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Uterine LMS

Parviz Hanjani MD

International Professor of Gynecologic Oncology

Professor emeritus of Gynecology

Temple University School of Medicine

Uterine Sarcomas

- Uterine malignant mesenchymal tumors
- Yearly no. **in USA 1200 from 65620**
- Few attempt in randomized clinical trials due to rarity
- Existing evidence from retrospective reviews
- Treatment recommendation from retrospective reviews and results:
- **(Empirical basis)**
- Use expert consensus and clinical experience

Gynecological Sarcomas

- 3-4% of all Gynecological malignancies
- Uterine sarcomas are 83% but only 1% of Gyn. Cancer
- 3-7% of all uterine cancer
- **Uterine LMS 52%**
- Surgery is the " **standard of care**"
- Outcome usually : poor
- **Most deaths are from LMS**

Uterine sarcomas histology classification

- Leiomyosarcoma
- Smooth muscle tumors of uncertain malignant potential (STUMP)
- Endometrial stromal tumor
  - -Stromal nodule
  - -Low grade stromal sarcoma
- -Undifferentiated endometrial sarcoma
- Adenosarcoma 6% and in younger pts.
- Carcinosarcoma (MMMT)

LMS
Epidemiology & risk factors

- Most without identifiable risk factors
- Increased risk in germ line p53 gene mutation carrier (Li Fraumeni syndrome)
- Increased risk with Rb mutations in survival of childhood retinoblastoma
- Survival of childhood Rhabdomyosarcoma who received RT
- Higher rate with HLRCC syndrome
- ?obesity and diabetes, Tamoxifen

LMS
Epidemiology

- most common subtype
- Annual incidence .8/100,000

- 40% of Uterine sarcomas

But Only

1-2% of uterine malignancies

Prognostic factors

- Pt. age, surgical margins, tumor size, tumor cellular atypia and grade, mitotic rate, LVSI, positive LN, necrosis,
- MSKCC: **Age, grade, mitotic rate, cervical extension, Locoregional Mets, distant Mets.**
- IHC and biologic markers; low expression of Ki67,p53,p16 & Hi expression of bcl-2 better Recurrence free survival
- Most important: Stage…….

LMS

- Mostly high-grade & Very aggressive
- High Recurrence and progression rate
- Prognosis poor even 60% being early stage
- +/- 50% stage I, 14% stage II but:

  RR 45%-75%

- OS: 25-76% (Stage I: 50-76%, stage II: ?60%,)
- OS for stage III-IV only 10-15%
- Site of recurrences ;in lung 40%,pelvis 13%

LMS

- Location at myometrium causes
  early LVSI
  Dissemination
- Chemotherapy resistant
- Time to first recurrence +/- 12-24 mos.
  (usually Death within 2yrs)

LMS
Histopathology

- High mitotic activity (>10-15 per 10 HPFs)
- Spindle cell with blunt ended nuclei &
- Hypercellularity
- Pleomorphism, hyperchromatism
- Severe nuclear atypia and necrosis
- No consistency : stage, size, pushing vs. infiltrating borders, **grade!**, vascular invasion
- Epithelioid; lack of necrosis, infiltrative border……
- Myxoid; hypocellur, infiltrative border

molecular biology Immunohistochemistry

- Desmin, h-caldesmon, smooth muscle actin, histone deacetylase8
- Often immuno-reactive for cd10
- Often epithelial markers; keratin & ema
- 40-70% of cases : ER+, PR+, +androgen receptors
- Multiple somatic mutation in LMS but no single signature mutation
- Genetic signature may in future to differentiate Aggressive form from indolent

Molecular profiling and therapeutic implication

- LMS is genetically heterogeneous
- Dominant mutation driver not identified
- Chromosomal loss at T. suppressor genes
- Hyperactivation cell proliferation pathway
- Most frequent mutated genes TP53 (51%)

  RB1 (15.1%

  BRCA2 (6.1%)

Uterine sarcomas staging FIGO 2009

- Leiomyosarcoma and endometrial stromal sarcomas
- Adenosarcomas
- Carcinosarcoma : staged as carcinomas of endometrium

LMS and ESS
FIGO staging 2009

- IA: tumor limited to uterus less than 5 cm
- IB: // // // > 5cm
- IIA: Extend to pelvis involving adnexa
- IIB: Extend to pelvis involving other organs
- IIIA: abdominal involvement one site
- IIIB: more than one site
- IIIC: metastasis to pelvic/para-aortic nodes
- IVA: tumor invades bladder or rectum
- IVB: distant metastases

LMS
Symptoms

- Hysterectomy for LM: 0.1-0.3%
- Mostly 35-75 years of age(spike at perimenopause))
- Abnormal Bleeding 56%,pelvic mass 54%,pelvic pain 22% (LM vs. LMS)
- Fast growing uterine size
- Hemoperitoneum, extra uterine extension, metastasis

LMS Diagnosis

- No test or imaging study to diagnose Pre-op
- Elevated Lactate dehydrogenase &/or Ca125 in some Pts.
- Endometrial sampling

Diagnosis of LMS Imaging studies

- Ultrsound
- CT Scan
- MRI
- In most Occasions LMS diagnosis is made at myomectomy or hysterectomy

LMS
surgical treatment

- TAH and if needed Cytoreduction
- No BSO before menopause in clinical early stage
- No need for routine Lymphadenectomy

