8）症例提示

症例　子宮内膜多発ポリープ（図83）

　49歳，閉経前．過多月経で受診し内膜肥厚精査で紹介受診．経腟超音波検査で内膜肥厚像と多発腫瘤像を示した．ファイバースコープでは，淡紅色で表面平滑で血管に乏しいポリープの多発を認めた．
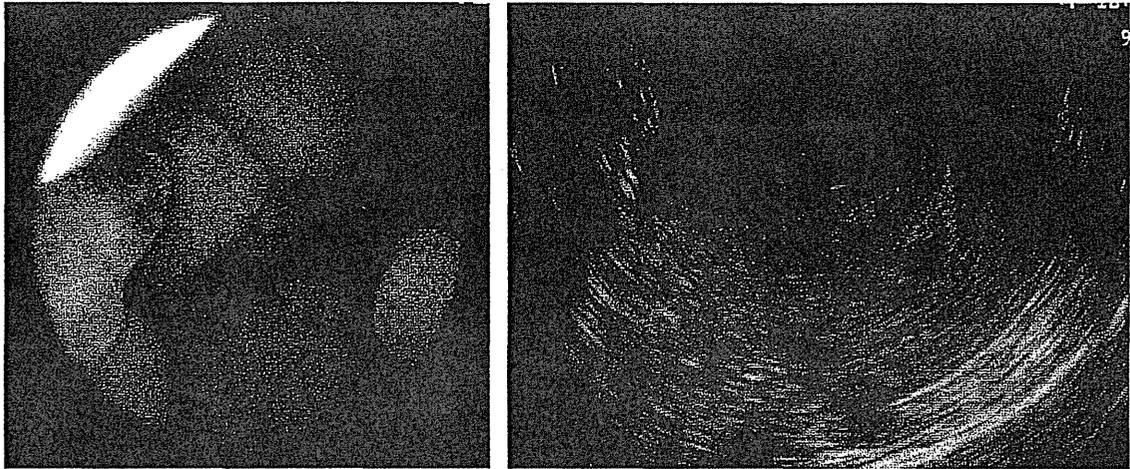

図83．子宮内膜多発ポリープ

症例　閉経後子宮内膜ポリープ（図84）

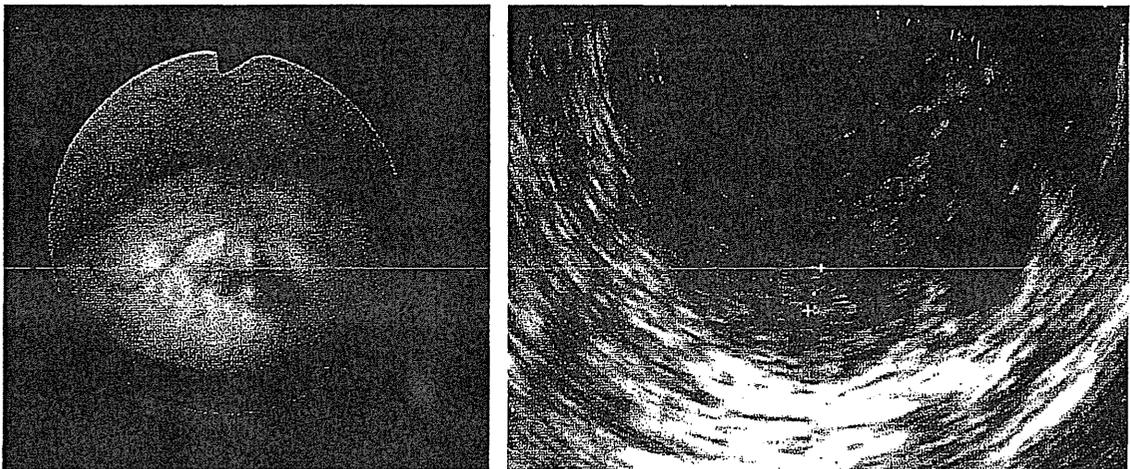　56歳，閉経後．内膜細胞診クラスⅢで紹介受診．経腟超音波検査で楕円状の小腫瘤像を呈し，ファイバースコープでは淡桃色の萎縮内膜を背景に白色，結節状腫瘤が出現，異型のない血管が少数走行する．

図84．閉経後子宮内膜ポリープ

92

症例　粘膜下筋腫（図85）

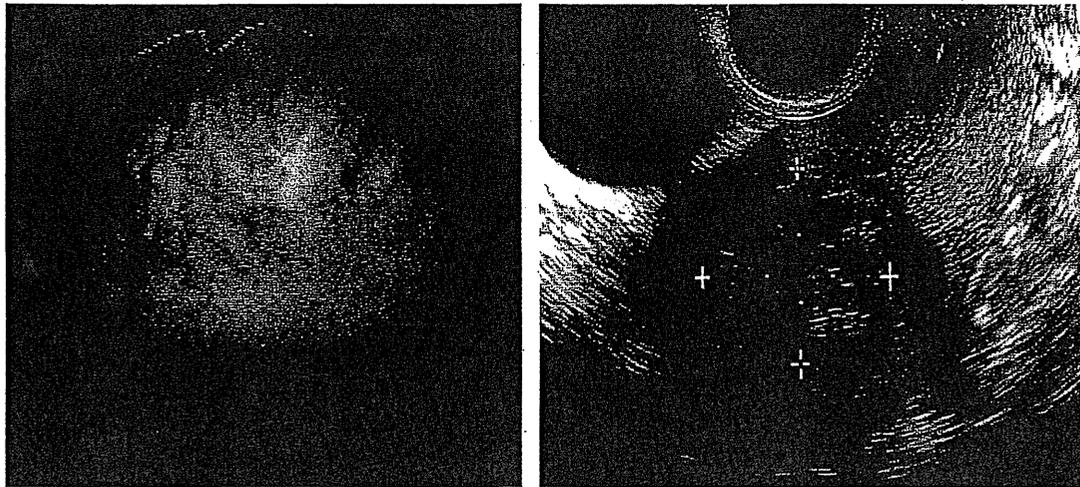31歳，月経困難症で超音波検査とMRI検査で子宮内膜腫瘍指摘．経腟超音波検査で類円形，充実性腫瘍をみる．ファイバースコープでは淡紅色，平滑な腫瘍を認め，拡張血管が走行するが異型は軽度である．

