Current Management of Localized Uterine Leiomyosarcoma

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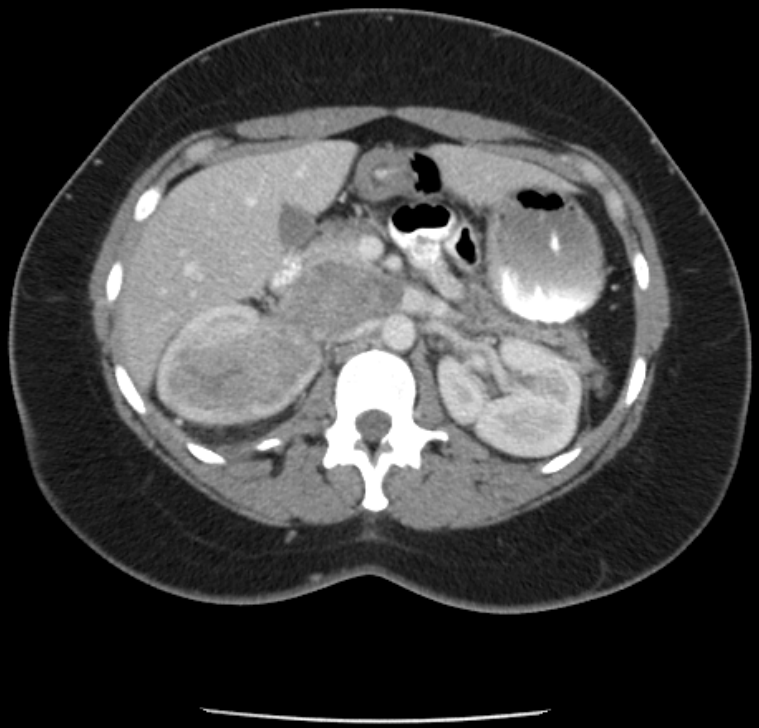
Case

- 2007: 30 yo BF G4Ab4 referred to REI for submucous fibroid on HSG
- Laparoscopically guided hysteroscopic resection: LMS
- TAH-RSO, pelvic & periaortic lymphadenectomy: 3cm LMS, - margins
- FIGO 1a
- Adjuvant tx?

Case

- Observed
- 2011: presented to ER with N&V, SOB
- Imaging: infiltrative appearing mass in the R kidney with dilated right renal vein and IVC likely represent renal cancer with tumor thrombus involving the renal vein and IVC, bilateral central PE

