

CASE #7— Advanced Uterine Leiomyosarcoma

Andres Poveda, MD

Area Clínica Oncología Ginecológica
Fundación Instituto Valenciano de Oncología
Valencia, Spain

apoveda@fivo.org acog@fivo.org



Clinical Case Summary

- A 57-year-old woman with postmenopausal bleeding and pelvic discomfort of 3 months
- Pelvic Exam And Transvaginal Ultrasound: Enlarged uterus with a suspicious tumor mass 12 X 9.8 X 9.8 cm located posteriorly
- MRI: Uterine enlargement and within approximately 11 cm tumor mass irregular central zones of low signal intensity suggesting extensive tumor necrosis; suspicious for uterine smooth muscle tumor. No evidence of extra-uterine abdominal spread.
- Endometrial Biopsy: Not definitive diagnosis
- Laboratory tests normal except LDH 10% UNL
- Chest X-ray: Normal
- Surgery: TAH, BSO and peritoneal washings for cytology
- Pathology: **Uterine leiomyosarcoma**, 10 cm in diameter, mitotic count > 20 per 10 hpf, cytologic atypia and necrosis

Uterine Leiomyosarcoma

- What about abdominal CT Scan?
- Why not lung + abdominal + pelvic CT Scan?

No imaging modality can offer a reliable preoperative diagnosis of uterine sarcoma:

- CT is unable to differentiate between different types of uterine pathology
- It seems that US and MRI are able to give better information of uterine pathology

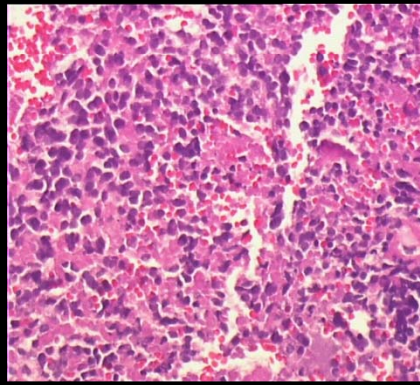
Part I:

- **For this patient, which of the following would you choose for postoperative management?**
 - 1. Pelvic irradiation**
 - 2. Adjuvant chemotherapy**
 - 3. Adjuvant progestational hormones**
 - 4. No postoperative therapy, but close follow-up only**

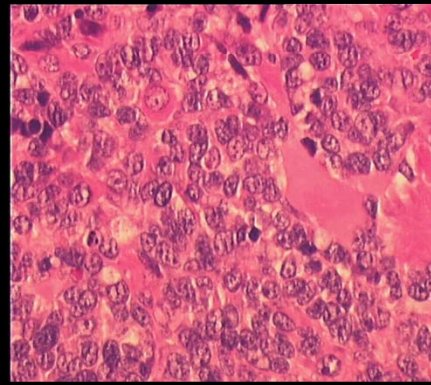
Histologic Classification of Endometrial Sarcomas

- **PURE**
 - **LEIOMYOSARCOMAS (35% to 40%)**
 - **MULLERIAN**
 - **ENDOMETRIAL STROMAL SARCOMAS (15%)**
- **MIXED**
 - **Mixed Mesodermal Tumors (CARCINOSARCOMAS) 40% to 45%**
 - **ADENOSARCOMAS**

