Role of Radiotherapy in Uterine Leiomyosarcoma

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BACKGROUND

- Leiomyosarcoma is the most common uterine sarcoma and is an aggressive neoplasm

- It is associated with poor prognosis and high risk of recurrence even among women with early-stage disease

BACKGROUND

- The group of mesenchymal tumours includes uterine leiomyosarcoma (uLMS, 65% of cases), endometrial stromal sarcoma (ESS, 21%) – traditionally divided into low grade (LG-ESS) and high grade–undifferentiated uterine sarcoma (5%) and other rare subtypes such as alveolar or embryonal rhabdomyosarcoma

BACKGROUND

- Despite a frequent presentation as localised resectable disease, the risk of recurrence of uLMS ranges between 50% and 70%:

with a 5-year OS rate of less than 50% in early stages and less than 15% in advanced stages

- The high rates of distant failure point towards the option of an adjuvant systemic therapy although no additional treatment (neither chemotherapy, nor radiation, nor hormone blockade) is proven to reduce the risk of relapse or to improve progression-free survival (PFS) and overall survival (OS)

BACKGROUND

- Beyond surgery, the effect of adjuvant treatment modalities such as radiotherapy, chemotherapy and hormonal therapy in US remains poorly understood and its role remains controversial

Adjuvant Radiotherapy

- Adjuvant radiotherapy (RT) appears to be of limited clinical value in women with early-stage or advanced-stage resected uLMS, and the retrospective nature of all the available data – except for a phase III randomised trial – makes it difficult to draw conclusion regarding its role in this setting

Adjuvant Radiotherapy

- The limited scope of adjuvant RT in uLMS was also confirmed by Wright et al in a retrospective study utilising Surveillance, Epidemiology and End Results (SEER) data; in this study, radiation failed to demonstrate survival benefit in early-stage uLMS (HR = 1.1, 95%CI: 0.9-1.4)

Adjuvant Radiotherapy

- The latest version of the National Cancer Comprehensive Network (NCCN) Guidelines suggests the possibility of using postoperative RT in selected cases after a multidisciplinary evaluation; in such cases, pathologic parameters such as cervical, serosal and parametrial involvement should be carefully considered.

- To summarise, the choice of adjuvant RT in uLMS should be determined on a case-by-case basis, balancing between the risk of relapse, patient performance status and side effects, considering the absence of a proven benefit.

Staging of Uterine Sarcomas (Excluding Adenosarcoma)

TNM	FIGO	Definition
T1	I	Tumor confined to the uterus
T1a	IA	Tumor is 5 cm or less in greatest dimension
T1b	IB	Tumor is more than 5 cm in greatest dimension
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissue
T3	III	Tumor involves abdominal tissues or regional lymph nodes
T3a	IIIA	Tumor extends to 1 abdominal site
T3b	IIIB	Tumor extends to more than 1 abdominal site
N1	IIIC	Tumor involves reginal lymph nodes
T4	IVA	Tumor invades bladder or rectal mucosa
M1	IVB	Distant metastases (liver, lung, bone)