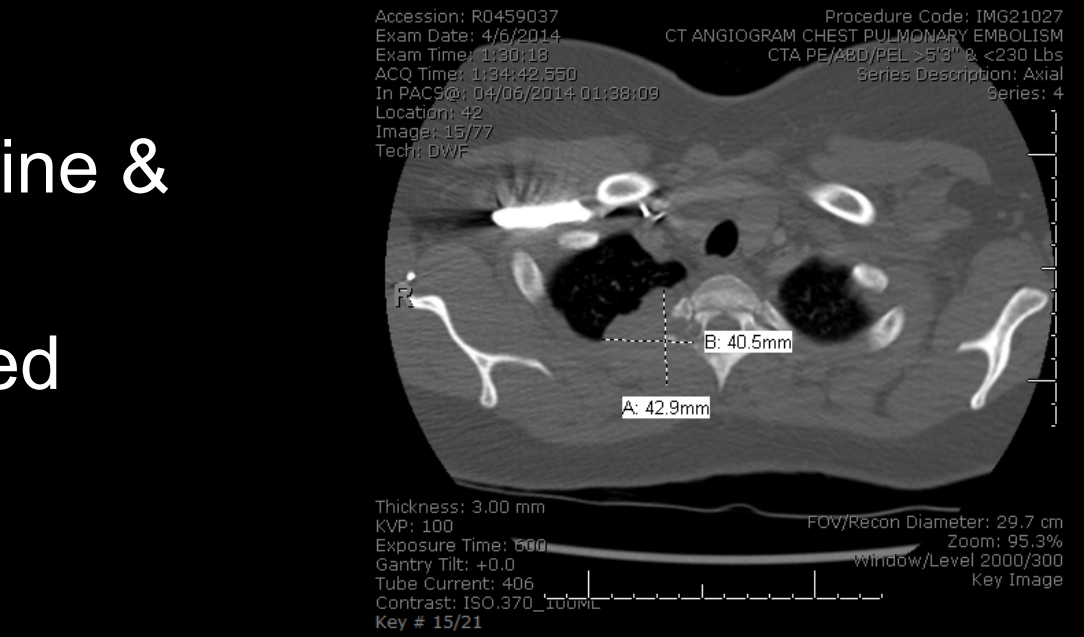


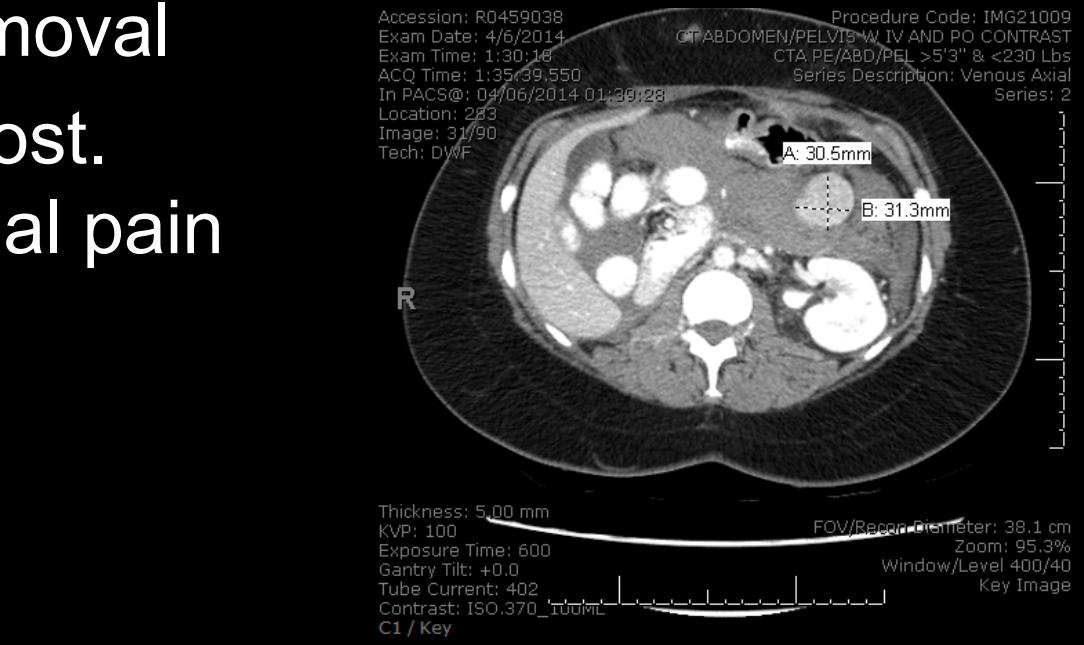
Case

- Radical nephrectomy; lymphadenectomy; caval, hepatic, pulmonary thrombectomy; hypothermic cardiac arrest. No gross residual. EBL: indeterminate. Transfused 25 units
- Path: LMS in kidney, nodes, thrombus
- Tumor board: recurrent uterine LMS
- Further tx?

