Provincial Endometrium Cancer Treatment Guidelines Appendices

Approved at the Provincial Gyne-Oncology Guideline Meeting
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Appendix 1: Summary of Studies Reviewing Extent of Lymph Node Evaluation in Endometrial Cancer

Chan et al (58):

Chan et al 2007 reviewed 11,443 endometrial cancer cases recorded in the SEER data base from 1990 to 2001. The goal of this review was to determine if a relationship exists between the number of lymph nodes retrieved and the probability of finding a positive lymph node. A logistic regression model was constructed in which the probability of finding at least one positive lymph node was the dependent variable. The independent variable of interest was the number of lymph nodes retrieved. Lymph node counts were categorized in increments of 5 (i.e. 1-5, 6-10, 11-15, 16-20, 20-25, >25). Multivariate analysis controlled for stage, grade, and year of diagnosis. Patients with papillary serous, clear cell, sarcomas, and stage IV disease were excluded.

Of the 11 443 patients, 638 (5.6%) had positive lymph nodes. More than half the patients (53.3%) had less than or equal to 10 lymph nodes removed during lymphadenectomy. Of the 638 cases with positive lymph nodes, only 27% were identified by lymph node counts up to 5 and only 46% were identified by inclusion of cases with lymph node counts up to 10. Inclusion of all cases with 20 or less lymph nodes retrieve captured 74% of cases with positive nodes, inclusion of all cases with 25 or less lymph nodes retrieved captured 85% of those with positive nodes, and inclusion of all cases with more than 25 lymph nodes retrieved captured over 90% of positive lymph nodes.

The logistic regression model identified the category of 21 to 25 lymph nodes retrieved as providing the greatest incremental gain in identification of positive lymph nodes (OR of 1.45; 95% CI 1.08-1.94 [$p<0.01$]). Removing more than 25 lymph nodes did not significantly increase the probability of detecting at least one positive node. The authors of this study suggested that removal of 20 to 25 lymph nodes be considered as the definition of adequate lymphadenectomy.

Panici et al (46):

Panici et al 2008 also looked at the influence of lymphadenectomy on patient survival by conducting a prospective randomized trial of HBSO versus HBSO and lymph node dissection in patients with endometrial cancer. The study enrolled 514 patients between 1996 and 2006. Patients were excluded if they had grade 1 endometrial cancer with less than 50% myometrial invasion on intra-operative pathological assessment. The protocol also required that at least 20 pelvic lymph nodes be removed and analyzed in the lymphadenectomy arm. Para-aortic lymphadenectomy was performed at the discretion of the surgeon. In the no lymphadenectomy arm, only bulky lymph nodes could be removed. Sample size was determined to detect an improvement of 8% in 5-year overall survival (from 80 to 88%) in the study (lymphadenectomy) arm with a significance level of 5% and power of 80%.

The median number of pelvic lymph nodes removed in the lymphadenectomy arm was 26 (interquartile range =21-35).

At a median follow up of 48 months, the hazard ratio for death (lymphadenectomy vs. no lymphadenectomy arm) was 1.1 (95% CI of 0.7 – 1.71 [P=0.50]). The 5 year disease free and overall survival rates in the intention to treat analysis were 81% vs. 85.9% and 81.7% vs. 90%. Therefore pelvic lymphadenectomy did not improve survival.
Statistically more patients in the lymphadenectomy arm were found to have stage IIIC disease (13.3% vs. 3.2% [95% CI 5.3%-14.9%, P<0.001]). The authors concluded that although pelvic lymphadenectomy did not improve survival, it did improve surgical staging.

Lutman et al. & Cragun et al (59, 60).

This retrospective review looked at 467 patients with FIGO stage I and II disease. All patients had HBSO and at least a pelvic lymph node dissection. The review spanned 1973 to 2002. The median number of lymph nodes removed went from 9 in the years 1973-1987 to 14 in the years 1988-2002 (P<0.0001). Compared to patients with distant recurrences, patients with no recurrence or vaginal recurrence had significantly more pelvic lymph nodes identified at initial surgery (P=0.012). Pelvic lymph node count was not associated with improved survival on univariate analysis. However, subset analysis revealed that higher lymph node count did correlate with improved survival in high-risk patients. Patients with high-risk histology who had ≥12 lymph nodes removed had a HR of overall survival (OS) and progression free survival (PFS) of 0.28 (P<0.002) and 0.29 (P<0.001) respectively. This translated to a 5 year OS of 84% vs. 69% (P<0.001) and 5 year PFS of 78% vs. 64% (P<0.001).

