - Vaginal Brachytherapy
- Chemotherapy
- Progestins

WPRT - Randomized

	N	Stage	XRT	PFS (Rad vs Non)	OS (Rad vs Non)
Roberts (GOG 99) 1998	390	IB, IC, IIA-B	WPRT 5040 Gy	96 vs. 88% (p=0.004) @ 2 yrs	96 vs. 89% (p=0.09) @ 3 yrs
Creutzberg (Portec) 2000	714	IB G2-3; IC G1-3	WPRT 4600 Gy	96 vs. 86% (p<0.001) @ 5 yrs (locoregional)	81 vs. 85% (p=NS) @ 5 yrs

WPRT – Site of Recurrence

	GOG 99	PORTEC
Vagina	7.4% vs 1.6%	10.2% vs 2.3%
Pelvis	4.0% vs 0.5%	3.4% vs 2.0%
Distant	5.5% vs 4.0	7.0% vs 7.9%

Vaginal Brachytherapy

	N	Stage	5 yr PFS (XRT vs NFT)	5 yr OS (XRT vs NFT)	Vag Recur (XRT vs NFT)
Graham '71	10	I	81 vs 64%	81 vs 70%	0 vs 12%
Aalders '80	54	I	88 vs 88%	89 vs 91%	1.9 vs
Piver '90	92	Ia-b G1-2	99%	93%	6.9%
Noyes '95	63	Ia G3 Ib G1-	98%	98%	0%
Eltabbakh	30	Ia-b G1-2	99%	-	0%
MacLeod '98	14	IA-IIIa	96%	91%	1.4%
Mohan '98	15	I	96%	99%	0%
Chadha '99	38	Ib G3 Ic G1-	87%	93%	0%
Ng '00	77	Ib G3 Ic G1-	82%	94%	9.1%

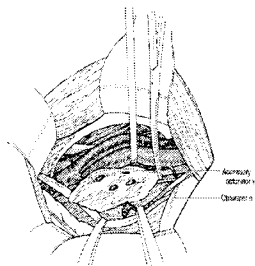
Adjuvant Therapy in Surgically Staged Early Stage:

- ~~No role for adjuvant therapy~~
- ~~The Glass is Half Full or Half Empty~~
- No role for adjuvant chemotherapy?
 - No good studies
- WPRT reduces recurrence by 2-8% (18% IC)
 - Salvage rates 50-80%
 - Only marginal improvement in survival 2-7%
 - Major complication rates 10-25%
- Vaginal brachytherapy reduces vaginal recurrence
 - Major complication rates 0-5%
 - May have a role in deep myometrial invasion or G3

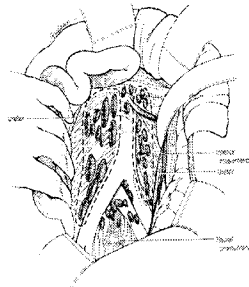
Laparoscopy in Endometrial Cancer

- Roles
 - Initial staging of early endometrial cancer
 - Clinical stage I & II disease
 - Staging of incompletely staged patients
 - Childers 13 pts
 - Extruterine disease found in 3
 - 1 (+) washings & 2 (+) PLN

Adequacy: Laparoscopic Pelvic LND



Adequacy of Laparoscopic PA LND



Laparoscopy in Endometrial Cancer – Adequacy of Lymph Node Dissection

	N	QI	% Conversion	% Complete P/PALN	#P/PALN
Childers	59	-	13.6%	93.5%	- / 6.3
Spirtos	40	<30	17.5%	87.5%	20.8 / 7.9
Possover	150	25.8	2.7%	61.3%	19.8 / 7.0
Dottino	94	25.7	3.2%	31.9%	11.9 / 3.7
Scribner	103	30.8	29.1%	100%	23.2 / 6.8

Laparoscopy in Endometrial Cancer

- Benefits compared to laparotomy
 - Shortened length of stay & improved quality of life –
 - Gemignani 2.7 days vs. 6.4 days w/ laparotomy (p<0.01)
 - Scribner 2.8 days vs. 5.6 days w/ laparotomy (p<0.0001)
 - Reduced hospital cost – Gemignani (1999)
 - room charges \$3130 vs \$6960 w/ laparotomy (p<0.01)
 - total charges \$11826 vs \$15189 w/ laparotomy (p<0.01)
 - Potential for reduction in bowel adhesions and radiation bowel injury in advanced stage disease – Fowler (1994)
 - Decreased post-operative complications

Cost Analysis of Laparoscopy vs. Laparotomy

- 19 patients underwent laparoscopy
- 17 patients underwent laparotomy
- The laparoscopic group required more OR time (237 vs. 157 minutes P<0.001)
- The laparoscopic group required shorter hospitalization (3.7 vs 5.2 days P<0.001)
- The cost of anesthesia was higher in the laparoscopic group (\$696 vs. \$444 P<0.001)
- Total costs hospital + surgical: (\$5198 Laparoscopy, \$5331 Laparotomy P=0.25 NS)