Case

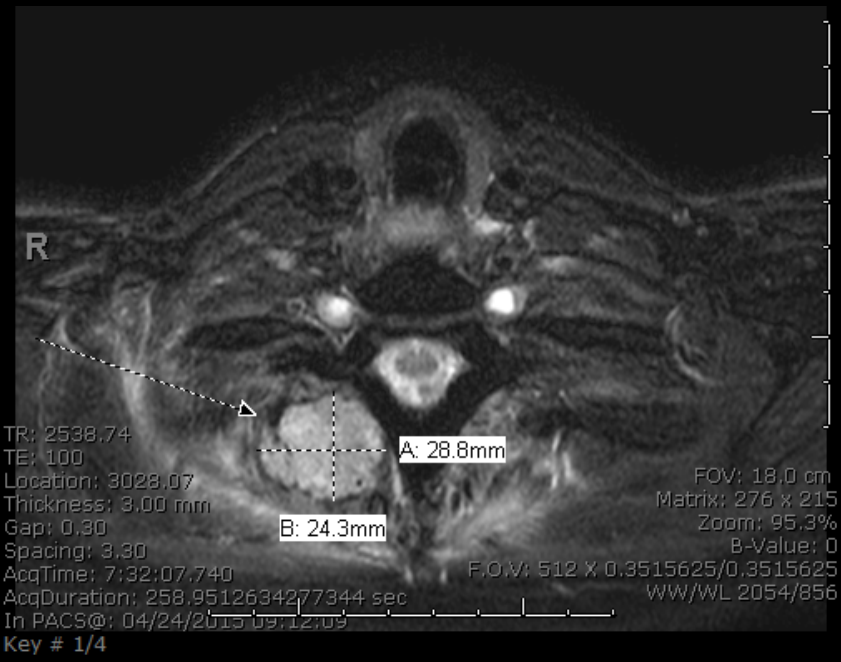
- Elected gemcitabine & docetaxel
- 6 cycles completed 12/11
- NED
- 2/14 mediport removal
- 4/14 presented post. chest & abdominal pain
- XRT to spine
- Further tx?





Case

- 5/14 Pazopanib started
- 9/14 modest decrease in most masses, improved QOL
- 4/15 increasing chest pain



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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Genentech BioOncology
Contracted Research	AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Takeda Oncology
Speakers Bureau	Genentech BioOncology