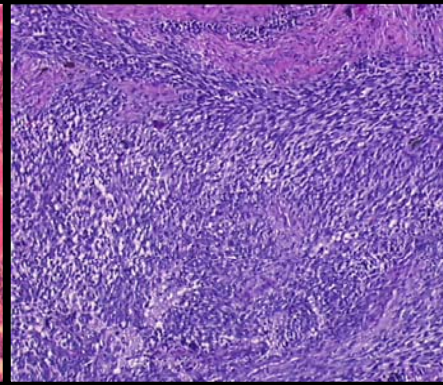
Histotypes of Sarcomas



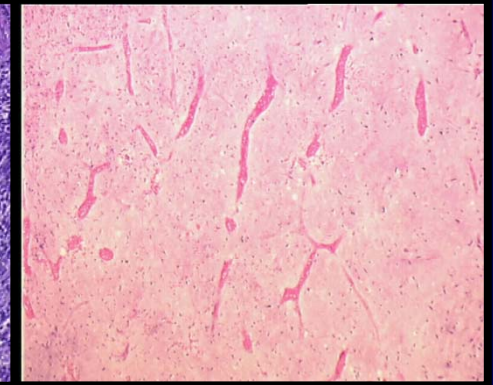
EFT



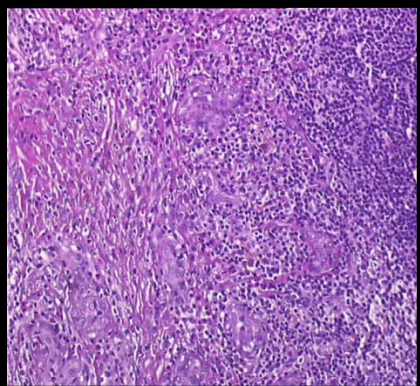
RMS



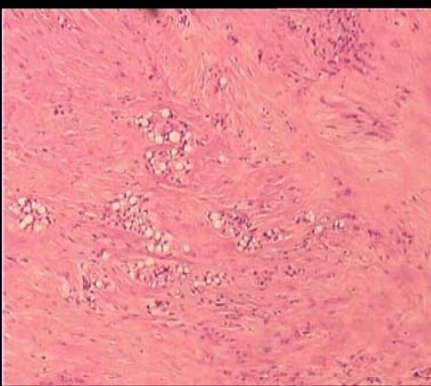
LMS



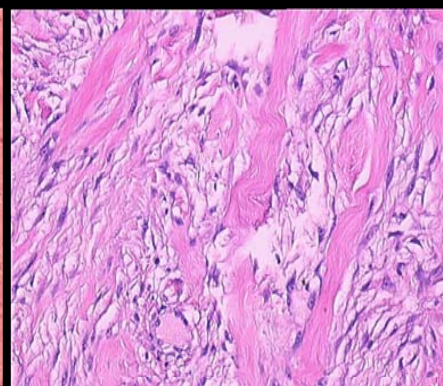
LIPOS



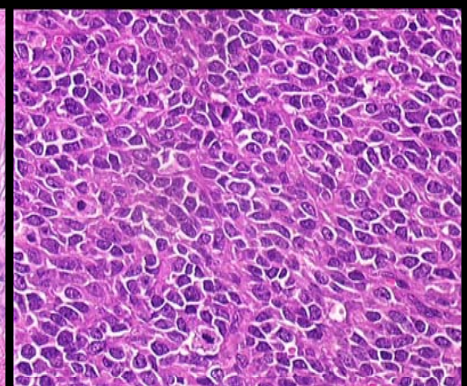
ANGIOS



HAEMANGIO

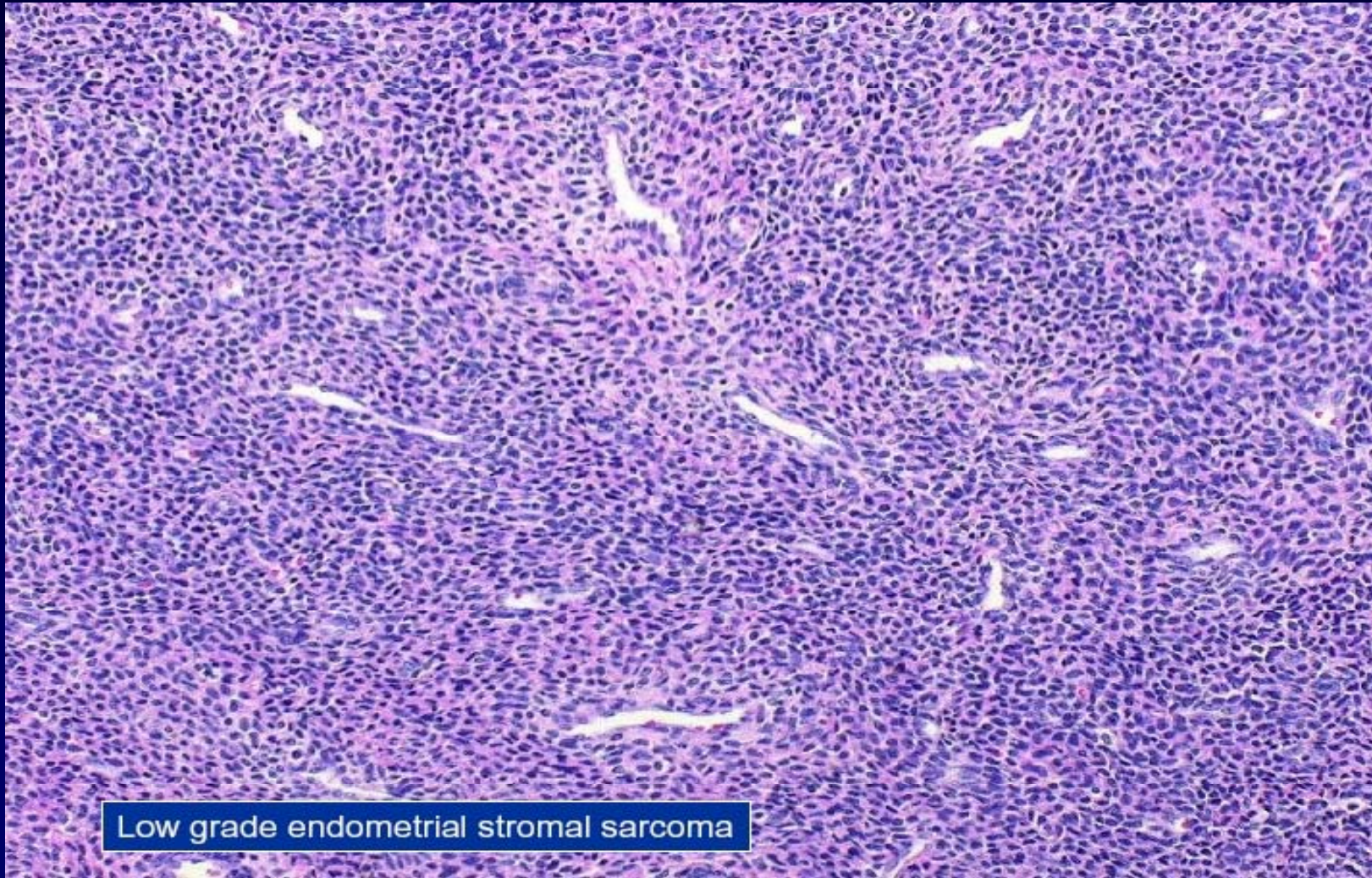


DESMOID



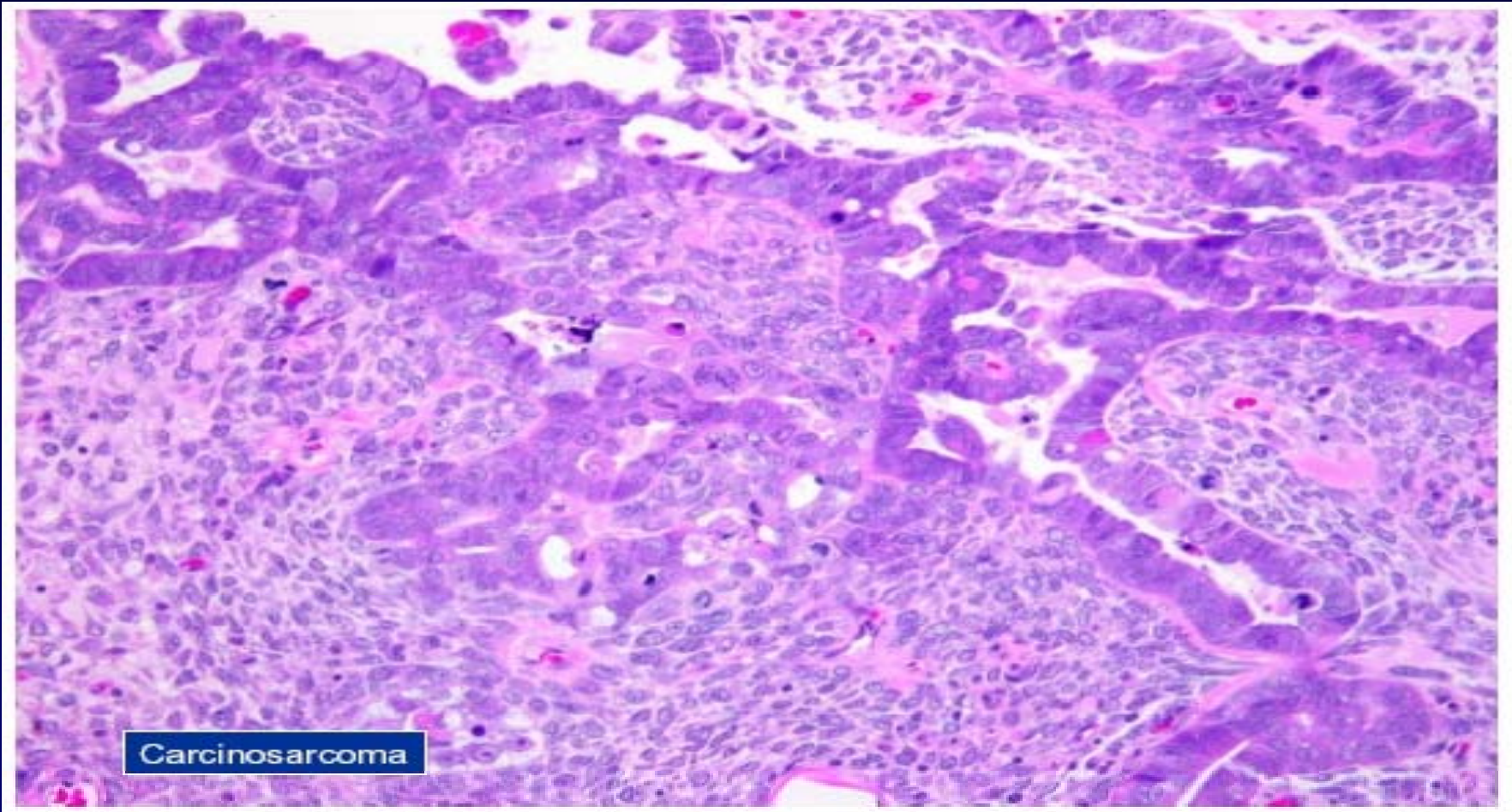
GIST

Histology of Rare Endometrial Tumor



Low grade endometrial stromal sarcoma

Histology of Rare Endometrial Tumor



Connective Tissue Tumors

5 (+?) Types of Sarcomas

- Associated with specific **translocations** generating fusion genes
 - Ewing $t(11;22)$, ...
 - Synovialosarcomas $t(X;18)$
 - Alveolar rhabdomyosarcomas $t(1;13)$, $t(2;13)$
 - DSRCT $t(11;22)$
 - etc...
- Kinase **mutations** (KIT, PDGFR in GIST)
- Gene **inactivation** (INI1 in rhabdoid tumors)
- Simple genetic alterations: **Amplifications** (mdm2+cdk4 in LPS)
- **Complex** genetic alterations (MFH, **LMS**, ...)
- ... β Catenin or APC **mutations** in AF/DT

New FIGO Staging for Uterine Sarcomas Leiomyosarcomas(LMS)

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	Tumor invades bladder and/or rectum and/or distant metastasis
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

**Two different substaging for LMS/ESS and adenosarcomas*

FIGO Committee on Gynecologic Oncology. *Int J Gynaecol Obstet.* 2009;104(3):179.

