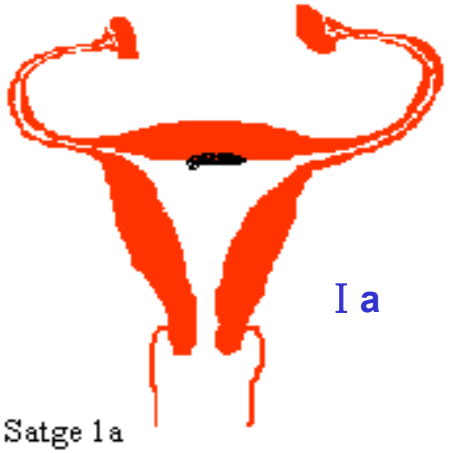
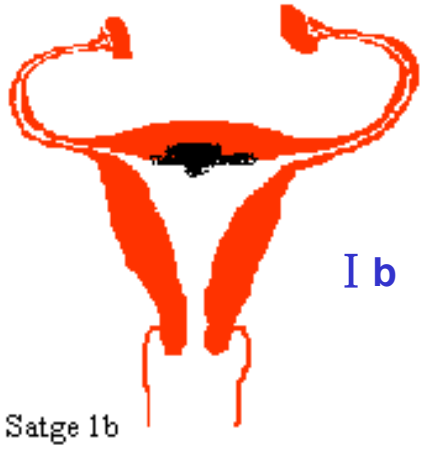
子宫内膜癌分期（FIGO　）

I　肿瘤限于子宫体
　　IA　肿瘤浸润深度<1/2肌层
　　IB　肿瘤浸润深度≥1/2肌层
II　肿瘤浸润宫颈间质，但无宫体外蔓延
III 肿瘤局部和（或）区域扩散
　　IIIA 肿瘤累及浆膜层和（或附件）
　　IIIB肿瘤累及阴道和（或）宫旁
　　IIIC盆腔淋巴结和（或）主动脉旁淋巴结转移
　　IIIC1盆腔淋巴结转移
　　IIIC2主动脉旁淋巴结转移伴有（或无）盆腔淋巴结转移
IV肿瘤浸及膀胱和（或）直肠粘膜，和（或）盆腔淋巴结转移
　　IV1肿瘤浸及膀胱或直肠粘膜
　　IV2远处转移，包括腹腔内和（或）腹股沟淋巴结转移