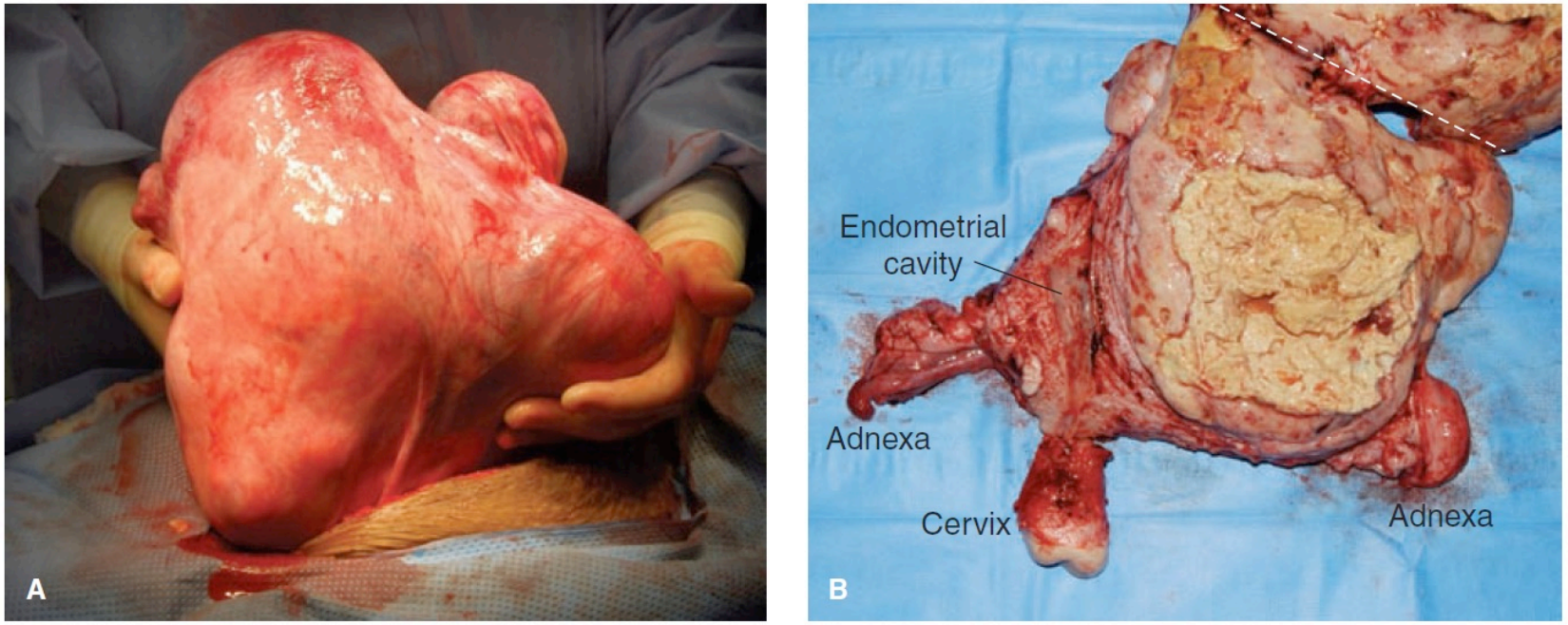

FIGURE 34-1 Leiomyosarcoma. **A.** Intraoperative photograph. **B.** Surgical specimen has been bisected and remains joined at the fundus. The other half of the specimen lies above the white dashed line and out of view. The large tumor lies to the right of the endometrial cavity. It has central necrosis seen as yellow amorphous debris with the tumor borders. (Photographs contributed by Dr. Martha Rac.)

Prognostic Factors in Early-Stage Uterine Sarcoma

A Gynecologic Oncology Group Study #40

Francis J. Major, M.D., John A. Blessing, Ph.D.,† Steven G. Silverberg, M.D.,‡ C. Paul Morrow, M.D.,§ William T. Creasman, M.D.,‖ John L. Currie, M.D.,¶ Edgardo Yordan, M.D.,# and Mark F. Brady, B.S.**

LMS: 3% node mets or + cytology, 5% adnexal mets

Background. A clinicopathologic evaluation of clinical Stage I and II uterine sarcoma was done by the Gynecologic Oncology Group from 1979–1988.

Methods. After all eligibility criteria were met, 453 cases were evaluable and analyzed for prognostic factors.

Results. Of the 301 mixed mesodermal tumors (MMT), 167 were homologous (HO), and 134 were heterologous (HE). Fifty-nine tumors were leiomyosarcomas (LM). The remaining 93 sarcomas were predominantly stromal cell and adenosarcomas. For this study, only the MMT or LM tumors were analyzed. The recurrence rate for all MMT was 53% (HO, 44%; HE, 63%). The recurrence rate for LM was 71%. The site of the first recurrence included the pelvis in 21% of MMT and 14% in LM. Factors significantly related to progression-free interval (PFI) by univariate analysis among MMT were adnexal spread, lymph node metastases, tumor size, lymphatic–vascular space involvement, histologic grade, cell type, age, peritoneal cytologic findings, and depth of uterine tumor site of invasion. The prognostic factors based on multivariate analysis were adnexal spread, lymph node metastases, histologic cell type (HO versus HE), and grade of sarcoma. For LM, the mitotic index was the only factor significantly related to PFI. *Cancer* 1993; 71:1702–9.

Key words: uterine sarcoma, carcinosarcoma, mixed mesodermal tumor, leiomyosarcoma.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Uterine Sarcoma