Uterine Sarcomas

Incidence, Outcome, and Survival

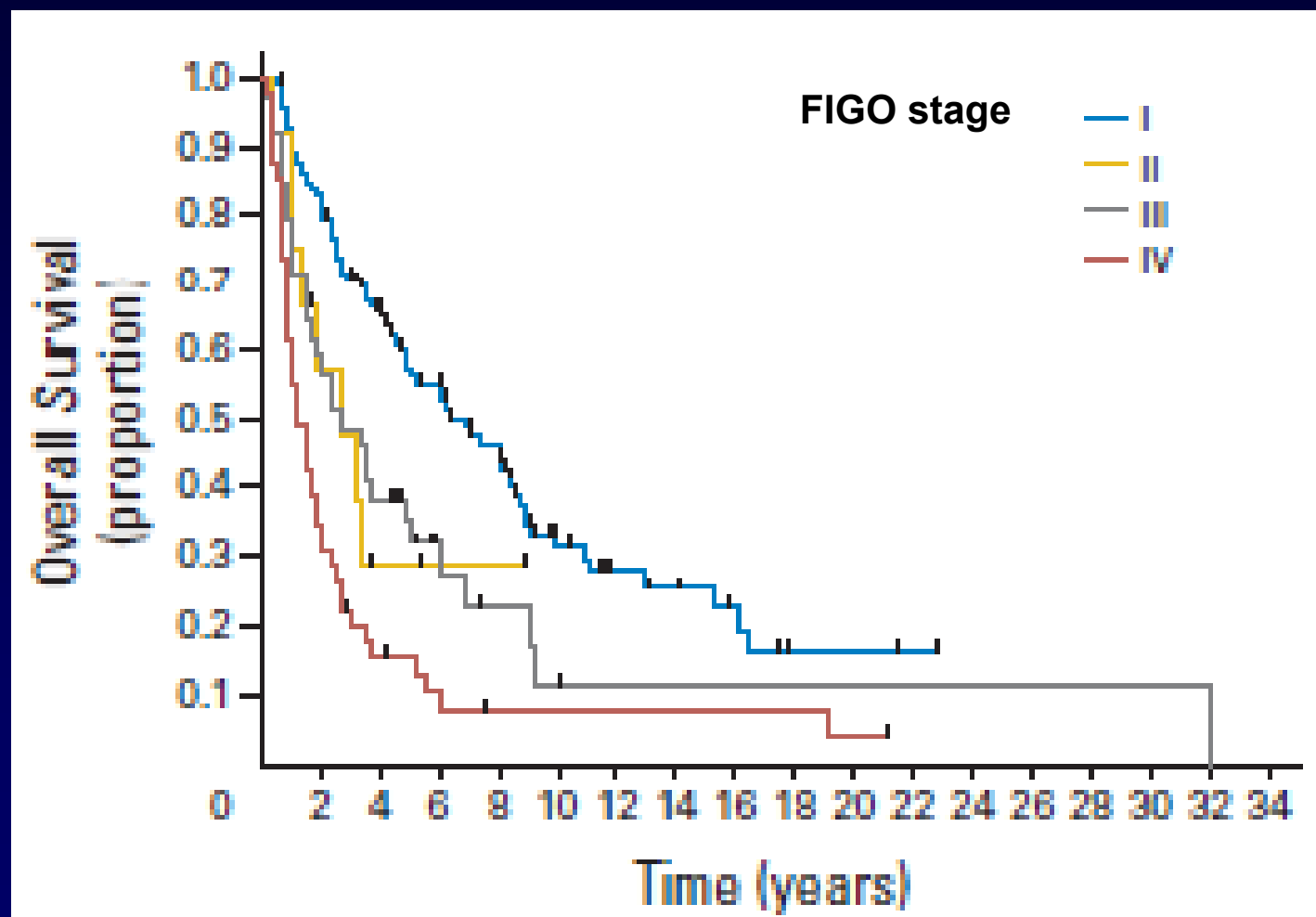
- **Comprise less than 1% of gynecologic cancers, 2% to 4% of uterine cancers**
- **Stage is the most significant predictor of outcome:**
 - **Confined to the uterus: 60% to 70% 5-year survival after surgery**
- **Precise role of adjuvant treatment remains unclear**
- **Major sites of failure: Pelvis, upper abdomen, & lung: Recurrence rate is 44% (homologous) - 63% (heterologous)**
- **Median survival of women with advanced or recurrent disease: <1 year**