手术病理分期（FIGO，1988，　）
Surgical Stage

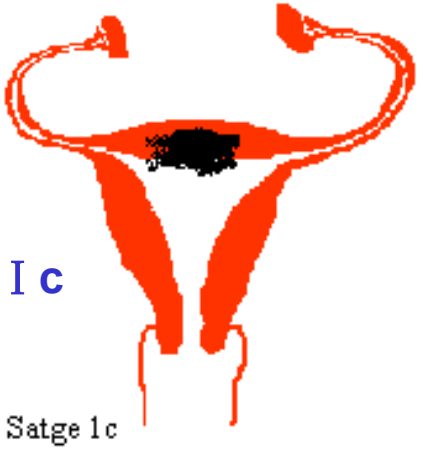
Ⅰa

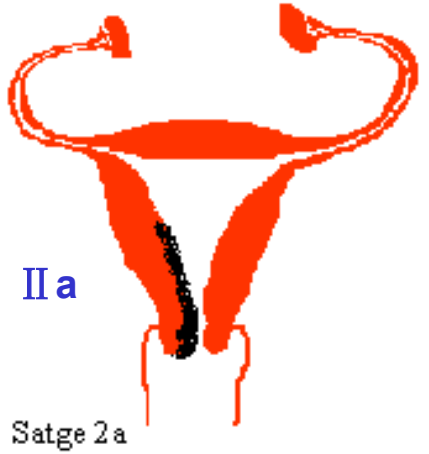


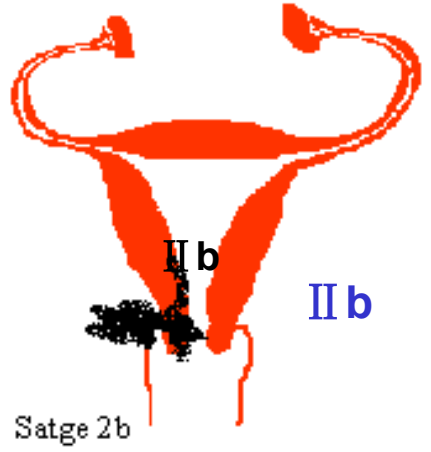


Ⅱ

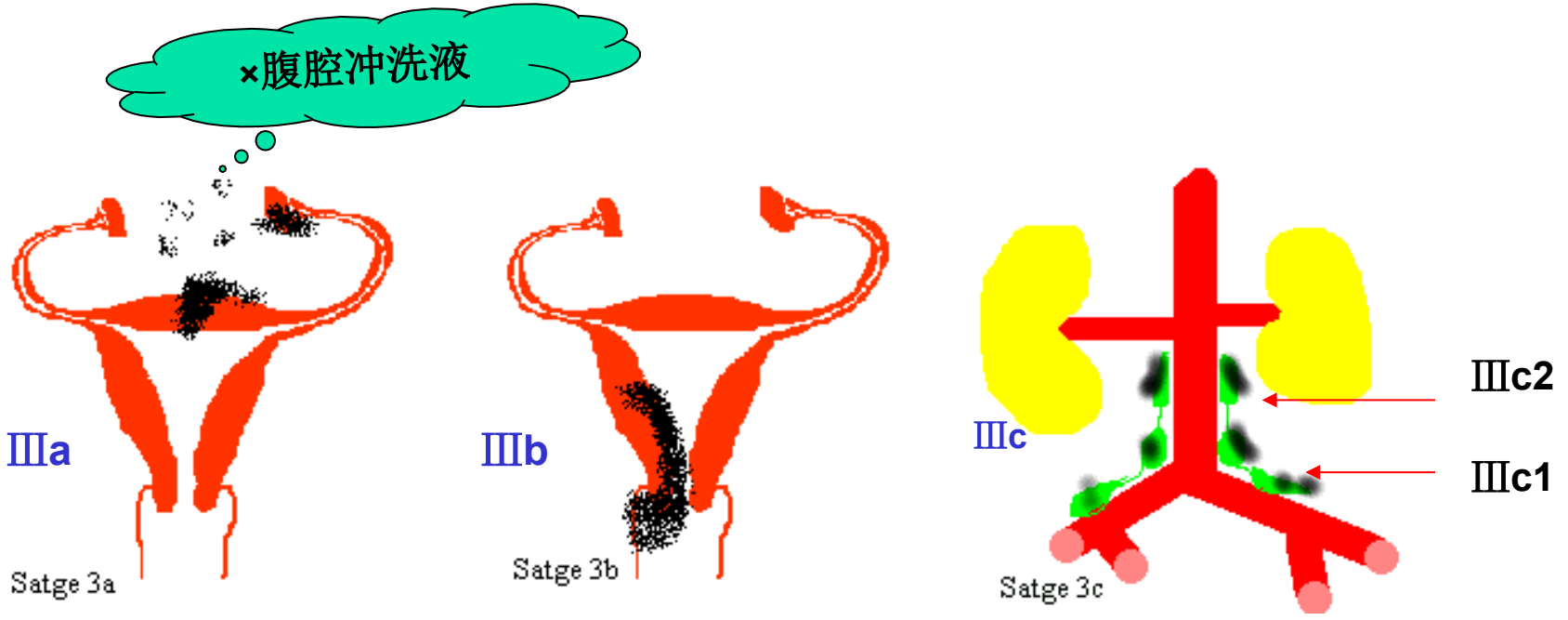
Ⅰb







手术病理分期（FIGO，1988，　）
Surgical Stage



Ⅳa期：癌瘤浸润膀胱或直肠粘膜
Ⅳb期：远处转移

早期子宫内膜癌

GOG：仅考虑细胞分化程度和肌层浸润，5年生存率92.7%

Relationgship between surgical-pathologic risk factors and outcome in stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol,1991,40:55-65.