Scriber DR, Gynecologic Oncology 1999

Laparoscopy in Endometrial Cancer

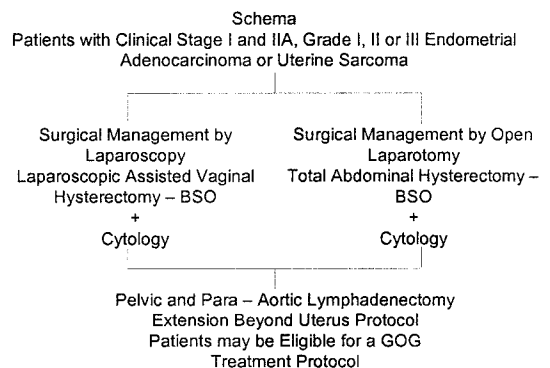
- Complications
 - Vascular injury 0.5-5%
 - Childers 2%, Spirtos 5%, Scribner 4.9%
 - Urinary Tract injury 1-2%
 - Saidi 1996 1.6% of 953 major operative laparoscopies (benign)
 - Childers 3.4%, Scribner 1%
 - Bowel herniation into trocar sites 0.1-0.3%
 - 3.1% 12mm vs. 0.23% 10mm (0.17% of 3560 laparoscopies)
 - Scribner 1%
 - Port site recurrence 1-2%
 - Ziprin (Colorectal CA) 0.71% & 0.33% isolated recurrence
 - *Abu-Rustum* (1080 Gyn CA) 2 pts (0.18%) both w/ Ov CA

Survival After Laparoscopy in Women with Endometrial Carcinoma

- 100 patients treated with laparotomy compare to 81 patients treated with laparoscopy
- 2-year and 5-year estimated recurrence – free survival (93% vs 94% and 90% vs 92%)
- 5-year overall survival (92% vs 92%)
- No difference with regard to sites of recurrence

Eltabbakh GH, Cancer 95, 1894:2002

GOG #LAP2



Laparoscopy in Endometrial Cancer

- **GOG LAP 2**

- Randomized trial of over 2500 patients
 - 1434 enrolled to date (957:477)
 - 29% 60-69 yo 26% 70-79 yo 6% ≥ 80 yo
- 191 (20.0%) converted to laparotomy
 - 22 (2.3%) due to bleeding
- 32 cancer related deaths
- 8 treatment related deaths
 - 6 PE, 1 hemorrhage, 1 MI s/p re-op for SBO

Laparoscopy in Endometrial Cancer

- **Conclusions**

- Appears to provide adequate nodal dissection
- Associated w/ shortened LOS & lower cost
- Complication rate acceptable w/ reduction in wound infection, post-op fever, and ileus
- Still Experimental

Outcome of Endometrial Cancer Patients Undergoing Surgery with Gynecologic Oncology Involvement

- 295 patients treated at a university hospital and 72 patients treated at a community hospital
- Groups were comparable for QI and comorbid conditions
- Patients treated at the university were older and with a higher Preoperative Severity Index

Pearl ML, ObstetGynecol 100,174: 2002

Outcome of Endometrial Cancer Patients Undergoing Surgery with Gynecologic Oncology Involvement Cont'd

- The time interval from biopsy to consultation and surgery were similar
- EBL and operative complications were similar
- No difference in percentage of patients who were properly staged
- Hospital stay was similar (3.9 days vs 3.6 days)
- Patients treated in the community are less likely to join clinical trials

Pearl ML, ObstetGynecol 100,174: 2002

Ancient History

- “Endometrial cancer is a chemo-resistant malignancy”
- “Radiation therapy is all that is available to help the patient if the cancer can't be cured by surgery or the disease recurs”
- “Whole abdominal radiotherapy is the ‘standard-of-care’ for stage 3 endometrial cancer”

GOG 122

- Randomized phase 3 trial abdominal/pelvic RT versus cisplatin/doxorubicin (n=396)
- Stage III/IV
- TAH, BSO, tumor debulking to < 2 cm
- Tumor confined to abdomen/pelvis
- No prior therapy (except progestin's)

GOG 122

- Platinum-based chemotherapy significantly improved both PFS (risk reduced 30%) and **overall survival** (risk reduced 34%) compared to whole abdominal irradiation.
- **CONCLUSION:** New “standard-of-care” is chemotherapy and not radiation in this clinical setting.

Which platinum-regimen should be used Stage III endometrial cancer?

- Cisplatin – doxorubicin
- **BUT:** Consider age of population, co-morbid medical conditions, and *known toxicity of this combination* (perhaps major reason considered “chemo resistant”)
- Is there an alternative chemotherapy regimen which is at least equally effective and much less toxic?

Why cisplatin in endometrial cancer?

- Carboplatin equally active in ovarian cancer (phase 3), equivalent objective response rates (phase 2) in endometrial cancer.
- Carboplatin substantially less toxic (emesis, nephrotoxicity, neurotoxicity)
- Carboplatin permits 3-hour infusional paclitaxel (versus 24-hr with cisplatin)

Why doxorubicin in endometrial cancer?

- Emesis, cardiotoxicity, vesicant properties
- Paclitaxel – at least equally active in phase 2 endometrial trials (no emesis, cardiotoxicity, non-vesicant)
- Paclitaxel-containing combination regimen superior survival compared to cisplatin-doxorubicin in metastatic/recurrent disease.

Carboplatin/paclitaxel in endometrial cancer

- *“Standard-of-care”* in ovarian cancer (another adenocarcinoma of gynecologic origin)
- *Highly active in metastatic endometrial cancer* (50% + objective response rates)
- *Substantially less toxic* than cisplatin/paclitaxel (doxorubicin abandoned a long time ago in ovarian cancer)
- *Easy to administer outpatient regimen*
- Optimize overall *quality-of-life*

Conclusion

- The practice of itinerary surgery is condemned by the American College of Surgeons and the SGO
- Issues concerning billing and and reimbursement
- The National Correct Coding Initiative developed by the CMMS forbids unbundling of procedures such as a lymph node