図85．粘膜下筋腫

症例　子宮内膜ポリープ（タモキシフェン服用3年）（図86）

63歳，検診で子宮内膜肥厚，内膜細胞診クラスII．経腟超音波画像では多発小囊胞状の内膜肥厚像を呈する．ファイバースコープでは淡紅色球状腫瘍を認め拡張血管が走行する．ポリープ表面に散在する微小囊胞を認める．
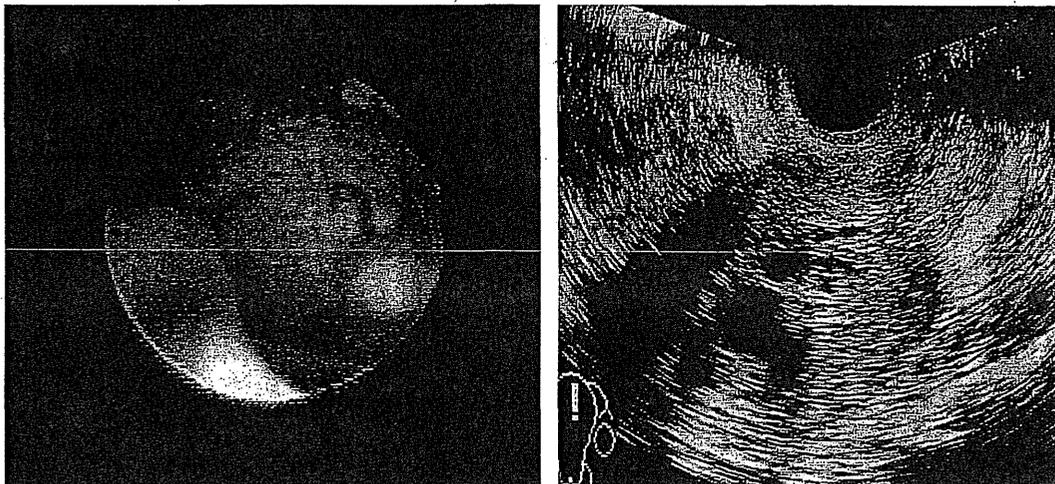

図86．子宮内膜ポリープ（タモキシフェン服用3年）

症例　単純型子宮内膜増殖症(図87)

44歳，過多月経があり，内膜細胞診クラスⅢ，超音波検査とMRI検査で内膜肥厚を認め精査で紹介受診．経腟超音波検査で，均一な内膜肥厚像を認める．ファイバースコープでは，小ポリープ様腫瘤が無数に増生するのを認めるが，異型血管は認めない．

図87．単純型子宮内膜増殖症
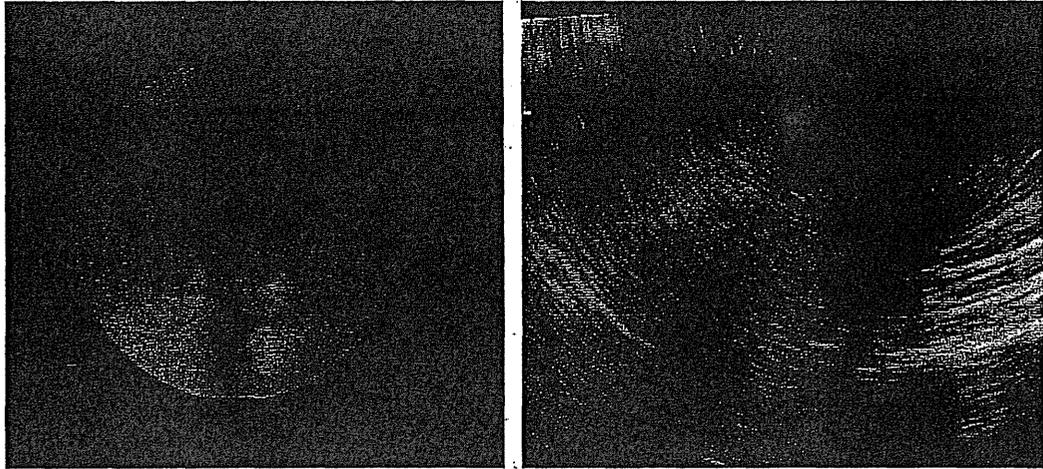
症例　複雑型子宮内膜異型増殖症(図88)

44歳，細胞診異常，超音波検査で内膜肥厚があり紹介受診．経腟超音波検査では，外縁に不整のない内膜に高輝度の小部分が充満する内膜肥厚像．ファイバースコープでは，小ポリープ状の平滑な腫瘤が不規則に増生する．血管に乏しく，出血像はみられない．
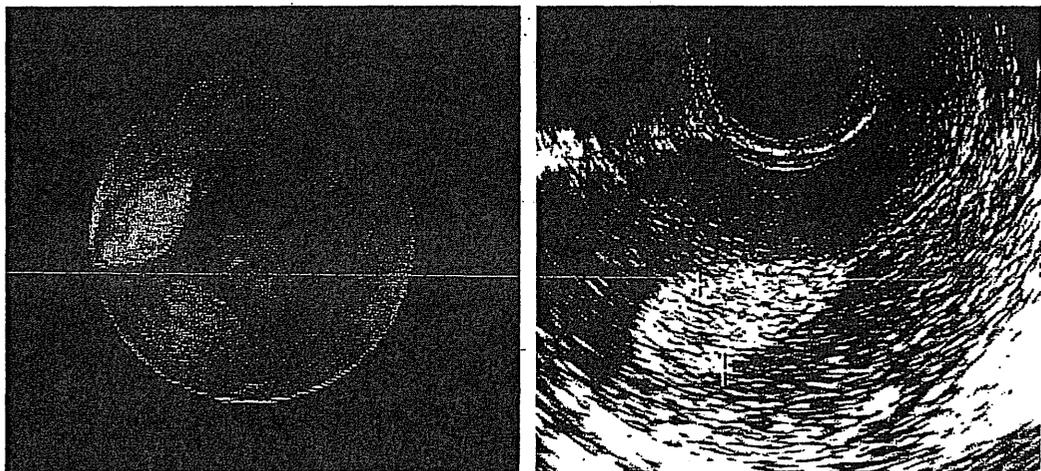
図88．複雑型子宮内膜異型増殖症