I期术后的辅助治疗

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2012
Endometrial Carcinoma

NCCN Guidelines Index
Uterine Neoplasms TOC
Discussion

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS	ADVERSE RISK FACTORS[m]	HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,n] G1	G2	G3
Completely surgically staged: Stage I — Stage IA (< 50%) myometrial invasion	Adverse risk factors not present	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
	Adverse risk factors present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT (category 2B for pelvic RT)	Observe or Vaginal brachytherapy and/or Pelvic RT
Stage IB (≥ 50%) myometrial invasion	Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or Pelvic RT
	Adverse risk factors present	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT	Pelvic RT and/or Vaginal brachytherapy ± chemotherapy[o,p] (category 2B for chemotherapy) or Observe (category 2B)

II期术后辅助治疗

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2012
Endometrial Carcinoma

NCCN Guidelines Index
Uterine Neoplasms TOC
Discussion

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,n,p]		
	G1	G2	G3
Completely surgically staged: Stage II[q,r] →	Vaginal brachytherapy and/or pelvic RT	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy ± chemotherapy[o,p] (category 2B for chemotherapy)
Completely surgically staged: Stage IIIA →	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy

问题

- 哪些需要术后辅助治疗
- 哪些腔内放疗足够
- 哪些的确需要盆腔放疗

术后复发及转移的高危因素

- **高危因素：**

  细胞学分化程度

  肌层浸润

  病理类型

- **相对高危因素：**

  年龄

  脉管瘤栓

  肿瘤大小

  子宫下段（宫颈腺体）受累

Prognostic Factors

Effect of individual prognostic factors on relative risk to survival

Prognostic factor	Relative risk
▪Endometrioid histology	
Grade 1	1.0
Grade 2	1.6
Grade 3	2.6
▪Serous histology	
Grade 1	2.9
Grade 2	4.4
Grade3	6.6
▪Myometrial penetration	
endometrium only	1.0
inner 1/3	1.2
inner 2/3	1.6
outer 1/3	3.0
▪Positive washings	3.0
▪Age	
45 years	1.0
65 years	3.4
Lymphovascular space involvement	1.5

Keys et Al. A phase III trial of Surgery vs with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. Gynec. Oncology. 92(3). 744-751. 2004

Prognostic Factors

危险因素	5年生存率
多于2个	17%
2个	66%
无或1个	95%

Creutzberg et Al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma;multicentric randomised trial. Lancet. 355: 1404-1411. 2000

危险度分组I（Risk Classification ）

- **低危组（LR）**:肿瘤限于子宫,侵犯肌层<50%,高、中分化

- **中危组（IR）**:侵犯子宫肌层≥50%,或G3,或宫颈受侵。再根据3个高危因素：脉管瘤栓，外1/3肌层受累，分化程度（G2，G3）

  中高危（HIR）：3个高危因素，任何年龄；

  2个高危因素及50至69岁；

  1个高危因素及70岁以上.

  中低危（LIR）：除上述中高危组以外的中危组

- **高危组（HR）**:子宫外或淋巴结转移。

Relationgship between surgical-pathologic risk factors and outcome in stage I and II carcinomaof the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol,1991,40:55-65.

A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: aGynecologic Oncology Group study.Gynecol Oncol. 2004 Mar;92(3):744-51.

危险度分组II（Risk Classification ）

- 低危组（LR）：局限于子宫内膜的G1和G2期的子宫内膜样腺癌
- 中危组（IR）：病变局限于子宫，但肌层受侵或宫颈间质受侵，包括 部分IA期，全部IB期，部分II期。再根据3个高危因素：脉管瘤栓，外1/3肌层受累，分化程度（G2，G3）
- 中高危（HIR）：3个高危因素，任何年龄；
- 2个高危因素及50至69岁；
- 1个高危因素，70岁以上.
- 中低危（LIR）：除上述中高危组以外的中危组
-
- 高危组（HR）：包括任何分化程度的宫颈大肿瘤受累，III期，IVA期，及特殊病理类型如papillary serous or clear cell uterine tumors

- Contemporary management of endometrial cancer.Lancet. Apr 7;379(9823):1352-60.