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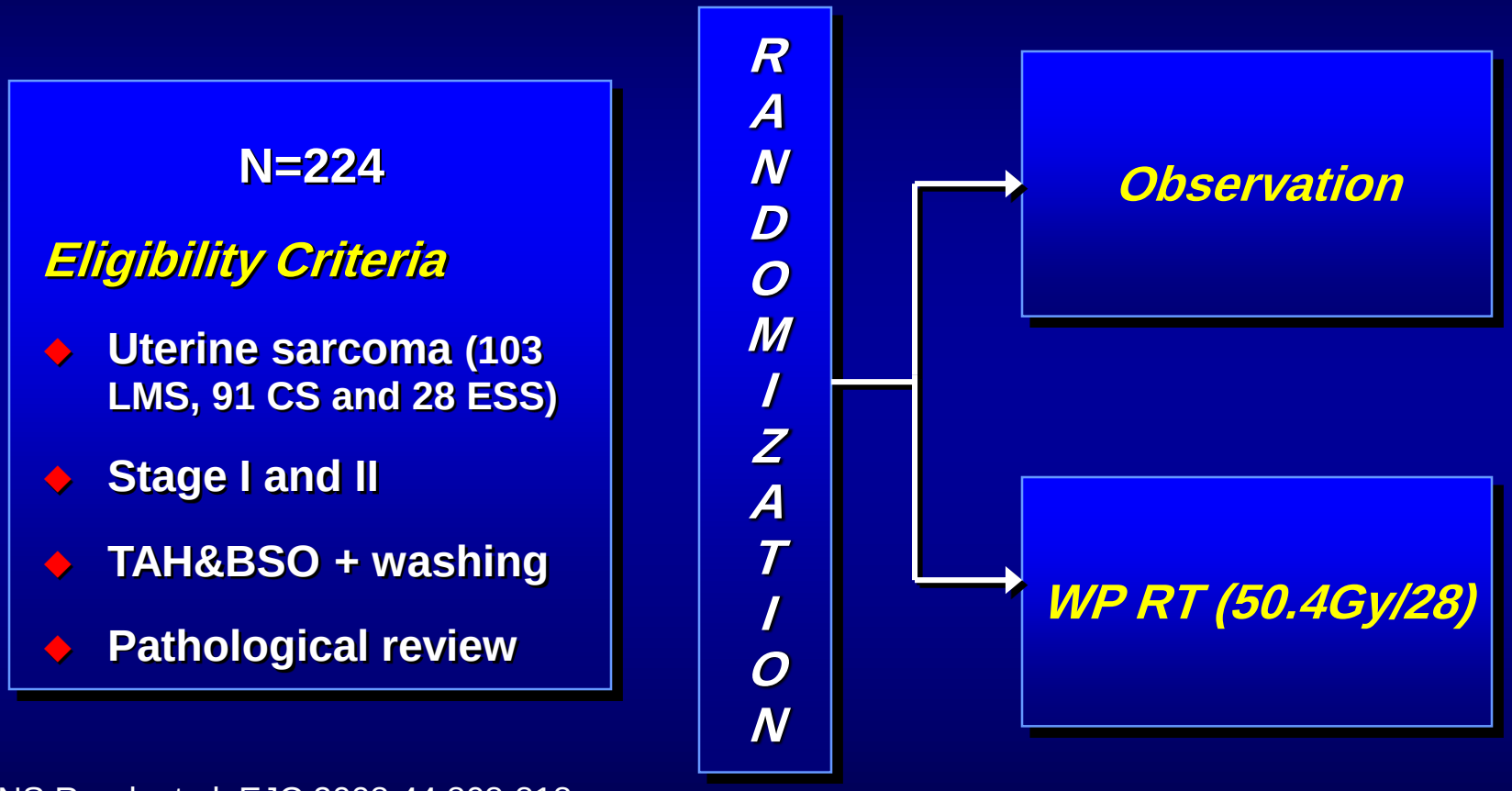
Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: An European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874)

N.S. Reed[a,*], C. Mangioni[b], H. Malmström[c], G. Scarfone[d], A. Poveda[e], S. Pecorelli[f], S. Tateo[g], M. Franchi[h], J.J. Jobsen[i], C. Coens[j], I. Teodorovic[j], I. Vergote[k], J.B. Vermorken[l]

Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, Tateo S, Franchi M, Jobsen JJ, Coens C, Teodorovic I, Vergote I, Vermorken JB; European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. 2008;44:808-818

EORTC 55874



NS Reed, et al. EJC 2008;44:808-818.

*reduction in local relapse for CS (14 versus 24, p = 0.004) without any benefit for LMS and without any benefit on OS or PFS.

No unexpected toxicity was seen in the radiation arm.

EORTC 55874

- The primary objective of the study was to evaluate whether adjuvant pelvic radiotherapy could decrease pelvic recurrence rate in patients with surgically completely resected uterine sarcomas and thereby decrease the recurrence of distant metastases.

- Secondary objectives included the evaluation of OS and PFS benefit and toxicity profile.

EORTC 55874

- For higher grades CS and ESS, the risk of local nodal disease falls between 12% and 18% and there is a greater risk of local or loco-regional recurrence which runs between 5% and 15% hence, local treatment might have been predicted to show a benefit.