Uterine Leiomyosarcomas

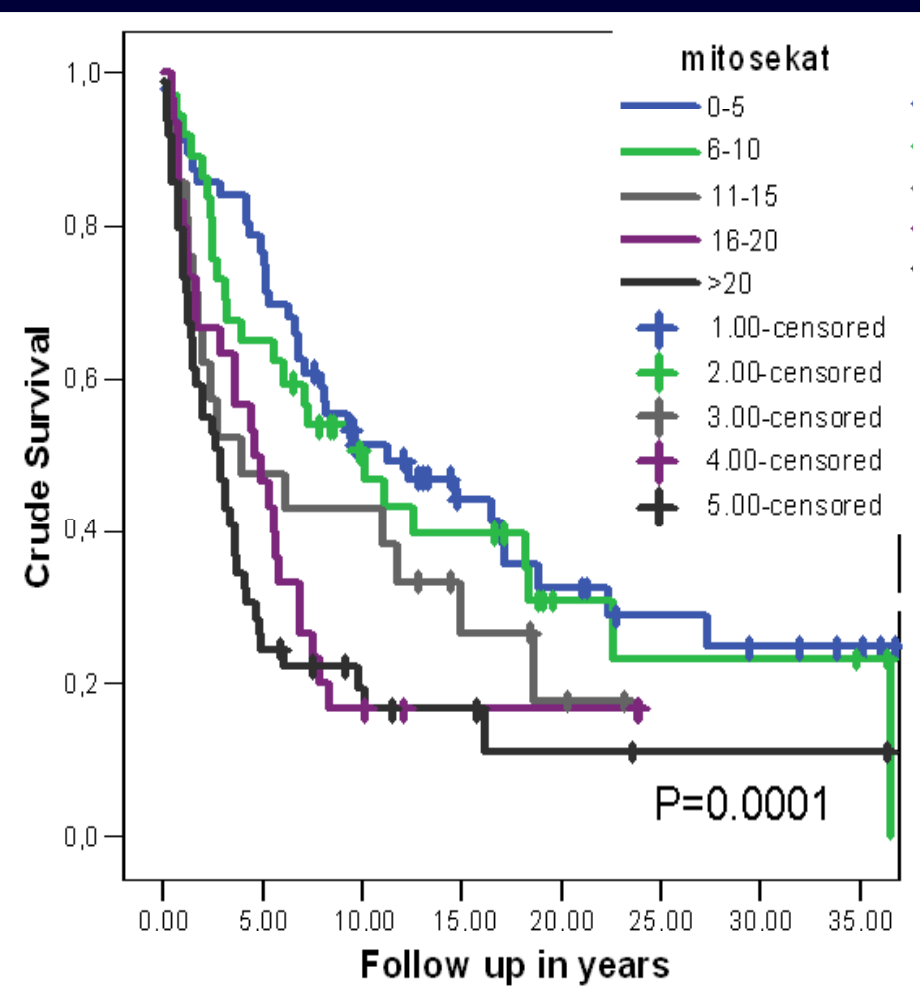
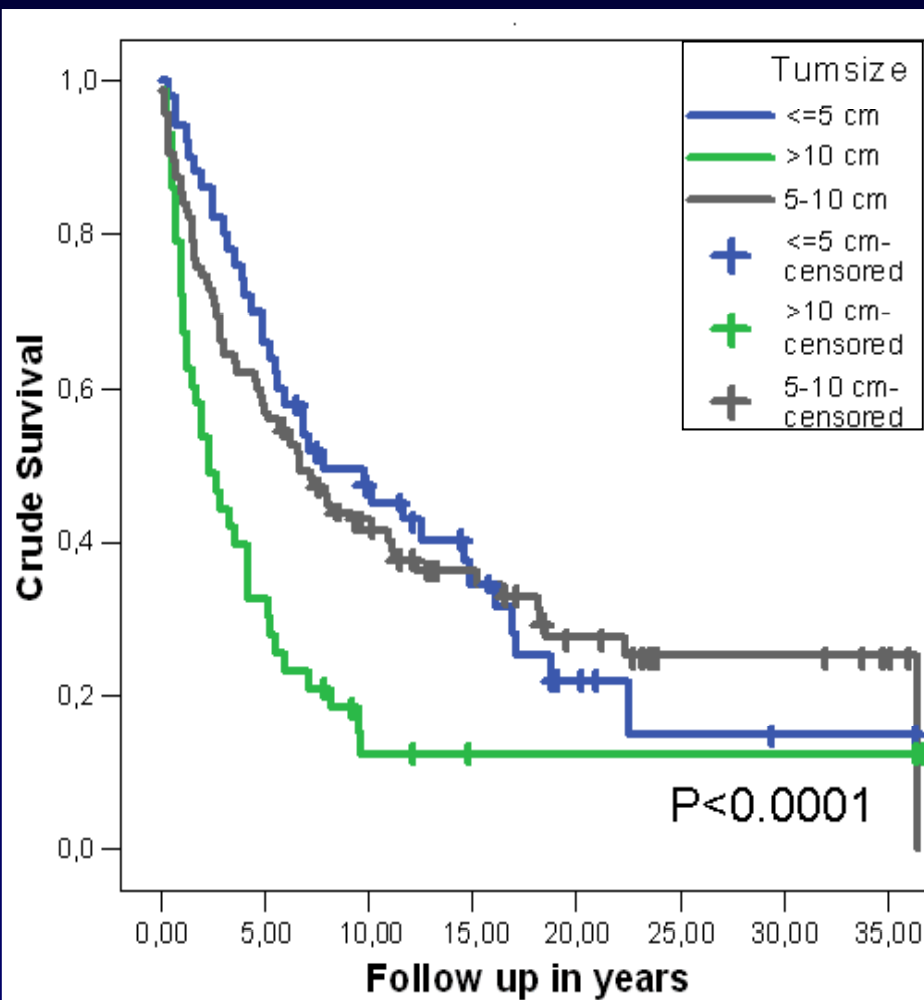
Incidence, Outcome, and Survival

- Comprise 35% to 40% of uterine sarcomas
- **Prognostic factors: Size (>5 cm) and mitotic index**
- Even confined to the uterus, 2-5 years survival of 50% are common
- **Adjuvant radiation therapy has no appreciable impact on recurrence**
- Median survival of women with advanced or recurrent disease: <10 months
- **No Level-1 data from adjuvant chemotherapy trials**

Outcome in Patients with Uterine Leiomyosarcoma Related to Stage



Crude Survival for Stage 1 LMS Related to Tumor Size and Mitotic Index



Kristensen GB, et al. Presented at: 12th Biennial Meeting of the International Gynecologic Cancers Society; October 25-28, 2008: Bangkok, Thailand.