NCCN Guidelines Index
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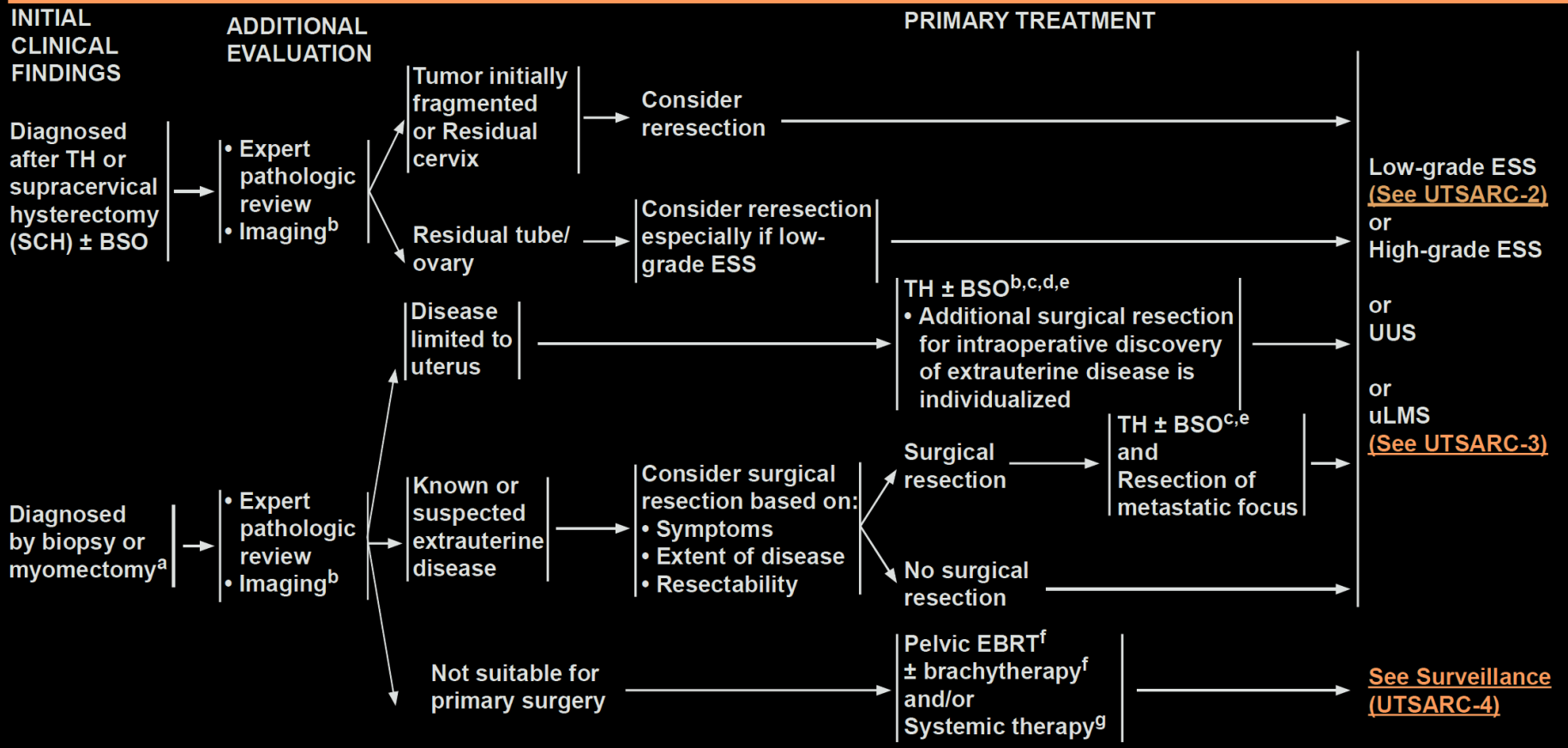


Leiomyosarcoma Staging

Staging for uterine sarcomas (leiomyosarcomas, endometrial stromal sarcomas, adenosarcomas, and carcinosarcomas)

(1) Leiomyosarcomas		
Stage		Definition
I		Tumor limited to uterus
	IA	<5 cm
	IB	>5 cm
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	> one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

GOG #20: Randomized Trial of Adjuvant Doxorubicin in Stage I-II Uterine Sarcomas

- +/- Dox 60 mg/m^2 IV q 3 wks X 8
- 11/73 - 7/82, n = 156
- 41 vs 53% recurred, 61 vs 60 mo. Survival
  - Not predicted by cell type
- "could not show a benefit for... adjuvant treatment"
  - Omura et al. JCO 3:1240 '85

GOG 20

- Pelvic RT
  - decreased pelvic recurrence
    - (23% vs 10%, p=0.028)
  - no change in PFS or OS
    - Omura JCO 3:1240 ’85
    - Hornback I J Rad Onc 12:2127 ‘86

Table 4. Therapy Versus Site of Recurrence

Site of Recurrence	Adjuvant Adriamycin: Irradiated	Adjuvant Adriamycin: No RT	No Chemotherapy: Irradiated	No Chemotherapy: No RT	Total
Leiomyosarcoma					
Lung	4	2	1	7	14
Abdomen	0	1	0	2	3
Pelvis	0	0	0	1	1
Vagina	0	3	0	1	4
Other	0	1	0	1	2
Unspecified	0	0	0	1	1
None	4	10	2	7	23
Heterologous					
Lung	3	0	5	0	8
Abdomen	0	0	1	0	1
Pelvis	1	1	0	0	2
Vagina	1	1	1	3	6
Other	0	0	0	3	3
None	7	5	5	8	25
Homologous					
Lung	0	1	5	1	7
Abdomen	0	1	1	1	3
Pelvis	2	0	0	2	4
Vagina	0	6	0	1	7
Other	0	0	1	0	1
None	7	8	4	7	26
Other cell types					
Lung	1	1	1	1	2
Abdomen	0	0	0	1	1
Pelvis	0	0	0	0	2
Vagina	0	0	0	1	1
Other	0	1	0	0	1
None	1	2	1	4	8
Total	31	44	28	53	156

NOTE. RT = Radiation therapy.