The most significant limitation of this study was its retrospective design. The survival benefit in the high-risk group most likely was a result of stage migration. The authors do not identify how many stage IIIC patients were identified in patients with ≥ l2 lymph nodes removed vs. those with ≤ 11 nodes removed.

Abu-Rustum et al (61).

This was a retrospective review of 1035 patients operated on between 1993 and 2004. The review looked at all patients with endometrioid type endometrial cancer; sarcomas, clear cell and papillary serous cancers were excluded. A ‘Classification and Regression Tree’ (CART) analysis was carried out in order to determine predictors of survival. In this cohort, 524 (51%) patients had lymphadenectomies. The median number of lymph nodes removed was 16. The CART analysis found that the removal of at least 10 lymph nodes was a predictor of improved survival. The resulting improvement in survival was likely a result of stage migration i.e. better identification of patients with advanced disease and should not be interpreted as demonstrating a therapeutic benefit of node dissection. However, the importance of an adequate lymph node count was once again brought out by this study.

Appendix 2: Endometrial Cancer Risk Groups

I. Low risk (<10% risk of recurrence)
   a. Stage IA grade 1
   b. Stage IB grade 1 LVS negative
   c. Stage IA, grade 2 LVS negative

II. Intermediate risk (10-20% chance of recurrence) (80)
   a. Stage IA grade 2 LVS positive
   b. Stage IA grade 3 LVS negative
   c. Stage IB grade 1 and grade 2

III. High-intermediate risk (25% chance of recurrence)(80):
   a. patients with stage I disease 70 years or older with any one of the following risk factors:
      i. tumor grade 2 or 3
      ii. deep myometrial invasion
      iii. presence of lymphovascular space involvement
   b. patients with stage I disease who are age 50 or over and have at least 2 of the above risk factors
   c. patients of any age with stage I disease and all 3 risk factors listed above

IV. High risk (>30% risk of recurrence)
   a. High risk stage I disease –
      i. grade 3 with deep myometrial invasion
   b. Stage II and greater
   c. High risk histological subtypes i.e. papillary serous, clear cell, and carcinosarcoma

Appendix 3: Evidence Supporting Risk Stratification

Evidence for risk categorization from adjuvant radiation treatment perspective:

- In the older staging age was not accounted for which is an independent predictor for locoregional recurrence. **Study by Luarain (Gynecol Oncol 1991) showed 7% increase in risk for every 1 year increase in age. 2 GOG studies reported by Zaino et (1996) and Keys et al (2004) correlated the age without come.**

- GOG 99 –Keys et al Gynecol Oncol 2004

Outer one-third myometrial invasion, grade 2 or 3 differentiation, or the presence of lymphovascular invasion within the cancer

  - Patients of any age with all three factors
  - Patients 50 to 69 years old with two factors
  - Patients 70 years or older with only one factor

- PORTEC 1 and 2 Creutzberg et al 2000,Nout 2008
  - Presence of 2 of 3 factors, age >60ys,outer half of myometrial invasion, Grade 3 histology.

Appendix 4: Evidence for managing Low Risk Group patients:

- GOG 33 – Morrow et al -Gynecol Oncol 1991.
  - Studied patterns of failure 1977-1983. Stage I and stage II (occult)
  - No recurrence noted in 72 patients with G I &2 without myo who did not receive adjuvant RT.

Eifel et al Cancer 1983 (1/127 patients had recurrence) and GOG 99 - Keys et, al GOG 99-Gynecol Oncol 2004(1.8% local recurrence at 4ys) for similar group of patients as in GOG 33.