Role of Adjuvant Chemotherapy in Uterine Sarcoma

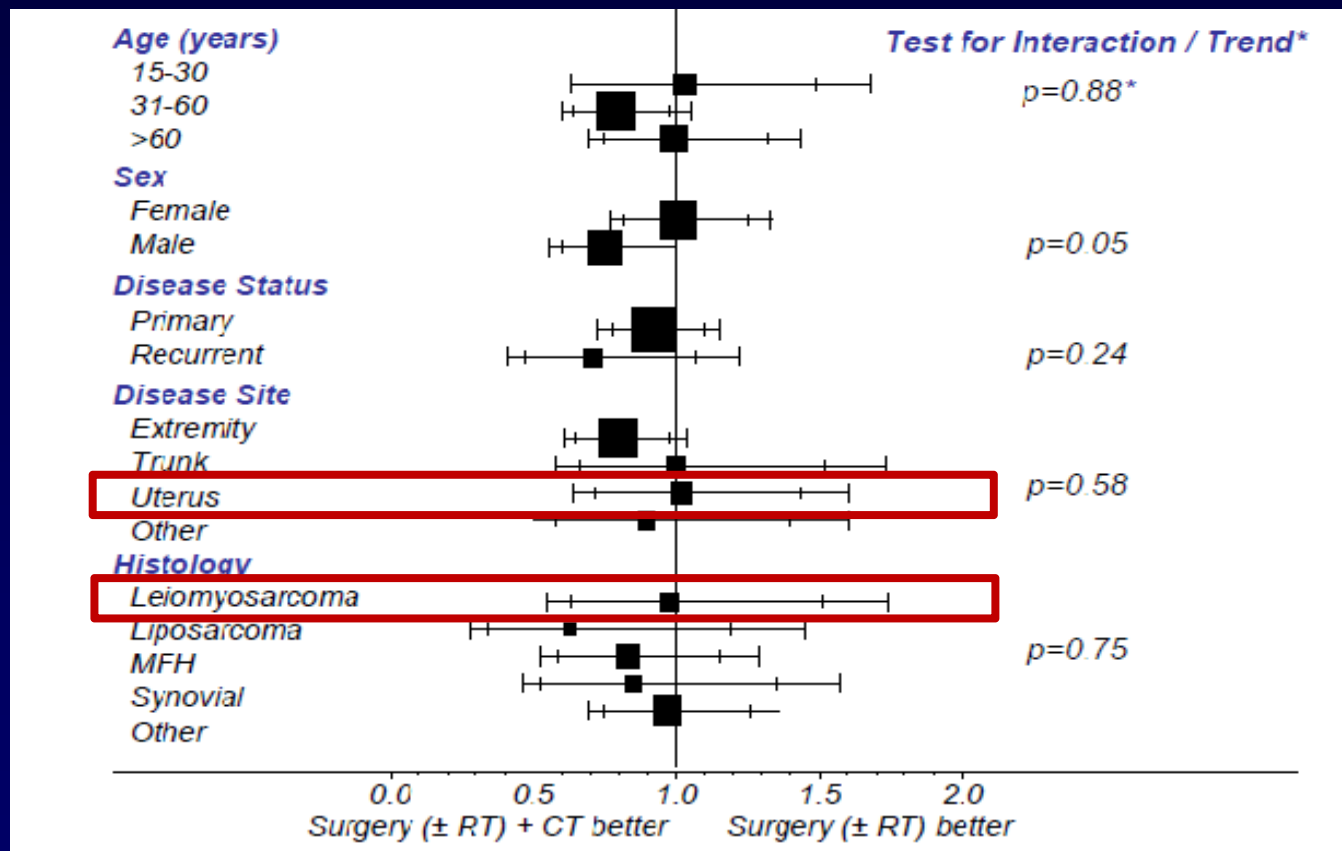
Single RCT:

- N = 156, FIGO I/II, uterine sarcoma
- **Doxorubicin 60 mg/m² q3w X 8 vs no chemotherapy**
- Nonsignificant trend for ↓ recurrences
- No effect on PFS or OS

SMALL STUDY, MIXED HISTOLOGY, SUBOPTIMAL CHEMOTHERAPY

Role of Adjuvant Chemotherapy in Uterine Sarcoma

- Meta-analysis of 1568 patients in 14 trials of adjuvant chemotherapy in soft tissue sarcoma (STS)
- Total group—improved local RFS, distant RFS, overall RFS; but no OS benefit
- Subgroup analysis—**263 patients with uterine sarcoma-no survival benefit**



SARC005 Trial

A phase II multicenter trial: Adjuvant treatment of high risk leiomyosarcoma :

4 cycles of gemcitabine/docetaxel, → by 4 cycles of doxorubicin

Eligibility:

- High-risk uterine LMS, FIGO stage I or II
- Pathology review of LMS high grade and /or mitotic rate greater than or equal to 5 mitoses/10 hpf
- No longer than 12 weeks from surgical resection of cancer
- No evidence of residual disease

Primary Endpoint:

- Two-year progression-free survival among women treated with this adjuvant regimen for high-risk uterine LMS

Secondary Endpoints:

- Tolerability/toxicity
- Improve understanding of behavior of uterine LMS through data collection

CLOSED FOR ACCRUAL

Role of Adjuvant Radiotherapy in Uterine Sarcoma

Study	FIGO Stage	N	Effect of Radiotherapy
Hornback et al, 1986 ¹	I/II	48	No benefit for local control/survival
Gadducci et al, 1996 ²	I-IV	89	Possible local control, no survival benefit
Knocke et al, 1998 ³	I-IV	30*	Judged beneficial *Noncomparative retrospective study
Bodner et al, 2003 ⁴	I-IV	21	No survival benefit
Giuntoli et al, 2003 ⁵	I-IV	62	Local control, no benefit for relapse

1. Hornback NB, et al. *Int J Radiat Oncol Biol Phys.* 1986;12(12):2127-2130. 2. Gadducci A, et al. *Gynecol Oncol.* 1996;62(1):25-32. 3. Knocke TH, et al. *Cancer.* 1998;83(9):1972-1979. 4. Bodner K, et al. *J Reprod Med.* 2003;48(2):95-100. 5. Giuntoli RL, et al. *Gynecol Oncol.* 2003;89(3):460-469.

Role of Adjuvant Radiotherapy in Uterine Sarcoma

Phase III EORTC-CGC prospective RCT :

- N = 224 (LMS 103, CS 91, ESS 28)
- TAH and BSO
- Stage I/II
- Randomized to RT (51 Gy/28# 5weeks) vs no RT
- Results:
 - ↓Local relapse with RT (14 vs 24, $P = .004$)
 - No effect on PFS, OS
 - ↑Local control for CS
 - No benefit for leiomyosarcoma

What I Would Recommend?