Uterine sarcomas& Tumor morcellation

- Do not Use laparoscopy for TAH if you do not have benign endometrial tissue sample

- **Do not use Marcellation for uterine myomas if you are not sure of being myomas or a benign process**

LMS

- Finding LMS on hysterectomy specimen removed for benign disease
- Finding LMS on a Supracervical hysterectomy

uterine limited LMS after surgery

- Recurrence risk over 50%
- Observation
- post surgery CT,MRI Why?
- ?PET/CT ?
- No increase in PFS or OS with **adjuvant chemotherapy**
- **In metastatic disease there is no effective treatment**

Radiation therapy

- Post op radiation is not helpful in OS or recurrence

LMS
treatment of advanced or recurrent

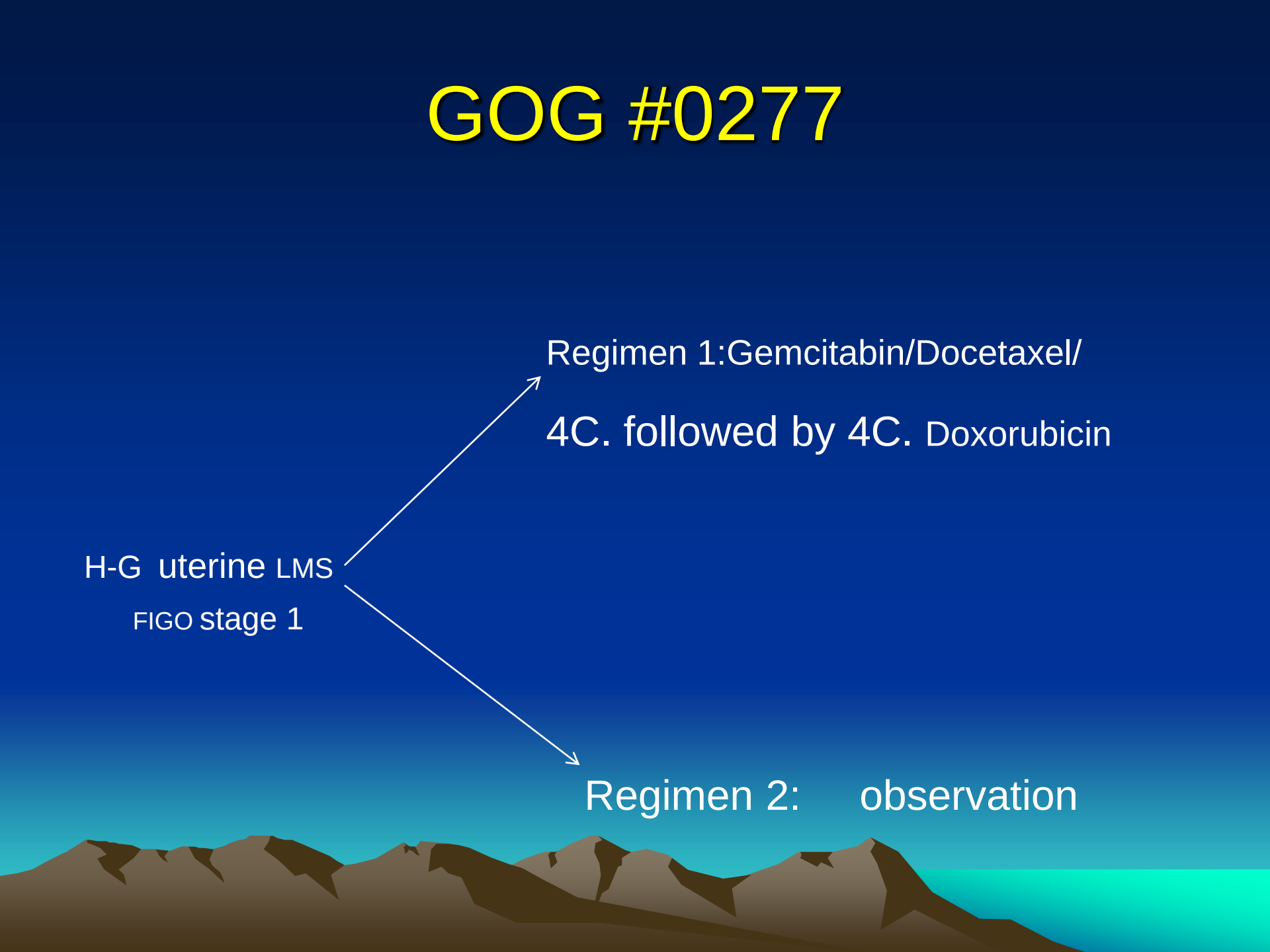
- Radiation therapy

- Chemotherapy ; doxorubicin, docetaxel/gemcitabine

  response rate 27%-36%

- Hormone therapy

GOG #0277


Regimen 1:Gemcitabin/Docetaxel/
4C. followed by 4C. Doxorubicin
H-G uterine LMS
FIGO stage 1
Regimen 2: observation

LMS
GOG-0250 phase III

Recurrence or advanced leiomyosarcomas

- Arm I: gemcitabine/docetaxel +G-CSF and bevacizumab
- Arm II: gemcitabine/docetaxel + G-CSF and palcebo