Meta-analyses (Johnson 2007; Kong et al., 2007)

Suggest that pelvic EBRT may improve DFS for high-risk patients, such as those with IC grade 3 disease. However, low risk endometrial cancer (517pts) RT was associated with increased risk of death compared to observation

Evidence based management for Low Risk group

- Surgery (Nodal involvement <5%)
- Medical management for those who wish to preserve fertility
- Adjuvant Radiation treatment - No role for EBRT
    - Risk of vault recurrence very small
        - Morrow et al, GOG-Gynecol Oncol 1991
        - Eifel et al Cancer 1983
        - Orr JW et al Astraughn et al Gynecol Oncol 2002
        - Keys et, al GOG 99-Gynecol Oncol 2004

Appendix 5: Evidence for managing Intermediate Risk Group patients:

Author	Patients, n	Study population	Control arm	Intervention arm	Surgical treatment
Aalders et al.[4]	540	Stage I adenocarcinoma	Vaginal brachytherapy	Vaginal brachytherapy plus pelvic radiation	TAH/BSO
Creutzberg et al.[15]	715	Stage IC G1, IB, C G2 IAG3	Observation	Pelvic radiation	TAH/BSO
Keys et al.[5]	448	IB/IC/II All node negative	Observation	Pelvic radiation	TAH/BSO pelvic and aortic node dissection
Susumu et al.[11]	385	IC-IIIC Stage IC/II made up 75% of study population	Pelvic radiation	Chemotherapy with CAP	TAH/BSO pelvic and aortic node dissection
Kuoppala et al.[10]	159	IA/B G3 IC-IIIA GI,2,3	Pelvic radiation	Pelvic radiation plus 3 cycles of CAP	TAH/BSO pelvic node dissection
Blake et al.[12] ASTEC/EN5	905	IA/B G3 IC G1,2,3, serous, clear cell ± positive pelvic nodes	Observation (50% received brachytherapy)	Pelvic radiation	TAH/BSO ± pelvic node dissection
Nout et al.[2] PORTEC -2	427	Age ≥ 60 + stage IC grade I or 2 or IB grade 3 Or stage IIA any age	External beam radiotherapy	Vaginal brachytherapy	TAH/BSO
Högberg et al.[14] /NSGO-EC-9501/ EORTC-5591	540	Stage I, no residual postoperative tumour, later amendment to add occult stage II, stage IIIA (cytology) and IIIC, pelvic nodes only (237 patients)	Pelvic radiotherapy Brachytherapy optional	4 cycles of doxorubicin/cisplatin or paclitaxel/ carboplatin (MD choice) and pelvic radiation Brachytherapy optional	TAH/BSO Lymphadenectomy optional

TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oopherectomy; CAP: cyclophosphamide-doxorubicin-cisplatin; ASTEC-EN5: Adjuvant external beam radiotherapy in the treatment of endometrial cancer; NSGO-EC: Nordic Society for Gynecological Oncology-Endometrial Cancer; EORTC: European Organisation for Research and Treatment of Cancer

Author	Local recurrence control arm, %	Local recurrence intervention arm, %	Overall survival control arm, %	Overall survival intervention arm, %
Aalders et al.[4]	6.9	1.9	91	89 (NS)
Creutzberg et al.[3]	14	4	85	81 (NS)
Keys et al.[5]	12, IHR 26	3, IHR 6	86	92 (NS)
Susumu et al.[11]			85	86 (NS)
Kuoppala et al.[10]			85	82
Blake et al.[12] ASTEC/EN5			84	84 (NS)
Nout et al.[2] PORTEC-2	1.6 vaginal recurrence 2.1 locoregional recurrence	1.8 vaginal recurrence 5.1 locoregional recurrence	79.6	84.8 (NS)
Högberg et al.[14]			72	79 HR 0.64 (95% CI 0.41 to 0.99) *P* = 0.04

NS: not significant; IHR: intermediate- to high-risk; ASTEC/EN5: Adjuvant external beam radiotherapy in the treatment of endometrial cancer

Aalders et al. (Ob Gyn1980):

- 540 patients with IB-IC any grade treated with TAH/BSO without LN sampling. 65% of patients had IB G1-2. Randomized to VC vs. VC → WP RT. VC = LDR 60 Gy to surface. WP RT = 40 Gy with central shielding at 20 Gy.
- Addition of WP RT decreased pelvic and vaginal recurrences (7→2%), but did not change OS (90%) because more DM in WP RT arm.
- On subset analysis,

- Patients with >50% myo and G3 had reduced mortality if received EBRT with improvement in LRR from 20→5%.
- Patients with LVSI mortality rate reduced from 26.7% to 9.1% (p<.01)

- Independent Poor prognostic factors = IC, G3, LVSI, age >60 years.