- metastases in LMS lies at about 4% and with a much higher incidence of lung metastases at presentation, hence one would anticipate that these tumours would be more likely to develop early distant recurrence rather than local recurrence and local pelvic treatment would be predicted to have lower benefit

EORTC 55874

- What seems clear is that LMS and CS are likely to be distinct tumours and require a different strategy for post-operative adjuvant therapy

- The side effects and toxicity in this study were acceptable and were comparable with those expected from historical studies. The incidence of radiation damage was low and did not lead to any serious complications

SEER database analysis

RESEARCH www.AJOG.org

ONCOLOGY

The role of radiation in improving survival for early-stage carcinosarcoma and leiomyosarcoma

Jason D. Wright, MD; Venkatraman E. Seshan, PhD; Monjri Shah, MD; Peter B. Schiff, MD, PhD; William M. Burke, MD; Carmel J. Cohen, MD; Thomas J. Herzog, MD

Wright JD, Seshan VE, Shah M, et al. The role of radiation in improving survival for early-stage carcinosarcoma and leiomyosarcoma. Am J Obstet Gynecol 2008;199:536.e1-536.e8.

SEER database analysis

- Among 1819 women with carcinosarcomas and 1088 women with leiomyosarcomas

- Radiation was administered to:

667 of the patients (37%) with carcinosarcomas

and to 235 of the patients (22%) with leiomyosarcomas

SEER database analysis

- In a multivariate model, adjuvant radiation reduced the risk of death by 21% in women with carcinosarcomas (hazard ratio, 0.79; 95% CI, 0.7-0.9).

- Radiation reduced mortality rates in patients with carcinosarcomas who had not undergone node dissection but had only a marginal effect on survival in node-negative women.

- Adjuvant radiation had no effect on survival for early-stage leiomyosarcomas (hazard ratio, 1.1; 95% CI, 0.9-1.4).

SEER database analysis

- Among patients with carcinosarcoma who underwent lymphadenectomy, the survival advantage that was conferred by adjuvant radiotherapy was modest (HR, 0.85; 95% CI, 0.70-1.03).

- For patients with carcinosarcoma who had not undergone lymphadenectomy, radiation was associated with a 25% reduction in mortality rate (HR, 0.75; 95% CI, 0.61- 0.91).

SEER database analysis

- Kaplan-Meier analysis demonstrated that survival was improved in women with carcinosarcomas who received radiotherapy (P = .001)

SEER database analysis

- A Cox model for leiomyosarcomas demonstrated no effect of radiation on survival (HR, 1.10; 95% CI, 0.89-1.38).
- Cancer-specific mortality rate was increased in patients > 65 years old and those with stage II tumors.
- Radiation had no effect on survival, regardless of whether lymphadenectomy was (HR, 1.16; 95% CI, 0.77-1.76) or was not (HR, 1.04; 95% CI, 0.80-1.36) performed.

SEER database analysis

- A Kaplan-Meier analysis revealed that radiation had no effect on survival for women with leiomyosarcomas (P =.252)

SEER database analysis

- A large series of patients who had been treated with surgery alone revealed that:

nearly 45% of carcinosarcoma relapses occur distantly

and up to 90% of leiomyosarcoma failures are associated with an extrapelvic component