症例　高分化型類内膜腺癌（図89）

64歳，性器出血があり，内膜細胞診クラスⅢ．経腟超音波検査では，明らかな腫瘤像なし．ファイバースコープでは，易出血性の乳頭状腫瘤が局在し，内膜は萎縮性である．
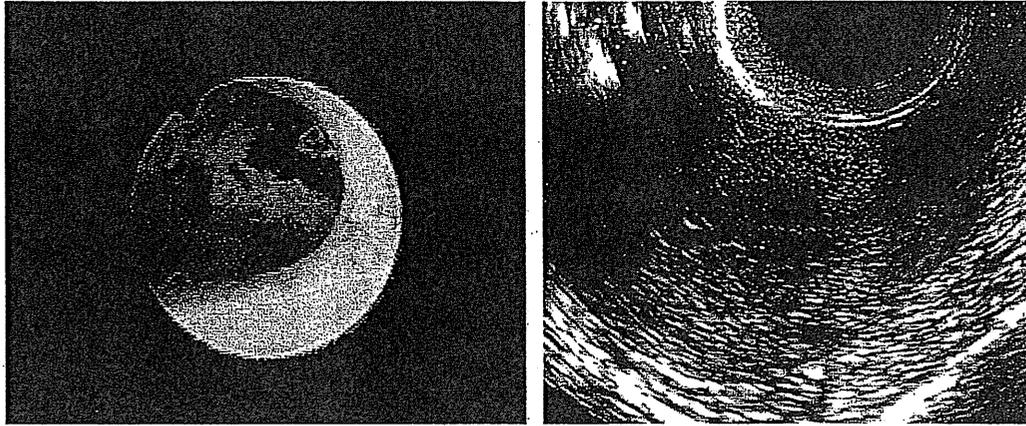
図89．高分化型類内膜腺癌

症例　癌肉腫（図90）

69歳，性器出血で受診．経腟超音波検査で不規則腫瘤像．ファイバースコープでは，淡紅色腫瘤形成，怒張，途絶走行する拡張異型血管が増生．内膜生検は類内膜腺癌G2と診断．

図90．癌肉腫

95

症例　漿液性腺癌(図91)

67歳，帯下で受診．内膜細胞診クラスⅤ．経腟超音波検査で小腫瘤様像(白円)．ファイバースコープでは，黄色調の凹凸のある結節状腫瘤を認め，摘出子宮で癌病巣(白円)を確認した．
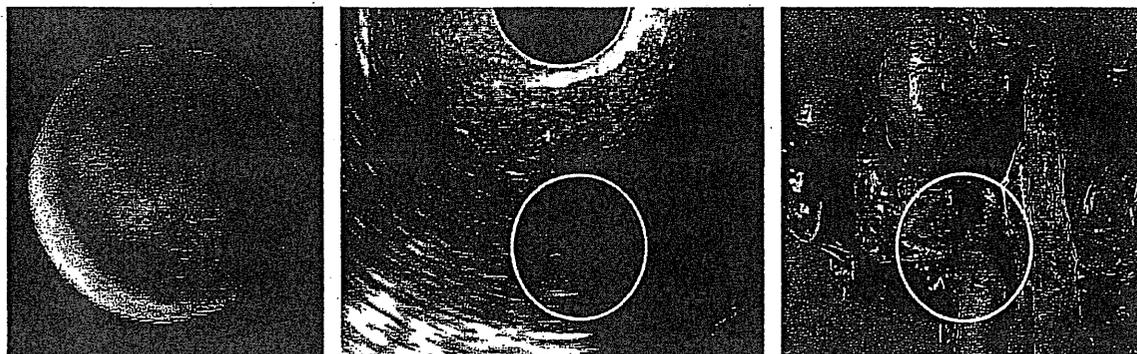
図91．漿液性腺癌

症例　子宮肉腫(図92)

52歳，持続性器出血，前医で肉腫を疑われ受診．経腟超音波検査で変性筋腫様像．細胞診は頸部クラスⅤ，内膜クラスⅠ．頸部生検でCIN1．3か月後の細胞診は頸部がクラスⅤ，内膜が不適の診断．5か月後にヒステロスコピーを施行した．ファイバースコープでは，拡張血管が走行する腫瘤と易出血性の不整内膜面を認め，肉腫の内膜露出を疑った．

図92．子宮肉腫

96
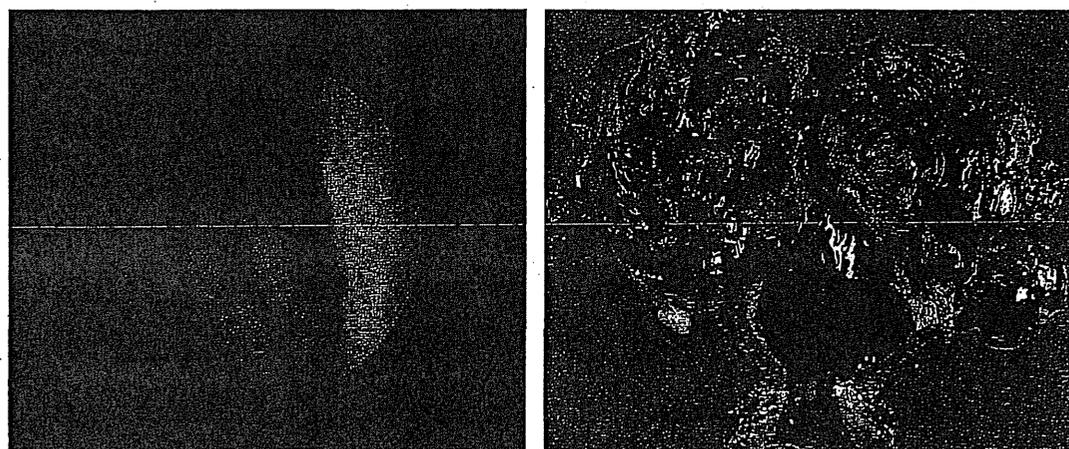
症例　高分化型類内膜癌，長期観察例(図93)