GOG 99 - Keys et al. 2004

Study done between 1987 - 1995. High intermediate risk group constituted only 1/3 of patient population however accounted for 2/3 of recurrences

- *392* with IB (60%), IC (30%), and occult II (10%) treated with TAH/BSO, pelvic and PALN sampling, and peritoneal cytology. Patients randomized to observation vs. post-op WP RT (50.4 Gy). 6-year F/U
- Two-third of patients had low–intermediate risk disease and one-third of patients were high-intermediate risk (G2-3, outer 1/3 involvement, and LVSI or age >50 years + 2 factors, or age >70 years + 1 factor).
- WP RT improved LRR (12→3%), mostly among high-intermediate risk patients(26→6%) compared to low–intermediate risk patients (6→2%). Majority of pelvic recurrences were in the vaginal cuff
- No difference in OS (86→92%), but not powered to detect OS

GOG 99 subset analysis for low intermediate risk showed:

- Improved local control 6-2% (HR 0.46 90%CI 0.19-1.11) NS
- No difference in distant recurrence 1.5 vs. 1.4. No difference in cancer specific mortality (HR 1.04)
- Significant toxicity G2-4, Hema 14vs 5pts,GI 64 vs. 5, Skin 15vs9, GI obstruction 6 vs. 1

PORTEC-1 - Creutzberg et al. 2000; Scholten et al. 2005

- *714* patients with IB G2–3 or IC G1–2 treated with TAH/BSO randomized to observation vs. WP RT (46 Gy).
- No LN dissection (only sampling of suspicious LN). 90% of patients had G1–2 and 40% were IB.
- WP RT decreased LRR (14→4%), with 75% of failures occurring in the vaginal vault. No difference in OS (81 vs. 85%) or DM (8 vs. 7%).
- **Update with 10-year f/u and central pathology review for 80% of patients confirmed WP RT continued to reduce LRR** (14→5%) without an OS benefit (66 vs. 73%), even after excluding IB grade 1 patients.
- Patients with 2 or more risk factors (age 60 years, Grade 3, and 50% myometrial invasion) had greatest LRR benefit with RT (23→5%).

ASTEC EN.5 (2009):

- *909 patients with IA/B* grade 3, IC any grade, or I-II papillary serous or clear cell histology randomized after surgery to observation or WP RT (40–46 Gy).

- However, vaginal cuff brachytherapy was used in 54% in EBRT group and 53% of patients randomized to the observation arm.
- There was no difference in 5-year OS (84%) or DSS (89–90%). WP RT reduced isolated pelvic or vaginal recurrences (6.1→3.2%).
- Increased acute toxicity (27→57%) and late severe toxicity (3→7%).
- **Bias here is the non-randomized VC RT, low RT compliance and QA.**

PORTEC 2 (Nout 2010):

- 427 patients with high-intermediate risk (age >60 years and IC grade 1–2 or IB grade 3; any age and IIA grade 1–2 or grade 3 with <50% invasion) randomized to WP RT (46 Gy) or VC brachytherapy (21 Gy HDR in 3 fx or 30 Gy LDR).
- EBRT Vs. VC Vault RT at 45 months
  - VC recurrence 1.6% vs. 1.8% (p.74)
  - Locoregional recurrence 2.1%vs5.1% (.17)
  - Distant recurrence 5.7%vs8.3% (.46)
  - Toxicity G1&2 53.8%vs12.6% lost significance after 24months of FU.
- No significant difference in 3-year VC relapse 0.9% VC vs. 2%
- No significant difference in 3-year WPRT vs. VC
  - OS (90 vs. 91%)
  - RFS (89 vs. 90%) and
- At 5–year 80 vs. 85% OS and 78 vs. 83% RFS

Patient-reported quality of life was better with VC brachytherapy.

Short comings in this study compared to Norwegian study reported by Alders which showed most benefit with RT for patients with >50% myo and G3, was excluded in PORTEC2. Almost 92% patient population in PORTEC2 was with G1 or 2 tumors. No outcome correlation with status of LVSI one of the most important risk factor.

Meta-analyses (Johnson 2007; Kong et al., 2007):

- Suggest that pelvic EBRT may improve DFS for high-risk patients, such as those with IC grade 3 disease.