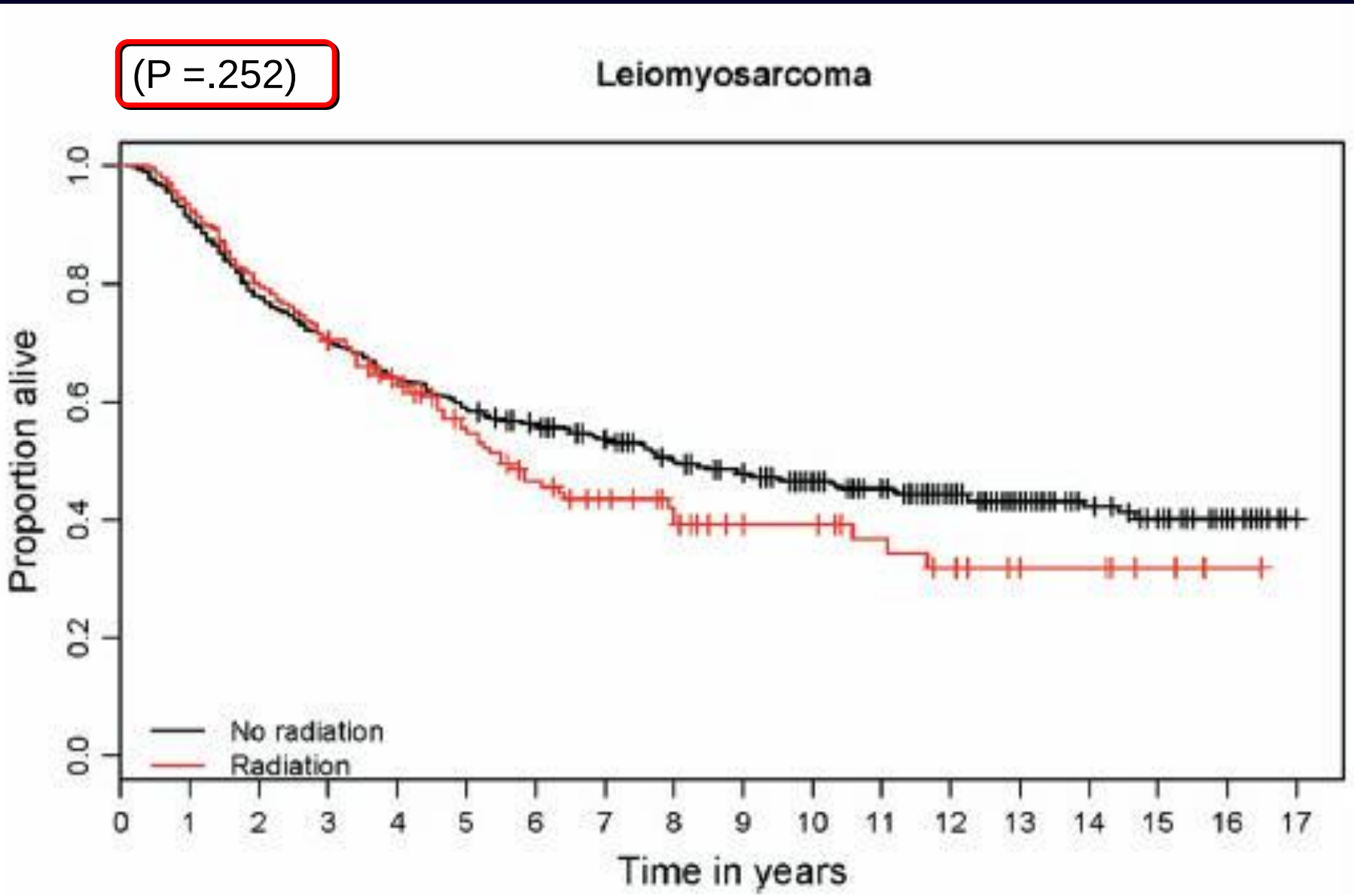
SEER database analysis

- Although SEER data provides a large, representative sample of women with uterine sarcomas, several limitations must be acknowledged. Although radiation use is recorded, data on the administration of chemotherapy are not collected

- For those women who did receive radiation, it was not possible to determine the quantity or quality of radiation, compliance with radiation, or the fields that were treated

- The SEER data set lacks comprehensive information of medical comorbidities, performance status, and patterns of recurrence

(P =.252)


Leiomyosarcoma
Proportion alive
0.0
0.2
0.4
0.6
0.8
1.0
No radiation
Radiation
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Time in years

SEER database analysis

- CONCLUSION:

Adjuvant radiotherapy improves survival for select patients with early-stage carcinosarcomas

but is of limited value for leiomyosarcomas

intraperitoneal morcellation

- A retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma found a twofold higher rate of recurrence, and significantly shorter median recurrence-free survival (10.8 vs 39.6 months; p = 0.002)

- George S, Barysauskas C, Serrano C et al. Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma. Cancer 120(20), 3154–3158 (2014).

intraperitoneal morcellation

- A more recent retrospective MITO group study, which examined outcomes of 125 patients ultimately diagnosed with stage I uterine leiomyosarcomas, reported a significant (p = 0.02) threefold increase in the risk of death for those who had morcellation or power morcellation compared with those who had no morcellation at initial surgery
  - Raspagliesi F, Maltese G, Bogani G et al. Morcellation worsens survival outcomes in patients with undiagnosed uterine leiomyosarcomas: a retrospective MITO group study. Gynecol. Oncol. 144(1), 90–95 (2017).