62歳，内膜細胞診クラスⅤ，ヒステロスコピーで異常なく5年間フォローし，病巣が可視化，生検で高分化型類内膜腺癌と診断．ファイバースコープで底部に拡張血管が走行する平滑な隆起病変が散在．摘出子宮の病理診断では複雑型子宮内膜異型増殖症内に類内膜腺癌G1が混在(円内)した．

図93．高分化型類内膜癌，長期観察例

右腎盂尿管癌術後の再発膀胱摘出後に腟に再々発した移行上皮癌の臨床病理学的検討

松岡　直樹・大亀　真一・小島　淳美・白山　裕子・松元　隆・横山　隆・野河　孝充

四国がんセンター　婦人科

Clinicopathological diagnosis of the vaginal and uterocervical recurrence of urothelial carcinoma following cystectomy

Naoki Matsuoka・Shinichi Ookame・Atsumi Kojima・Yuko Shiroyama
Takashi Matsumoto・Takashi Yokoyama・Takayoshi Nogawa

Sikoku cancer center, department of gynecology

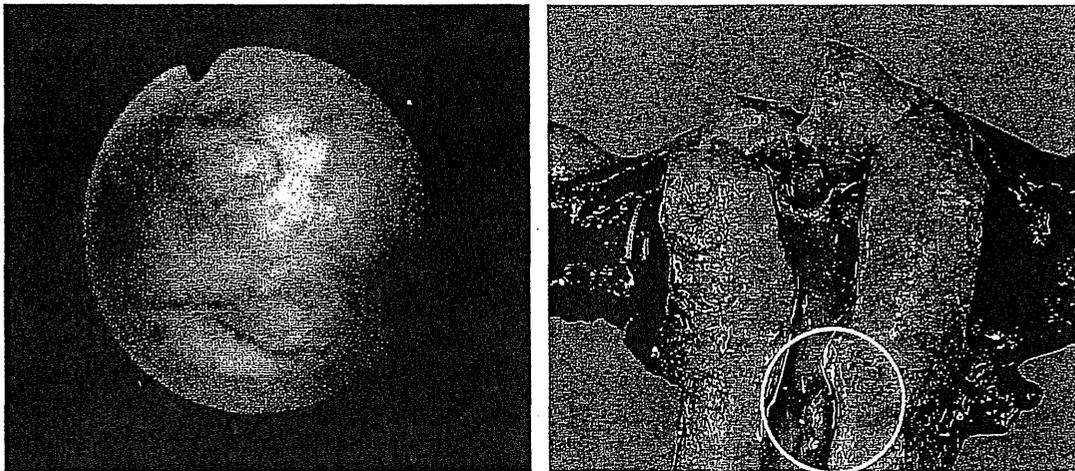腎盂尿管癌（移行上皮癌）は下部尿路へ進展するが，術後腟転移は極めて稀である。膀胱再発術後に腟，子宮頸部に再々発した移行上皮癌について臨床病理学的に文献的考察を交えて検討した。患者は74歳，5経妊3経産，64歳で食道癌手術の既往があり，71歳時に右腎盂尿管癌で右腎臓・尿管摘出，73歳時に膀胱再発し膀胱と尿道を摘出した。1年後，腟出血にて婦人科初診となり，診察で乳頭状腫瘍の腟全体への進展が認められた。腟の細胞診でclass V，組織診で移行上皮癌を病理診断され，子宮，両側附属器，腟全摘術を施行した。子宮頸部から腟全体に低乳頭状の未熟な移行上皮様腫瘍細胞が増生し，腎盂尿管癌の組織像と類似した形態を示し，免疫染色でkeratin 7, 20の両方が陽性であったことから腎盂尿管癌再々発と診断された。

以上より腎盂尿管癌などの移行上皮癌の既往患者には，リンパ行性や血行性，腟"implantation"などによる腟への進展も念頭にいれて積極的に外陰部および腟にも十分注意した婦人科検診を行うことが重要であることが示唆された。

Upper urinary tract cancer often spreads to the lower urinary tract, although vaginal recurrence of urothelial carcinoma following surgery is rare. We report a case of vaginal and uterocervical recurrence of urothelial carcinoma following cystectomy with clinicopathological diagnosis. The patient was a 74-year-old woman with a history of right upper urinary tract cancer. She underwent right nephroureterectomy when she was 71 years old, and after 2 years, she underwent cystectomy because of recurrence in the bladder. After 1 year of observation without treatment, she experienced vaginal bleeding, and papillary tumors spread throughout the vagina. The cytodiagnosis of the vagina was class V, and the histopathological diagnosis of the biopsy was transitional cell carcinoma (TCC). She underwent hysterectomy, bilateral salpingo-oophorectomy, and total vaginectomy. From the uterine cervix and vagina, the growth of papillary and immature cells similar to TCC was observed. Immunohistochemical analysis demonstrated intense reactivity of tumor cells for both cytokeratin 7 (CK7) and cytokeratin 20 (CK20), indicating that the TCC cells were of urinary tract origin. Histological and immunohistochemical examinations of the vagina revealed the recurrence of urothelial carcinoma. This case suggests the importance of careful, regular gynecological examinations in patients with a history of TCC.