SEER (Lee et al. 2006):

- Review of 21,249 patients with stage I disease treated with (19.2%) or without (80.8%) adjuvant RT.
- **Adjuvant RT improved OS and RFS for IC grade 1 and IC grade 3–4 patients, similar to results among patients who had a surgical LN examination.**

Evidence based management for Intermediate Risk group:

Patient tailored treatment is required.

- Depending on risk factors patients may be offered. Vault treatment only or EBRT + Vault radiation.
- Stage II disease needs to receive EBRT+ vault
- These patients are candidates for GOG 249, a phase III trial of pelvic RT or vaginal brachytherapy plus carboplatin and paclitaxel

Un-staged Intermediate Risk disease:

Evidence for Risk of LN involvement:

GOG 33 – Creasman et al Cancer 1987:

- Tumor limited to endometrium <5% (all Grades)
- Invading mid 1/3 of Myo 5-10% (all grades)
- Invading outer 1/3 Myo
    - 10% for Grade 1
    - 20% for Grade 2
    - 30% for Grade 3
- Good correlation with grade and myometrial invasion as well noted in GOG 33

PORTEC data- Creutzberg et al 2011:

- Randomized to TAH+BSO+Washings +/- LND
- No significant difference in OS after median FU of 13ys
- *Significantly lower locoregional recurrence*
- Not significant difference in rate of distant metastasis (9vs7%)

MRC ASTEC DATA 2009:

1408 clinically diagnosed as having corpus confined disease

- LND did not have impact on OS or PFS

LN metastasis as a function of various factors

Pelvic, Para-aortic, Risk Factor Histology	Patients	*n* (%)
Endometrioid	599	56 (9)
Others	22	2 (9)
Grade		
1 Well	180	5 (3)
2 Moderate	288	25 (9)
3 Poor	153	28 (18)
Myometrial invasion		
Endometrial	87	1 (1)
Superficial	279	15 (5)
Middle	116	7 (6)
Deep	139	35 (25)
Tumor location		
Fundus	524	42 (8)
Isthmus/Cervix	97	16 (16)
Capillary-like space involvement		
Negative	528	37 (7)
Positive	93	21 (23)
Other extra uterine metastasis		
Negative	586	40 (7)
Positive	35	18 (51)
Peritoneal cytologic findings		
Negative	537	38 (7)
Positive	75	19 (25)

Evidence based management for unstaged corpus confined disease:

- Based on GOG 33, offer patients for completion of staging as the management plan might change
- Based on PORTEC and ASTEC data, offer pelvic RT+/- Vault RT. However remember these 2 studies excluded intermediate risk stage 1b, GIII (AJCC 2009)

Appendix 6: Studies on Patients with Extra-Uterine Disease

GOG 122 (Randall et al. 2006)

- *Three hundred and ninety-six p*atients with III/IV disease treated with surgery with maximal residual disease ≤2 cm.
- 21% of patients had UPSC in each arm.
- Randomized to WART (30 Gy + 15 Gy pelvic boost + 15 Gy para-aortic boost if pelvic LN+ or no sampling of pelvic and para-aortic LN vs. chemo (doxorubicin + cisplatin every 3 weeks × 7c → cisplatin × 1c).
- Chemo improved 5-year OS (42→55%) and DFS (38→50%), but increased grade 3–4 hematologic, gastrointestinal, and cardiac toxicity.
- **Ontario Canada group (Lupe et al. 2007) Thirty-three patients with III/IV disease treated with carboplatin/paclitaxel every 3 weeks × 4c, then pelvic RT 45 Gy, then 2 more cycles chemo. PART and/or VC HDR were optional.**
- **2-year DFS and OS 55%, with only 3% pelvic relapse.**

These findings suggest that the pelvic control achieved is similar to intermediate risk group with the use of pelvic RT.

RTOG 9708 (Greven et al. 2006)

- Phase II trial of 46 patients with grade 2–3 disease with either >50% myometrial invasion and cervical stromal invasion or pelvic-confined extra uterine disease treated with WP RT (45 Gy) and cisplatin on days 1 and 28.
- Four-year pelvic, regional, and distant recurrence rates were 2%, 2%, and 19%, respectively.
- **Four-year OS and DFS were 85% and 81%, respectively. There were no recurrences for stages IC, IIA, or IIB.**
- These patients were definitely at a higher risk of the intermediate risk group; however, the locoregional control was similar showing the importance of RT besides systemic chemo as in previous studies.