intraperitoneal morcellation

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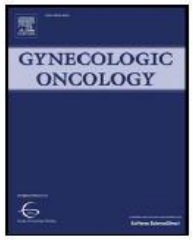


Review

Impact of morcellation on survival outcomes of patients with unexpected uterine leiomyosarcoma: A systematic review and meta-analysis

Giorgio Bogani [a], William A. Cliby [b], Giovanni D. Aletti [c,*]

[a] *Programme in Oncology and Experimental Medicine, University of Insubria, Varese, Italy*
[b] *Gynecologic Surgery Unit, Mayo Clinic, Rochester, MN, USA*
[c] *Department of Gynecologic Oncology, IEO, Milan, Italy*

9 HIGHLIGHTS

intraperitoneal morcellation

- 202 patients were included: 75 (37%) patients had morcellation of ULMS, while 127 (63%) patients had not.

- A meta-analysis of these studies showed that morcellation increased the overall (62% vs. 39%; OR: 3.16 (95% CI:1.38, 7.26) and intra-abdominal (39% vs. 9%; OR: 4.11 (95% CI: 1.92, 8.81) recurrence rates as well as death rate (48% vs. 29%; OR: 2.42 (95% CI: 1.19, 4.92).

LMS

- Postoperative radiotherapy is not effective for stage I (disease confined to the uterus) disease, but some patients with stage II (disease extending beyond the uterus) disease may have local control benefit from radiation, especially those with positive margins.

DGGG and OEGGG guideline 2019

DGGG and OEGGG guideline 2019

- Sarcoma of the Uterus. Guideline of the DGGG and OEGGG (S2k Level, AWMF Register Number 015/074, February 2019)
  - DGGG ➔ German Society of Gynecology and Obstetrics
  - OEGGG ➔ Austrian Society of Gynecology and Obstetrics

Consensus-based Recommendation 2.E14	
Expert consensus	**Strength of consensus +++**
Radiotherapy should not be carried out after complete resection of a stage I/II LMS.	

DGGG and OEGGG guideline 2019

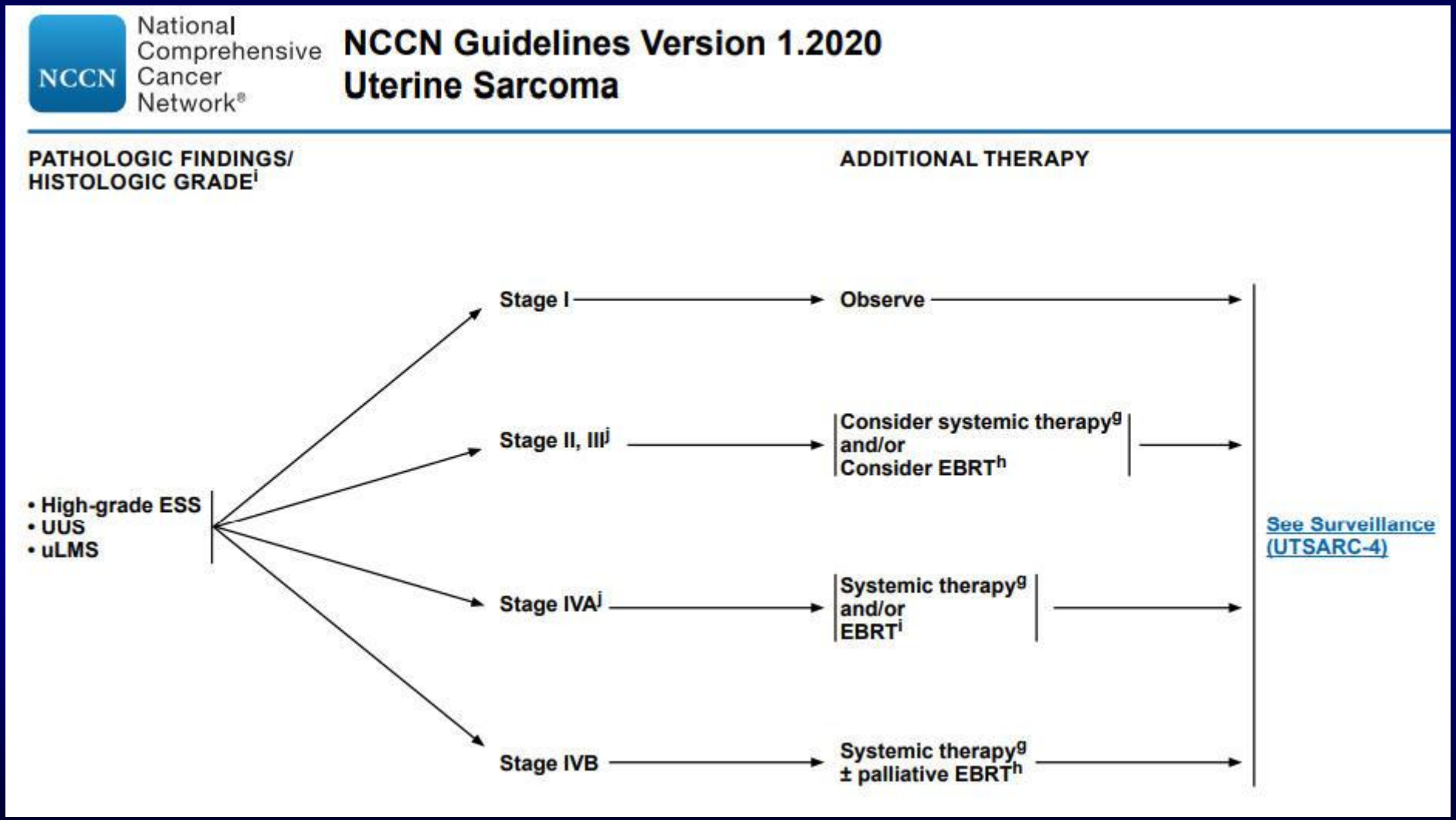
- Radiotherapy can be considered in patients with:

R1/2 resection

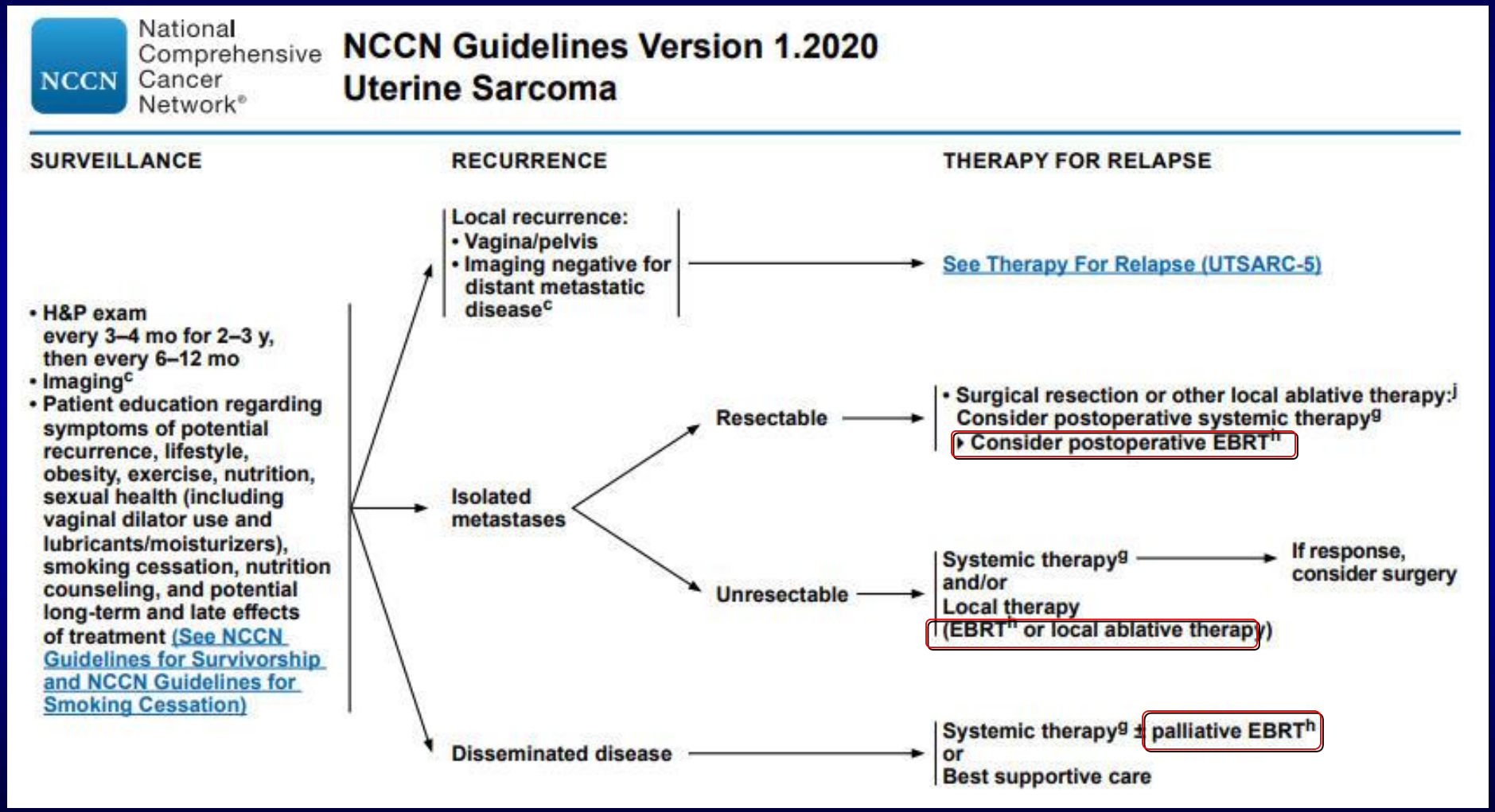
and locally advanced disease if the tumor is limited to the pelvis