緒　　言

腎盂尿管癌（移行上皮癌）は下部尿路へ進展することがあるが，術後の腟転移は極めて稀である。腎盂・尿管に発生した移行上皮癌の術後に膀胱再発し，膀胱・尿道摘出後，腎盂尿管癌の膀胱再発が認められ膀胱・尿道摘出および回腸導管造設術後に腟，子宮頸部に再々発した症例について臨床病理学的に検討した。

症　　例

患者：74歳，女性
主訴：腟出血
産科歴：5経妊3経産
家族歴：母　食道癌，兄　胆管癌
既往歴：64歳　食道癌手術
原病歴：71歳時，右尿管・右腎盂癌（移行上皮癌）にて

右腎臓と右尿管摘出術を施行した（StageⅢ pT3NXM0,
G3）。2年後，膀胱に再発認め，膀胱・尿道摘出および
回腸導管造設術施行した。この1年後，腟出血があり当
科初診となった。

診察・検査所見：
初診・入院時所見；身長151cm，体重42.2kg，PS=0，胸
腹部に理学的検査異常なし
内診所見；腟粘膜にびまん性に粗・粒状赤色病変あり。
子宮は萎縮し，卵巣は触知せず。外陰部異常なし。
コルポスコピー；小乳頭状腫瘍が子宮頸部から腟全体に
進展（図1）
細胞診（子宮頸部～腟）；classV　角化傾向のない類円～
多角形で粒状体を有する腫瘍細胞がびまん性に出現（図
2a）
組織診（子宮頸部～腟）；移行上皮癌。間質への浸潤は
なく，腟・子宮の切除断端は陰性。子宮内膜・筋層・両
側付属器に腫瘍性変化認められず。
末梢血液像；RBC 381×10⁴/μl, Ht 30.4%, Hb 9.0g/dl,
WBC 3600/μl, Plt 35.7×10⁴/μl
　　…軽度貧血を認めた
生化学；GOT 17IU/l, GPT 10IU/l, LDH 180IU/l, ALP
308IU/l, BUN 23.7mg/dl, Cre 0.80mg/dl, Na 142mEq/l,
K 4.9mEq/l, Cl 106mEq/l
　　…軽度BUN上昇あり
腫瘍マーカー；SCC 1.0ng/ml, CEA 4.4ng/ml, CA19-9
6U/ml, CA125 8U/ml
　　…全て上昇なし
PET-CT；子宮頸部・腟にFDGの明らかな集積認めず，
遠隔転移所見なし。
MRI；子宮，腟に明らかな腫瘤やリンパ節の腫大認めず，
子宮内に小筋腫を多数認めた。

治療経過：
　画像および病理検査から腟・子宮頸部へ限局する腎盂
尿管癌の腟－子宮頸部再発と診断した。このため，根治
的切除が可能と判断し子宮，両側付属器，腟全摘出術を
施行した。手術時間は4時間32分，出血量2247ml，輸血
8単位 1120mlであった。手術中に特に合併症なく，術
後経過は良好であり術後14日目に退院となった。その後
は再発なく外来で経過観察していたが，婦人科手術より
2年4ヶ月後に直腸周囲に再発が認められた。当院泌尿
器科入院にて化学療法施行したが病期進行のため，直腸
再発1年6ヶ月後に永眠となった。
　摘出子宮および腟の肉眼的所見は，苺状・乳頭状腫瘍
がびまん性に広範囲に腟から子宮頸部への表層進展を認
めた（図3）。病理組織検査は子宮頸部から腟全体の上
皮に低乳頭状の未熟な移行上皮様腫瘍性細胞の増生を認

め（図2b, c, d），3年前の腎盂尿管癌の組織像と類似
した形態を示した（図4）。免疫染色で移行上皮に特徴
的なサイトケラチン7, 20（CK7, CK20）が陽性（図5）
となり，腎盂尿管癌の腟壁への再々発と診断した。

<center>考　　察</center>

　本症例では腎盂尿管癌の初回手術の2年後に膀胱へ再
発，さらに膀胱摘出の1年後に腟再発を認めた。まず腟
癌について，続いて腎盂尿管癌などについてそれぞれの
文献的解釈を含めて今回の症例の発生機序を考察してい
く。はじめに腟癌は原発性と転移性に大別され，原発性
腟癌は女性生殖器の悪性腫瘍のおよそ3％と極めて稀で
あり，ほとんどは転移性腟癌である。原発性腟癌の組織
型別の発症頻度は扁平上皮癌が80％以上を占めており，
他に腺癌，肉腫，黒色腫などが報告されている[1]。また
転移性腟癌は子宮内膜や子宮頸部，膀胱および腎などの
生殖泌尿器および直腸からの転移が多く，乳房，肺など
への転移も報告されている[2]。
　腎盂，尿管および膀胱はいずれも尿路上皮粘膜を有
するため腎盂尿管癌と膀胱癌は尿路上皮癌と総称され
る。尿路上皮癌の約95％以上が移行上皮癌であり，残り
の5％が腺癌，扁平上皮癌である[3]。また尿路上皮癌で
は同一細胞を起源として腫瘍細胞が後述する尿路内播腫
により多中心的に発生することが示唆されており，腎
盂尿管癌の術後の膀胱への再発率は約40％と言われてい
る[4]。また，移行上皮癌が尿路系以外の部位に認められ
ることは極めて稀であり，これまでの報告数は国内外合
わせて15編程度と少なく[5]-[8]，発生機序は原発性と転
移性の2種類に大別される。原発性の腟移行上皮癌は
これまで5例程度しか報告されておらず極めて稀であ
る[9]。腟以外にも卵巣や卵管，子宮内膜などの原発性女
性生殖器移行上皮癌が報告されている。発生学上，尿路
上皮とミュラー管系上皮は同じ尿生殖洞由来であること
から，卵巣や卵管などの女性生殖器にも移行上皮癌が生
じうると考えられている。
　転移性腟移行上皮癌の症例については，Singerらは閉
経後の女性患者について非浸潤性の膀胱移行上皮癌が外
陰部Paget病様の形態を示し，腟内へ浸潤性に乳頭状の
転移を認めた症例を報告している[5]。またChinらは膀胱
の移行上皮癌が膀胱全摘除術後に腟へ局所的に再発した
症例を同時期に術後再発しなかった症例と比較して報告
している[6]。これらの報告では，尿路上皮癌の初回治療
から腟へ転移として認められるまでの期間は平均で4.3
年（0-14年）であり，治療は内視鏡による切除や子宮・
腟全摘が行われている[7]。また腟以外にも子宮内膜，子
宮頸部，卵管，卵巣などへの転移性移行上皮癌の発症
が報告されている[10]。転移の発現機序としては血行性転
移，リンパ行性転移，播種などが考えられている。播種