There was a subsequent RTOG 9905 with similar aim for patients with >50% myo or involvement of cervix only, closed because of non-accrual.

EORTC 55991: Phase III study showed PFS 75% vs. 82% in favor of chemo RT for high risk early stage. Currently 2 studies looking in to this are GOG 249 and PORTEC3.

Italian (Maggi et al. 2006):

- 345 patients IC G3, Stage II G3 with >50% myometrial invasion, and IIIA-IIIC. Randomized to pelvic RT 45–50 Gy vs. CAP chemo (cyclophosphamide/doxorubicin/cisplatin) monthly x 5c.
- Note 64% of the patients had stage III disease.
- No difference in 7-year OS 62% or PFS 56–60%.
- RT delayed LF (11→7%)
- Chemo delayed DM (21→16%)

Japanese GOG (JGOG) (Susumu et al. 2008):

- 385 patients with stage IC-III with >50% myometrial invasion treated with surgery and pelvic LN dissection randomized to pelvic RT (45–50 Gy) vs. CAP chemo (cyclophosphamide, doxorubicin, cisplatin) every 4 weeks for 3c. Only 3% received brachytherapy.
- No difference in 5-year PFS (82–84%) or OS (85–87%).

On subset analysis,

- No difference for Stage ICG1-2 <70 years
- But chemo improved PFS (66→84%) and OS (74→90%) for higher-risk group (ICG3 or IC >70 years or stage II or IIIA (+cytology)).
- Seven percent pelvic failures in each arm, but fewer vaginal recurrences in RT arm.
- No differences in extra pelvic recurrences (~15%).

Appendix 7: Studies on Patients with Uterine Carcinosarcoma

Uterine Papillary Serous Carcinoma Consortium:

142 patients with Stage I. Suggested Observation.(patients were treated with RT vs. chemo after surgery)

- **GOG 94 Sutton et al Gyn Onc 2006This was a phase II study.**
- **At 5ys 51% recurrences were in field**
- **5ys PFS 38% for UPSC and 54% for CCC**
- **Suggestion was for systemic chemo.**

GOG 150 (Wolfson et al. 2007):

- *Two hundred and thirty-two* patients with stage I-IV uterine carcinosarcoma < 1 cm residual and/or no extra abdominal spread randomized to WART (whole abdomen 30 Gy/pelvis 49.8-50 Gy at 1 Gy bid or 1.5 Gy QD) vs. chemotherapy (cisplatin/ifosfamide/mesna × 3c).
- No significant difference in recurrence rate or survival between the two arms.

EORTC 55874 (Reed et al. 2008):

Two hundred and twenty-four women with stage I/II of all uterine sarcoma subtypes after TAH/BSO/washings with optional nodal sampling randomized to observation vs. post-op WP RT (50.4 Gy).

- RT reduced LRR (22% vs. 40%), but had no effect on OS, PFS, or DM.
- **In subset analysis, WP RT increased LC for carcinosarcomas, but not leiomyosarcomas.**

Fields et al 2008: Gynecol Oncol

Trial	Description
Fields et al	■ 30 patients with stages I–IV UPSC were treated with pelvic radiation therapy (RT) "sandwiched" between 6 cycles of paclitaxel/platinum (TP) chemotherapy after TAH/BSO ■ Pelvic RT equals 45 Gy in 25 daily fractions with a four-field pelvic technique; a para-aortic field was added when 2 or more lymph nodes were positive; patients also received vaginal brachytherapy ■ TP equals 3 cycles of paclitaxel and platinum (cisplatin or carboplatin) were given every 3 weeks; the final 3 cycles were also given every 3 weeks after radiation therapy ■ Median survival for all patients was 34 months ■ Stages I–II patients had a 3-year DFS and OS of 69 and 75%, respectively ■ Stages III–IV patients had a 3-year DFS and OS of 54 and 52%, respectively ■ Grades 3–4 neutropenia, thrombocytopenia, or anemia occurred in 42, 1, and 3%, respectively

SEER data base review Wright et al 2008. Adjuvant RT possible survival benefit with early MMM but not LMS.

Mayo clinic report Giuntoli et al 2003.

- 208 patients with LMS. RT no impact on DSS (p=0.06) but associated with significant improvement in LR