However

- Nonrandomized trials have reported improved survival following adjuvant chemotherapy with or without radiation therapy
  - van Nagell et al. Cancer 57:1451 ’86
    - VAC better than XRT, p=.02
  - Piver et al. J Surg Onc 38:233 ’88
    - 63% vs 36% 5 yr survival +/- doxorubicin
    - 89% CYVADIC

EORTC-GCG 55874: Post Operative Radiotherapy in Patients with Uterine Sarcomas

- Pelvic EBRT vs observation
- 1987-90, n=224
- 14% vs 24% local relapses (p = 0.004)
  - Not in LMS
- No significant impact on either progression-free or overall survival

  - Reed et al. Eur J Ca 44:808 ‘08

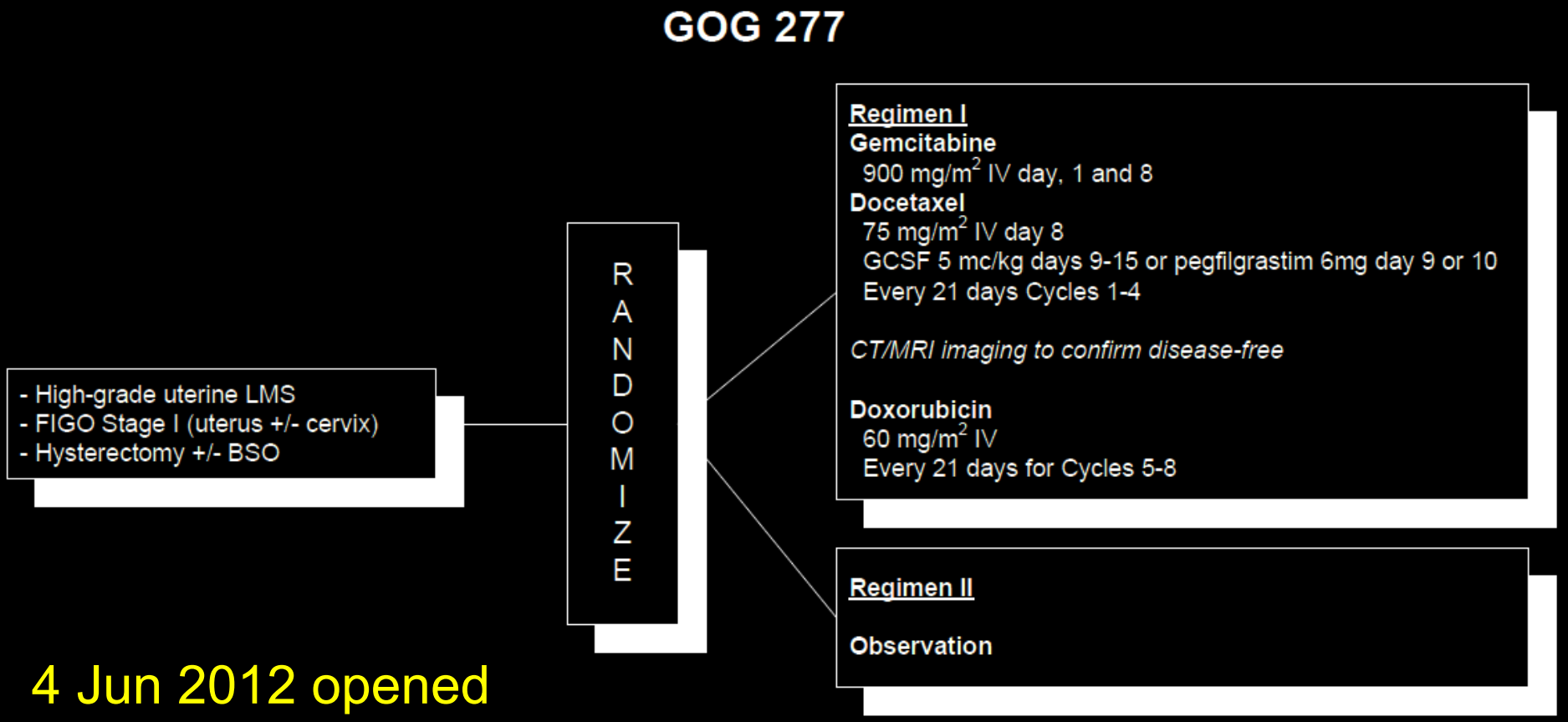
Adjuvant chemo in early uterine LMS: systematic review and meta-analysis