危险度分组III（Risk Classification ）

- 低危组（LR）:I期子宫内膜样腺癌，G1和G2期，肌层受侵〈50%

- 中危组（IR）：其它的I期子宫内膜样腺癌。
- 中低危（LIR）：年龄<60岁；
- G1或G2且肌层受累>50%；
- G3肌层受侵<50%；
- 无脉管瘤栓。
- 中高危（HIR）：年龄>60岁；
- G1或G2且肌层受累>50%；
- G3肌层受侵<50%.

- 高危组（HR）：I期的G3且肌层受累>50%，II期，III期的子宫内膜样腺癌,及特殊病理类型如papillary serous or clear cell uterine tumors.
-
- Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000 Apr 22;355(9213):1404-11.
- The Role of Radiotherapy in Endometrial Cancer:Current Evidence and Trends。Curr Oncol Rep ( ) 13:472-478

低危组

子宫内膜样腺癌IA期，肌层受侵〈50%，G1和G2期

- 5年生存率达95%以上；
- 放疗不能改善局控率（包括阴道残端），总复发率及总生存率；
- 增加治疗相关并发症
- 局部复发后治疗仍取得高生存率。

- 结论：不需要辅助治疗

- Elliott P, Green D, Coates A, et al. The efficacy of postoperative vaginal irradiation in preventing vaginal recurrence in endometrial cancer.
- Int J Gynecol Cancer 1994; 4: 84－93.
- Karolewski K, Kojs Z, Urbanski K, et al. The effi ciency of treatment in patients with uterine-confined endometrial cancer. Eur J Gynaecol Oncol 2006; 27: 579－84.
- Touboul E, Belkacemi Y, Buff at L, et al. Adenocarcinoma of the endometrium treated with combined irradiation and surgery:study of 437 patients. Int J Radiat Oncol Biol Phys 2001; 50: 81－97.
- Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol 2000; 182: 1506－19.
- Sorbe B, NordstromB, Maenpaa J, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. Int J Gynecol Cancer ;19: 873－78.

中危组及高危组（早期子宫内膜癌）

目前无令人信服的研究证实辅助治疗提高生存率。

- 中低危组
- 中高危组

术后辅助放疗

	Sample size	Inclusion criteria	Surgery	Treatment	Locoregional recurrence	Overall survival
Norwegian Radium Hospital[57]	540	Stage I (all)	TAH or BSO	Brachytherapy *vs* brachytherapy and pelvic radiotherapy	7% *vs* 2% (5 year) p<0·01	89% *vs* 91% (5 year) p=N
PORTEC-1[55]	715	Stage IB (grade 2, 3), stage IC (grade 1, 2)	TAH or BSO (LNS allowed)	Observation *vs* pelvic radiation	14% *vs* 4% (5 year), p<0·0001	85% *vs* 81% (5 year), p=0
GOG 99[56]	392	Stage IB, stage IC, stage II occult	TAH or BSO or LNS	Observation *vs* pelvic radiation	12% *vs* 3% (2 year), p=0·007	86% *vs* 92% (4 year), p=0
ASTEC[58]	905	Stage IA or IB (grade 3), IC, IIA	TAH or BSO with or without LNS	Observation *vs* pelvic radiation	6·1% *vs* 3·2% (5 year), p=0·02	84% *vs* 84% (5 year), p=0
PORTEC-2[59]	427	Stage IC (grade 2, 3, age >60 years), IB (grade 3, age >60 years), IIA	TAH or BSO with or without LNS	Brachytherapy *vs* pelvic radiation	5·1% *vs* 2·1% (5 year), p=0·42	86% *vs* 82% (5 year), p=0

TAH=total abdominal hysterectomy. BSO=bilateral salpingo-oophorectomy. LNS=lymph node surgery. NS=not significant.

***Table 3*: Randomised controlled trials of adjuvant therapy for intermediate-risk endometrial cancer**

Contemporary management of endometrial cancer. Apr 7;379(9823):1352-60

The Norwegian trial

方法： 540 患者，手术+镭腔内放疗后，随机分为不加盆腔放疗组及加盆腔淋巴结放疗.随访3-10年。

结果：

1. 盆腔放疗组阴道残端及盆腔的复发率明显下降(1.9 vs 6.9%, P < .01)
2. 盆腔放疗组远处转移率则增加 (9.9 vs 5.4%).
3. 5年生存率无差异（91% vs 89%）
4. G3，肌层浸润大于50%的患者在局控率和总生存率上可能受益（18% vs 27%），但样本量小，无统计意义。

Aalders J, Abeler V, Kolstad P, Onsrud M.Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980 Oct;56(4):419-27.