図1　子宮腟部コルポスコピー像：
　　　小乳頭状腫瘍が腟全体に進展

図3　摘出子宮および腟：苺状・乳頭状腫瘤がびまん性に広範囲に
　　　腟から子宮腟部へ表層進展
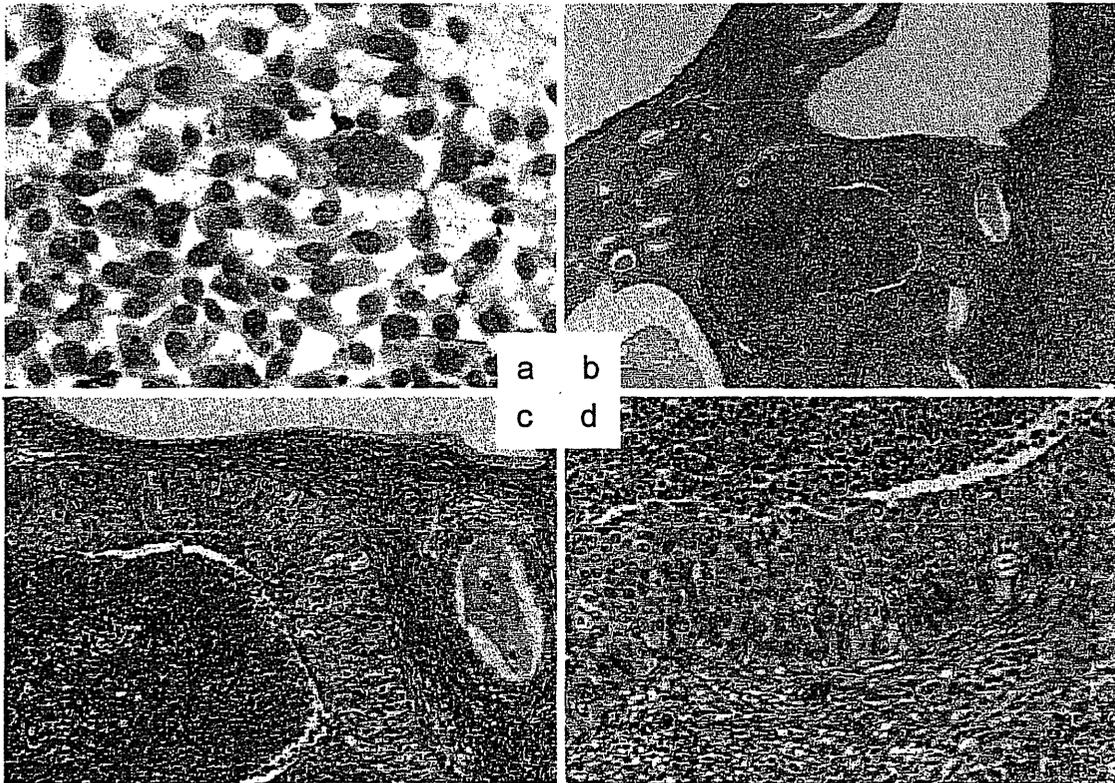
図2　子宮頸部細胞診（a：対物 ×40），組織診（b：対物 ×5，c：対物 ×10，d：対物 ×20）
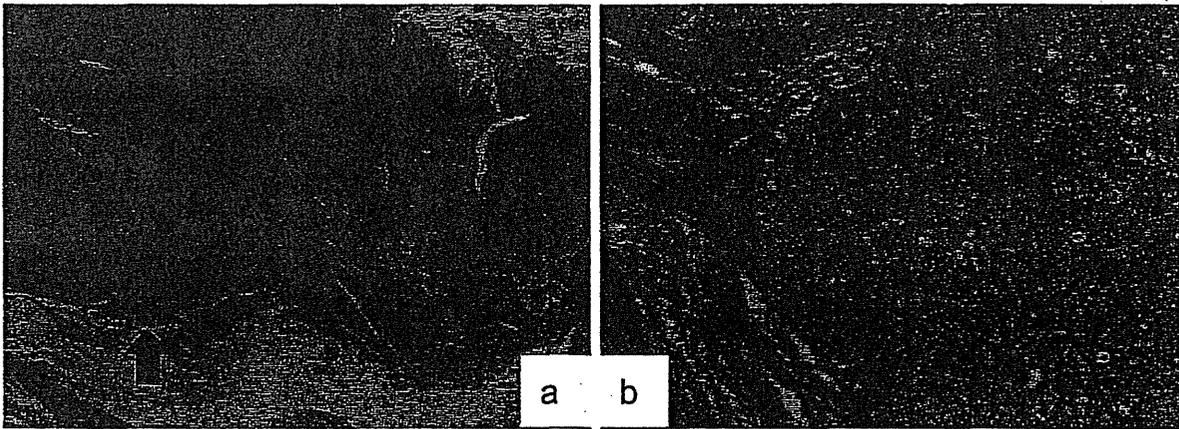
図4　初回手術 尿管癌（移行上皮癌）組織診：矢印部に筋層浸潤を認めた
（a：対物 ×5，b：対物 ×20）
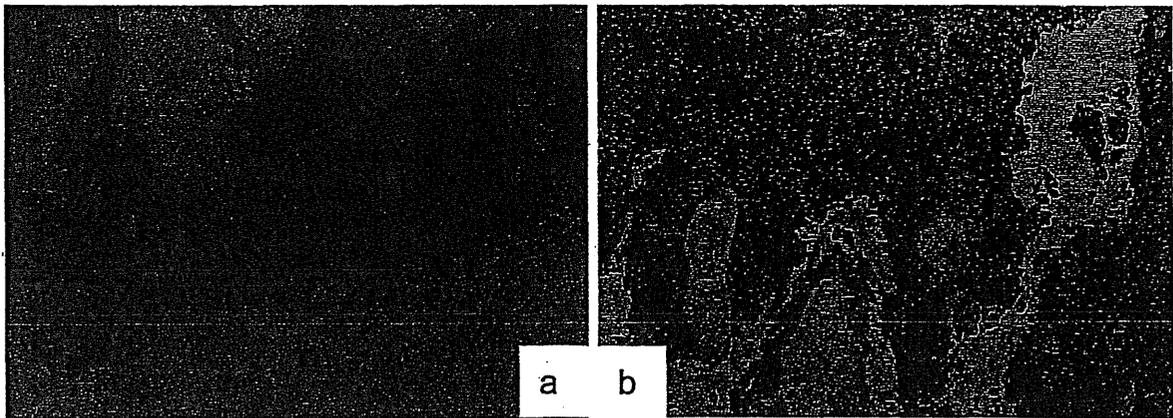
図5　腟組織免疫染色像（a：CK7 陽性，b：CK20 陽性）