Part I:

- For this patient, which of the following would you choose for postoperative management?
 1. Pelvic irradiation
 2. Adjuvant chemotherapy
 3. Adjuvant progestational hormones
 4. No postoperative therapy, but close follow-up only

Clinical Case: Course of Disease

Part II:

- 18 months after diagnosis at routine follow up:
Chest X-ray: 3 nodules in the right lower lobe
CT scan: confirm findings of X-ray: Lung nodules sizes of 1.0, 1.3 and 2.5 cm. The remainder of restaging evaluation is negative.
- Patient is asymptomatic. ECOG performance status is 0.
- **Which of the following treatment would recommend now?**
 1. Surgical resection alone
 2. Surgical resection followed by chemotherapy
 3. Chemotherapy followed by surgical resection
 4. Chemotherapy alone

Uterine Sarcomas Lung Metastases

- In old retrospective series, relapse to lung has been reported in 52% to 84% of cases
- Survival rates up to 43% have been reported
- Prognostic factors:
 - Unilateral localization
 - No extrathoracic tumor

Isolated pulmonary metastases can be considered for resection

Advanced Uterine Sarcomas Single-Agents Activity in Phase II Trials

Agent	LMS Response	CS Response
Doxorubicin	25%	10%
Ifosfamide	17%	32%
Paclitaxel	9%	18%
Cisplatin	5%	19%
Topotecan	11%	10%
Gem-Docetaxel	27% to 36%	Await GOG 130E

Uterine Leiomyosarcomas

Single-Agents Activity in Phase II Trials

Drug	RR	Ref
Doxorubicin	20	Omura 1983
Ifosfamide	17	Sutton 1992
Paclitaxel	9-18	Various
Topotecan	11	Miller 2000
Oral Etoposide	7	Rose, 1998
Trimetrexate	4	Smith 2002
Temozolamide	18	(Geico, ASCO 06)
ET-743 (trabectedin)	19.2	Pooled data

UTERINE LEIOMYOSARCOMAS

Phase II Multi-Agent Studies

Regimen	RR	Ref
Doxorubicin 50 mg/m ² + Ifosfamide 5 g/m ²	30%	Sutton et al, 1996
Doxorubicin 75 mg/m ² + Ifosfamide 10 g/m ²	49%	Leyvraz et al, 2006
Gemcitabine 900mg/m ² , d1&8 + docetaxel 100mg/m ² , d8 * With G-CSF support	18% to 53% 27% second-line	Hensley et al, 2002 Bay et al., 2006 Hensley et al, 2008

What I Would Recommend for This Patient at the Time of Progression to the Lung?

Part II:

1. Surgical resection alone
2. Surgical resection followed by chemotherapy
3. Chemotherapy followed by surgical resection
4. Chemotherapy alone

Clinical Case: Course of Disease

Part III:

- After right lower lobectomy patient decides against chemotherapy and 9 months later presents with fatigue, cough, and pelvic pain. CT scans confirm more than 10 small bilateral pulmonary nodules and a recurrent pelvic mass.
- Symptomatic, ECOG performance status is 1.
- **What treatment would you recommend at this point?**
 1. Doxorubicin + ifosfamide
 2. Docetaxel + gemcitabine
 3. Paclitaxel + carboplatin
 4. Doxorubicin single agent
 5. Progestational agent
 6. Clinical trial of trabectedin
 7. Supportive care only

Uterine Leiomyosarcomas

Single-Agents Activity in Phase II Trials

Drug	RR	Ref
Doxorubicin	20	Omura 1983
Ifosfamide	17	Sutton 1992
Paclitaxel	9-18	Various
Topotecan	11	Miller 2000
Oral etoposide	7	Rose, 1998
Gem-docetaxel	25-36%	Maki. 2008
Temozolamide	18	(Geico, ASCO06)
ET-743 (trabectedin)	19.2	Pooled data

Trabectedin (ET-743)

- **DNA-binding agent, derived from a marine tunicate (*Ecteinascidia turbinata*) and now produced synthetically**
- **Unique mechanism of action with no crossresistance with other chemotherapeutic agents**
- **Approved by EMEA for:**
 - **Advanced STS in adults** after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents
 - **Relapsed platinum-sensitive ovarian cancer** (in combination with PLD)

Trabectedin and Uterine LMS

- 56 patients with advanced U-LMS, heavily pretreated (median 3 CT lines) received trabectedin within an expanded access program
- Median age 56 years, median number of metastatic sites 2, most frequent metastatic site lung (89%)
- Objective RECIST response rate of 20%
- Clinical benefit rate of 51%
- Progression free rate at 6 months >35%
- In 20% of cases therapy was continued for ≥ 8 courses

Hormonal Therapy and Uterine Leiomyosarcoma

- Expression of ER and PR show wide variation (ER 18% to 87%; PR 18% to 80%)
- Scarce data in the literature regarding hormonal therapy, mostly **case reports**:

	N	Target	Hormone	Clinical response	Response duration
Uchida (1996) ^{27*}	1	Progesterone receptor	Medroxyprogesterone	PR	3-75 years
Hardman (2007) ^{28*}	1	Oestrogen receptor	Anastrozole	PR	1 year
Koivisto-Korander (2007) ⁴⁰	1 of 3	Progesterone receptor	Mifepristone	PR	3 years
O'Cearbhaill (2009) ^{29*}	34	Oestrogen receptor	Aromatase inhibitor (74% letrozole)	9% PR	5 months

N, number of pts; PR, partial remission

What I Would Recommend?