- N = 360, 1 prospective & 4 retrospective studies
- Chemo +/- XRT not better than observation [OR: 0.79 (95%CI: 0.48, 1.29)], or XRT [OR: 0.90 (95%CI: 0.42, 1.94)]
- Local recur:
  - Chemo vs obs [OR: 0.84 (95%CI: 0.44, 1.60)],
  - Chemo +/- XRT vs XRT [OR: 3.45 (95%CI: 1.02, 11.73)]
- Distant recur:
  - Chemo vs not [OR: 0.80 (95%CI: 0.50, 1.28)],
  - Chemo +/- XRT vs obs [(OR: 0.99 (95%CI: 0.60, 1.64)],
  - Chemo +/- XRT vs XRT [OR: 0.49 (95%CI: 0.24, 1.03)]
    - Bogani et al. Gyn Onc 143:443 ‘16

GOG 87L: Fixed dose rate Gemcitabine & Docetaxel for LMS

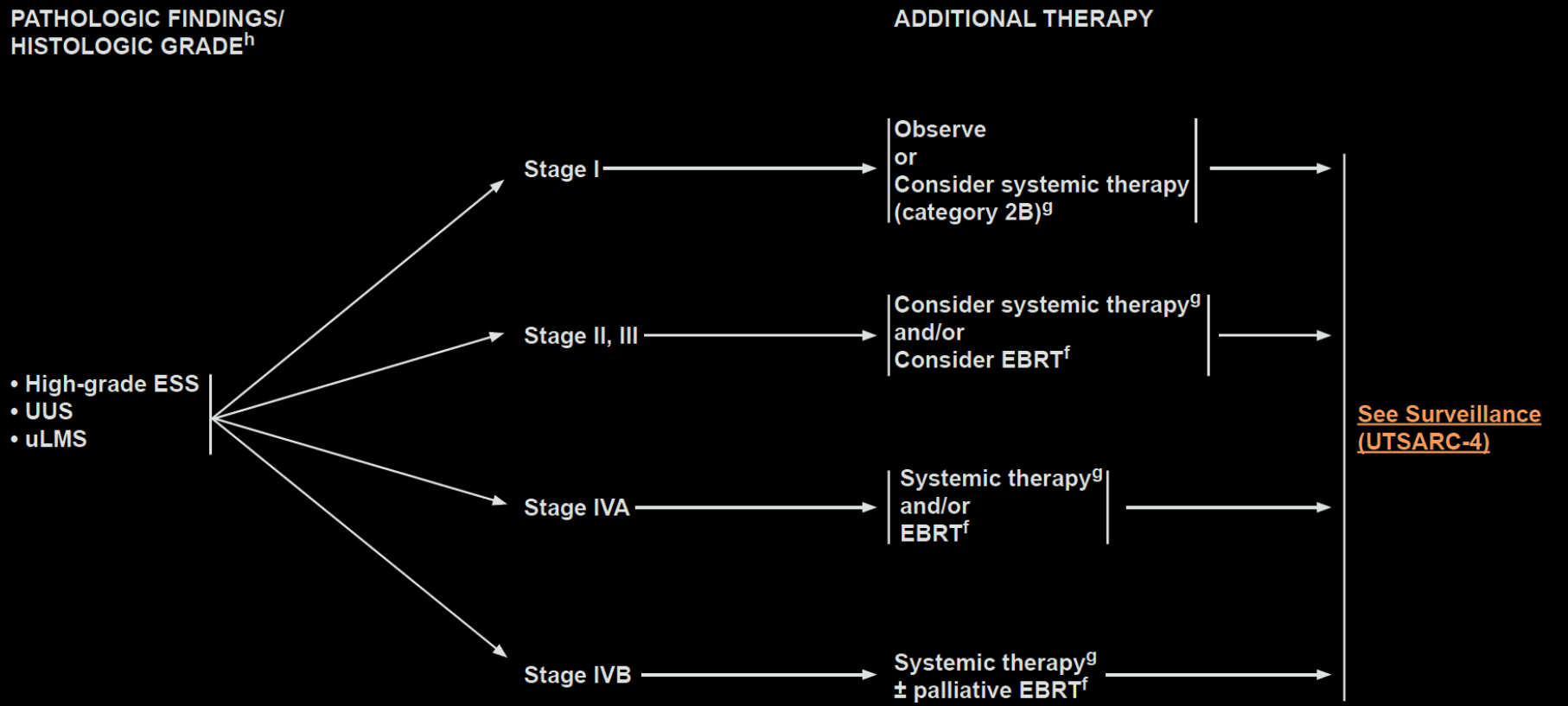
- Gemcitabine 900 mg/m^2 d1+8, docetaxel 100 mg/m^2 d8, & GCF q21d
- N = 42, 39 evaluable
- G 3/4 neutropenia 17%
- CR 5% + PR 31% = 36%
- PFS 4.4 mo, R duration 6 mo
- “achieves high objective response rates as first-line therapy”
  - Hensley et al. Gyn Onc 109:329 ‘08