については，排尿や膀胱鏡による観察時の灌流液の流出
入により腫瘍細胞が下流へ流されて腟内へ流入し，腟に
"implantation" すると提唱している[11]。

　ここで，腟に移行上皮癌を認めた場合の発生機序を検
討する際にはCK7およびCK20の免疫染色が用いられる
ことが多い。原発性の尿路移行上皮癌の場合はCK7陰性・
CK20陽性を呈し，腟への転移性の移行上皮癌の場合は，
CK7およびCK20のいずれも陽性を呈する[12]。また，原
発性の腟移行上皮癌の場合は，組織が移行上皮細胞の形
態を有していても尿路由来の移行上皮癌の免疫染色の傾
向と異なり，CK7は陽性であるがCK20は陰性を呈する。
腟だけでなく卵巣や卵管，子宮内膜などの女性生殖器移
行上皮癌も同様であり，これはミュラー管の特性が表現

されているためと考えられている。

　本症例において腟に移行上皮癌を認めた場合の発生機
序を考察する。まずCK7およびCK20がいずれも陽性で
あることから原発性移行上皮癌は否定的であると言え
る。また，摘出子宮および腟の病理所見で子宮・腟の断
端，子宮内膜・筋層に腫瘍性変化が認められなかった事
などから膀胱からの直接浸潤は考えにくい。ここで，右
腎盂尿管癌術後に膀胱癌が再発した原因が，排尿や灌流
液により腫瘍細胞が下流へ移動したことによるもので
あれば，腟へも同様に腫瘍細胞が流下，腟内へ流入し
"implantation" された可能性が挙げられる。その場合，
腟移行上皮癌の組織像が腎盂尿管癌の組織像と類似した
形態を示したことを踏まえると，膀胱再発し尿路変更術

がなされるまでの期間に右腎盂尿管癌の腫瘍細胞が腟へ"implantation"したと考えるのが妥当であろう。その他，リンパ行性や血行性による転移では尿路変更された後も転移が生じる可能性が考えられるが，播種との相違を証明することは難しい。

　本症例の考察より，腎盂尿管癌や膀胱癌などの尿路上皮癌の既往患者には，腟への進展も念頭において積極的に外陰部および腟にも十分注意した婦人科検診を行うことが重要であることが示唆された。

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【連絡先】
松岡　直樹
四国がんセンター婦人科
〒791-0280　愛媛県松山市南梅本町甲160
電話：089-999-1111　FAX：089-999-1100

Contemporary management of endometrial cancer

Jason D Wright, Nicanor I Barrena Medel, Jalid Sehouli, Keiichi Fujiwara, Thomas J Herzog

The treatment of endometrial cancer has changed substantially in the past decade with the introduction of a new staging system and surgical approaches accompanied by novel adjuvant therapies. Primary surgical treatment is the mainstay of therapy but the effectiveness and extent of lymphadenectomy has been challenged, and its acceptance as a routine procedure varies by country. The role of radiation has evolved and chemotherapy has been incorporated, either alone or combined with radiation, to treat the many patients in whom cancer recurs because of a tumour outside the originally radiated pelvic and lower abdominal area. Use of traditional adjuvant chemotherapeutics has been challenged in clinical trials of new agents with improved side-effect profiles. Novel agents and targeted therapies are being investigated. Research into genetic susceptibility to endometrial cancer and the potential genetic aberrations that might translate into therapeutic interventions continues to increase. Substantial global variability in the treatment of endometrial cancer has led to examination of long-accepted norms, which has resulted in rapidly changing standards. International cooperation in clinical trials will hasten progress in treatment of this ubiquitous cancer.

Introduction

Endometrial cancer is a major cause of morbidity and mortality for women worldwide, with nearly 200 000 cases diagnosed every year; it is the seventh most common malignancy.[1] Incidence differs between regions: it is the most common cancer of the female genital tract and the fourth most common cancer after breast, lung, and colorectal cancers in North America and Europe.[2,3]

Most women with endometrial cancer are diagnosed at an early stage with uterine-confined tumours, often after having vaginal bleeding. Despite the overall favourable prognosis of endometrial cancer, some women have aggressive neoplasms such as high-grade or deeply invasive lesions, or tumours consisting of non-endometrioid cells such as papillary serous or clear cells, and are at substantial risk of recurrence and death. Prognostic factors include age, race, stage, grade, ploidy, depth of invasion, tumour size, receptor status, and cell type.[4] The most common pattern of presentation is postmenopausal bleeding, and diagnosis is generally via endometrial biopsy or dilatation and curettage (figures 1, 2).