PORTEC-1
(Postoperative Radiation Therapy in Endometrial Carcinoma)

方法：715I期子宫内膜样腺癌，G1肌层浸润大于50%，G2，G3肌层浸润小于50%. TAH-BSO，随机分为术后体外放疗（46Gy/2Gy）和不加治疗组。

结果：

1. 局部复发率：5年 4% vs 14% (p<0.001)，10年 5% vs 14% (p<0.001)
2. OS：5年 81% vs 85% （p=0.31）. 10年：68% vs 73% （p=0.14）。
3. 肿瘤相关死亡率：5年 9% vs 6% (p=0.37).10年 10% vs 8% (p=0.47).
4. 治疗相关并发症：25% vs 6% (p<0.0001).
5. 阴道复发后5年生存率64%，盆腔复发及远处转移11%。
6. 未加放疗组局部复发75%位于阴道残端，治疗后5年生存率70%。
7. 局部复发相关高危因素：G3，大于60岁，肌层浸润大于50%。

Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000 Apr 22;355(9213):1404-11.

Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys. 2005;63:834–8.

PORTEC-1

结论:

- I期子宫内膜癌，术后放疗可降低局部复发率，但不提高总生存率.
- 放疗增加治疗相关并发症.
- 60 岁以下和G2肌层浸润小于50%的I期患者不建议术后放疗.

Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000 Apr 22;355(9213):1404-11.

Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys. 2005;63:834–8.

GOG99

方法：448 IR（IB, IC, and II ），其中HIR 33%，TAH-BSO+淋巴结切除术，随机分成盆腔放疗（50.4Gy/1.8Gy）和不加治疗组。

结果：

1. OS无差异：4年 92%（放疗组） vs 86%（对照组）(RH: 0.86; P=0.557).
2. 放疗减少局部（阴道及盆腔）复发： 18 （对照组）and 3 （放疗组）；
3. HIR组CIR（累积复发率）： 2-year 26%（对照组） versus 6%（放疗组）；4年27% vs 13%；
4. HIR组复发率增加；
5. LVSI与淋巴结转移，远处转移强相关。
6. 治疗相关严重并发症：4年13%；

A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study.Gynecol Oncol. 2004 Mar;92(3):744-51.

GOG99

结论:

1. 早期子宫内膜癌中危组，术后辅助放疗降低复发风险，不提高总生存率
2. 术后辅助放疗限于HIR。
3. 术后放疗增加治疗相关并发症。

A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study.Gynecol Oncol. 2004 Mar;92(3):744-51.

ASTEC and EN5 trials

方法: 905， FIGO stage IA and IB G3; IC 和IIA all grades; 特殊病理类型，手术（淋巴结是否切除不限），随机体外放疗（40-46Gy）或观察. 腔内治疗不限，包括观察组。

结果:

OS：5年两组均为84%, hazard ratio 1.05 (95% CI 0.75-1.48; p=0.77).

观察组53%进行腔内治疗, 5 years 局部复发率 6.1%. 体外放疗组为3.2%

结论: 早期子宫内膜癌体外放疗既不能减少局部复发，也不能提高生存率。

Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet. ;373:137–46. Largest randomized trial comparing pelvic EBRT to no adjuvant treatment after surgery for stage I EC.

术后辅助放疗

样本人群：21,249 patients ，stage IA-IC， node-negative endometrial adenocarcinoma。

19.2%接受放疗，包括EBRT(62.5%)， VBT(17.9%) ， both(26.4%)

结论：IC期患者，术后辅助放疗提高了总生存率和相对生存率（p〈0.001）

Lee CM, Szabo A, Shrieve DC, Macdonald OK, Gaff ney DK. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. JAMA 2006; 295: 389–97.

Meta分析1

分析对象：5个临床实验比较EBRT对I期子宫内膜癌的作用。.