Leiomyosarcoma: Stage I



4 Jun 2012 opened
38/216 accrued
9 Sep 2016 closed

International Rare Cancers Initiative - Gynaecological sarcoma: EORTC



Phase 2 Trial of Aromatase Inhibition With Letrozole in Patients With Uterine Leiomyosarcomas Expressing Estrogen and/or Progesterone Receptors

Suzanne George, MD[1]; Yang Feng, MS[2]; Judith Manola, MS[2]; Marisa R. Nucci, MD[3]; James E. Butrynski, MD[1]; Jeffrey A. Morgan, MD[1]; Nikhil Ramaiya, MD[4]; Richard Quek, MD[1]; Richard T. Penson, MD[5]; Andrew J. Wagner, MD, PhD[1]; David Harmon, MD[5]; George D. Demetri, MD[1]; and Carolyn Krasner, MD[5]

BACKGROUND: Advanced uterine leiomyosarcoma (ULMS) is an incurable disease. A significant percentage of cases of ULMS express estrogen and/or progesterone receptors (ER and/or PR). To the authors' knowledge, the role of estrogen suppression in disease management is not known. **METHODS:** The authors performed a single-arm phase 2 study of the aromatase inhibitor letrozole at a dose of 2.5 mg daily in patients with unresectable ULMS with ER and/or PR expression confirmed by immunohistochemistry. Tumor assessments were performed at baseline, 6 weeks, 12 weeks, and every 8 weeks thereafter. Toxicity was monitored throughout treatment. The primary endpoint was the progression-free survival at 12 weeks. **RESULTS:** A total of 27 patients was accrued, with a median of 2 prior treatment regimens (range, 0-9 treatment regimens). The median duration of protocol treatment was 2.2 months (range, 0.4 months-9.9 months). The 12-week progression-free survival rate was 50% (90% confidence interval, 30%-67%). The best response was stable disease in 14 patients (54%; 90% CI, 36%-71%). Three patients, all of whom had tumors expressing ER and PR in > 90% of tumor cells, continued to receive letrozole for > 24 weeks. The most common reason for treatment discontinuation was disease progression (85%). Letrozole was found to be well tolerated. **CONCLUSIONS:** Letrozole met protocol-defined criteria as an agent with activity in patients with advanced ULMS. Patients with the longest progression-free survival rate were those whose tumors strongly and diffusely expressed ER and PR. ***Cancer* 2014;120:738–43.** © *2013 American Cancer Society.*

UC1644: A Randomized Phase II Study of Letrozole Versus Observation in Patients with Newly Diagnosed Uterine Leiomyosarcoma

- Randomized phase II
- Hysterectomy with uterus confined LMS
- ER by IHC
- Letrozole 2.5mg po QD
- PFS > 24 months