NCCN 2020

NCCN


National Comprehensive Cancer Network®
NCCN Guidelines Version 1.2020
Uterine Sarcoma
PATHOLOGIC FINDINGS/ HISTOLOGIC GRADE[i]
ADDITIONAL THERAPY
• High-grade ESS
• UUS
• uLMS
Stage I
Observe
Stage II, III[j]
Consider systemic therapy[g] and/or Consider EBRT[h]
Stage IVA[j]
Systemic therapy[g] and/or EBRT[i]
Stage IVB
Systemic therapy[g] ± palliative EBRT[h]
See Surveillance (UTSARC-4)

NCCN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Uterine Sarcoma
SURVEILLANCE
RECURRENCE
THERAPY FOR RELAPSE
• H&P exam every 3–4 mo for 2–3 y, then every 6–12 mo
• Imaging[c]
• Patient education regarding symptoms of potential recurrence, lifestyle, obesity, exercise, nutrition, sexual health (including vaginal dilator use and lubricants/moisturizers), smoking cessation, nutrition counseling, and potential long-term and late effects of treatment (See NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation)
Local recurrence:
• Vagina/pelvis
• Imaging negative for distant metastatic disease[c]
See Therapy For Relapse (UTSARC-5)
Isolated metastases
Resectable
• Surgical resection or other local ablative therapy:[j] Consider postoperative systemic therapy[g]
• Consider postoperative EBRT[h]
Unresectable
Systemic therapy[g] and/or Local therapy (EBRT[h] or local ablative therapy)
If response, consider surgery
Disseminated disease
Systemic therapy[g] ± palliative EBRT[h] or Best supportive care

NCCN

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NCCN Guidelines Version 1.2020
Uterine Sarcoma

RECURRENCE | **THERAPY FOR RELAPSE**

Radiologically isolated vaginal/ pelvic recurrence[c]

No prior RT →

Surgical exploration
+ resection
± IORT (category 3 for IORT)
Consider preoperative EBRT[h,k]
± systemic therapy[l]

→ **For residual disease:**
Consider EBRT ± brachytherapy[h,k]
± systemic therapy[l]

or

EBRT[h]
± brachytherapy[h]
± systemic therapy[l]

Prior RT →

Surgical exploration + resection ± IORT ± systemic therapy[l]
(category 3 for IORT)
or
Systemic therapy[l]
or
Selected re-irradiation with EBRT[g] and/or brachytherapy[h]

Take home message

- Radiotherapy can be considered in patients with:

R1/2 resection

and locally advanced disease if the tumor is limited to the pelvis