结果:

低危组(IA, IBG1，G2) ：OR for overall survival 0.71; 95% CI 0.52-0.96).

中危组 (IC G1/2 and IBG3)：OR 0.97; 95% CI 0.69-1.35.

高危组（IC G3 ）：DFS OR 1.76; 95% CI 1.07-2.89

结论:

中低危组(IA, IBG1，G2)不能从术后EBRT获益。

高危组（IC G3 ）： DFS可获益10%。

Survival and recurrent disease after postoperative radiotherapy for early endometrial cancer: systematic review and meta-analysis. BJOG. 2007 Nov;114(11):1313-20. Epub 2007 Sep 5.

Meta分析2

分析对象：8个随机临床研究比较I期子宫内膜癌术后辅助放疗（EBRT或/和VBT），单纯VBT和观察组。其中6个研究为高质量研究。

结论:

低危患者不建议术后辅助放疗。

EBRT（with or without VBT）减少局部复发风险，但总生存率，肿瘤相关死亡率及远处转移率未获益。

HIR亚组，EBRT不能提高OS，VBT可有效控制阴道残端复发。

由于HR亚组入组有限，不排除EBRT生存率获益可能。

EBRT增加治疗相关并发症，降低生活质量。

未来增加对高危因素的定义及研究

Adjuvant radiotherapy for stage I endometrial cancer。Cochrane Database Syst Rev. Apr 18;4:CD003916.

术后辅助放疗

- 辅助放疗减少局部复发，但不影响总生存率。
- 放疗后相关并发症尤其是严重并发症增加。
- 局部复发率与高危因素相关。
- LIR辅助放疗局控率无明显改善(<5%)。
- 辅助放疗建议限于有局部复发高位因素如HIR和HR亚组。

放疗方式选择

- EBRT
- VBT
- Both

PORTEC-2(EBRT VS VBT)

- 方法: 427，HIR（stage I or IIA endometrial carcinoma），手术，pelvic EBRT (46 Gy in 23 fractions; n=214) or VBT (21 Gy high-dose rate in three fractions, or 30 Gy low-dose rate; n=213).

- 结果:
- 预计5年阴道复发率：1.8% for VBT and 1.6 for EBRT (HR 0.78, 95% CI 0.17-3.49; p=0.74).
- 5年局部复发率： 5.1% for VBT and 2.1% for EBRT (HR 2.08, 0.71-6.09; p=0.17).
- 5年盆腔复发率：1.5% (0.5-4.5) versus 0.5% (0.1-3.4) (HR 3.10, 0.32-29.9; p=0.30),
- 远处转移率： 8.3% [5.1-13.4] vs 5.7% [3.3-9.9]; （HR 1.32, 0.63-2.74; p=0.46).
- OS： 84.8% [95% CI 79.3-90.3] vs 79.6% [71.2-88.0]; （ HR 1.17, 0.69-1.98; p=0.57)
- DFS：82.7% [76.9-88.6] vs 78.1% [69.7-86.5]; （HR 1.09, 0.66-1.78; p=0.74).
- 急性胃肠道毒性：12.6% [27/215] vs 53.8% [112/208]).

- Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. Mar 6;375(9717):816-23.

PORTEC-2(EBRT VS VBT)

结论：

VBT与EBRT在局部复发，远处转移及生存率无差异。

VBT相对EBRT可减少治疗相关并发症，提高生活质量。

VBT建议作为HIR的术后辅助治疗。

The Norwegian trial(VBT VS EBRT+VBT)

方法： 540 患者，手术+镭腔内放疗后，随机分为不加盆腔放疗组及加盆腔淋巴结放疗.随访3-10年。

结果:

1. 盆腔放疗组阴道残端及盆腔的复发率明显下降(1.9 vs 6.9%, P < .01)
2. 盆腔放疗组远处转移率则增加 (9.9 vs 5.4%).
3. 5年生存率无差异（91% vs 89%）
4. G3，肌层浸润大于50%的患者在局控率和总生存率上可能受益（18% vs 27%），但样本量小，无统计意义。

Aalders J, Abeler V, Kolstad P, Onsrud M.Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980 Oct;56(4):419-27.