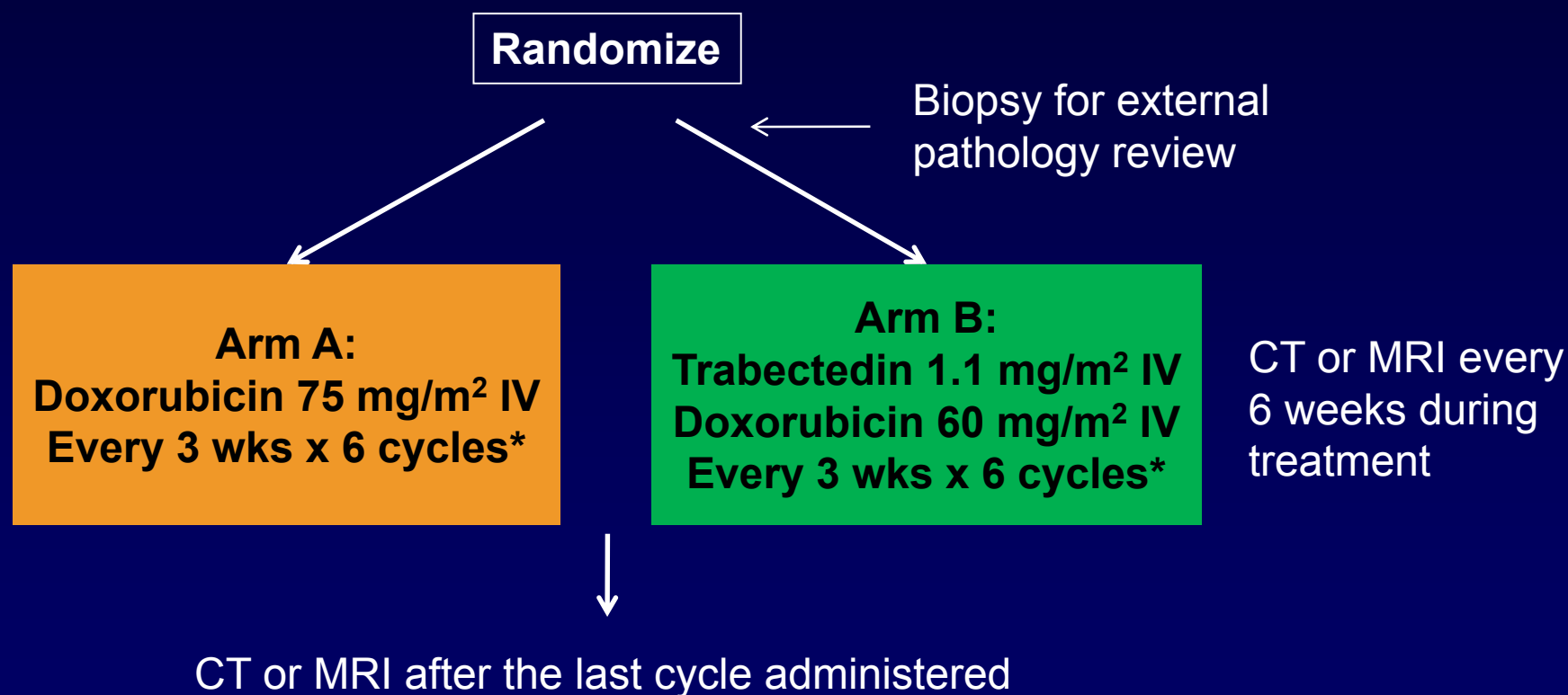
- The role of either radiotherapy or chemotherapy remains undefined
- THE BEST OPTION:

To include this patients in clinical trials!!!!

Leiomyosarcoma

- **GOG0250:** Randomized Phase III Evaluation of Docetaxel, Gemcitabine, & G-CSF +/- Bevacizumab in the Treatment of Recurrent or Advanced Leiomyosarcoma

GEIS20-ET743-DOX-08: Randomized Phase II Trial of Doxorubicin ± Trabectedin for First-Line Treatment of Patients with Advanced Soft Tissue Sarcoma—Schema



*Maximum 6 cycles in absence of disease progression or unacceptable toxicity

Clinical Trials of Targeted Therapy in STS Including Uterine LMS and ESS

	Drug	Target	Sarcoma	Phase	Status
NCT00474994	Sunitinib (SU11248)	Cellular signalling by targeting multiple RTKs (PDGFRs, VEGFRs, KIT, RET, CSF-1R, FLT3)	Metastatic, locally advanced, or locally recurrent non-GIST sarcoma (including all uterine sarcoma)	2	Completed
NCT00414076	Letrozole vs observation	Aromatase enzyme	Uterine leiomyosarcoma	2	Recruiting
NCT00659360	AZD0530	SRC and ABL	Recurrent locally advanced, or metastatic soft-tissue sarcoma (including ESS)	2	Recruiting
NCT00753688	Pazopanib	PDGFRs, VEGFRs, and KIT	Metastatic soft-tissue sarcoma that has relapsed or not responded to treatment	3	Recruiting
SUCCEED trial	Deforolimus	mTOR	Metastatic soft-tissue or bone sarcoma	3	Recruiting

RTKs—receptor tyrosine kinases. PDGFR—platelet-derived growth-factor receptor. VEGFR—vascular endothelial growth factor receptor. CSF—cerebral spinal fluid. FLT—Fms-like tyrosine kinase. GIST—gastrointestinal tumour. SRC—proto-oncogene tyrosine-protein kinase Src. ABL—Abelson murine leukaemia viral oncogene. mTOR—mammalian target of rapamycin.

Amant F, et al. *Lancet Oncol.* 2009;10(12):1188-1198.

Better Results from GROUPS vs INDIVIDUAL Investigators



Thank You!!