Endometrial cancer occurs most frequently in postmenopausal women. The most important risk factor for endometrial cancer is exposure to unopposed oestrogen. Case-control studies[5,6] have suggested that the risk for women who use unopposed oestrogen is two-times to ten-times higher than for non-users. As a result of the production of oestrone by adipose tissue, obesity is also an important risk factor for endometrial cancer.[7] Results of a meta-analysis[8] showed that endometrial cancer was one of the cancers most strongly associated with obesity. Similarly, tamoxifen is associated with a slightly increased risk of endometrial cancer. In women with breast cancer using tamoxifen, the relative risk for the development of endometrial cancer compared with controls was 7·5 (1·6/1000 vs 0·2/1000).[9]

Although most endometrial cancers are thought to be sporadic, some women have a genetic predisposition for the disease. The most common genetic syndrome associated with endometrial cancer is hereditary non-polyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome,[10] which is an autosomal dominant cancer-susceptibility syndrome. It is most often due to an inherited mutation in one of the DNA mismatch repair genes MLH1, MSH2, MSH6, or PMS2.[10,11] Endometrial cancer associated with HNPCC occurs in young women.[11] The lifetime risk of endometrial cancer in women with HNPCC has been estimated at 40–60%.[12,13]

Endometrial cancers have been broadly classified into two types.[14] Type I neoplasms, which are most common, include endometrioid adenocarcinomas. Type I neoplasms generally arise from atypical endometrial hyperplasia and are oestrogen dependent. Type II neoplasms include more aggressive histological variants such as clear-cell and serous carcinomas and uterine carcinosarcomas. Non-endometrioid tumours are less common than endometrioid tumours but are associated with disproportionately high mortality. Our Review focuses on type I endometrial tumours. Treatment frameworks for endometrial cancer have changed substantially in the past decade because traditional modes of management have been challenged, and novel approaches have emerged. Several initiatives designed to improve outcomes are being assessed. We discuss unresolved issues about the route and extent of surgical staging, use of adjuvant therapy for patients at intermediate and high risk, and treatment of recurrent disease.

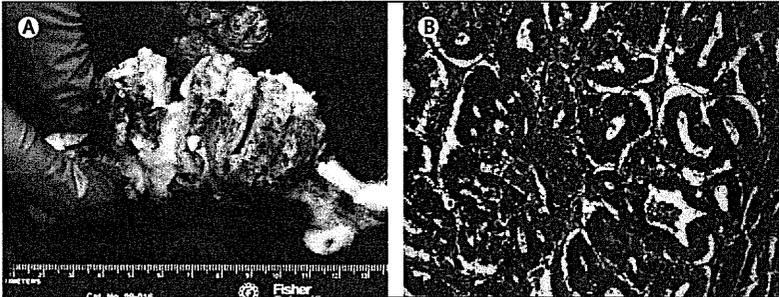### Search strategy and selection criteria

We searched Medline, Current Contents, and PubMed, between Jan 1, 1980 and Jan 31, 2011 with the search terms "uterine cancer" and "endometrial cancer". We included select references from articles identified by this strategy. We included only papers published in English between 1980 and 2010, plus abstracts converted to final publications up to Nov 15, 2011.
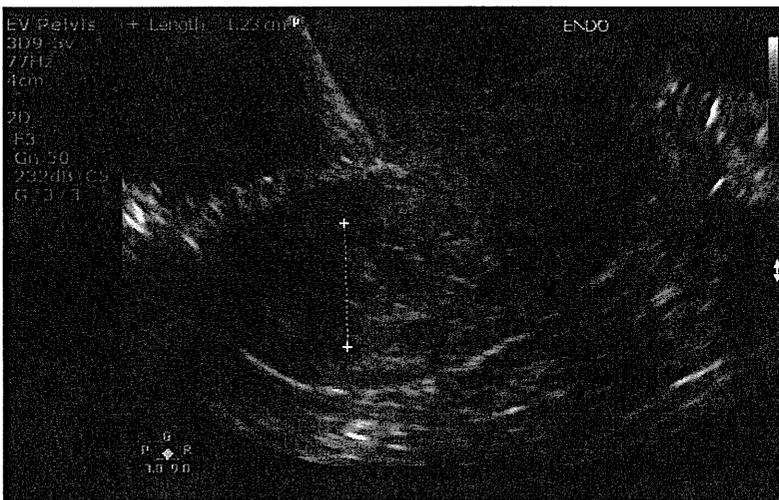
Figure 1: Endometrial adenocarcinoma
(A) Tumour invading 60% into the uterus wall. (B) Micrograph of well differentiated endometrioid type adenocarcinoma. The tumour has endometrial glands and stroma. Magnification ×40.

Figure 2: Transvaginal ultrasound of the uterus
Cross-sectional image of the uterus shows a thickened endometrial lining (12·3 mm) characteristic of endometrial cancer.

	Description
Stage I	Tumour confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
Stage II	Tumour invades cervical stroma, but does not extend beyond the uterus*
Stage III	Local or regional spread of tumour, or both
IIIA	Tumour invades the serosa of the corpus uteri or adnexae, or both†
IIIB	Vaginal or parametrial involvement, or both†
IIIC	Metastases to pelvic or para-aortic lymph nodes, or both†
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumour invades bladder, or bowel mucosa, or distant metastases, or all three
IVA	Tumour invasion of bladder or bowel mucosa, or both
IVB	Distant metastases, including intra-abdominal metastases or inguinal lymph nodes, or both

At all stages, tumour grade can be 1, 2, or 3. *Endocervical glandular involvement should be considered only as stage I and no longer as stage II. †Positive cytology has to be reported separately without changing the stage.

Table 1: International Federation of Gynecology and Obstetrics staging system for endometrial cancer, 2009[21]

Pathological factors and staging

Spread to the regional lymph nodes is the most important prognostic factor for women with endometrial cancer.[15–18] A series of surgicopathology studies associated several uterine risk factors including tumour grade, myometrial invasion, lymphvascular space involvement, and cervical stromal invasion with an increased risk of nodal metastasis and decreased survival.[4,19,20] For example, the risk of lymph-node metastasis is five-times greater in women with deeply myoinvasive tumours than in those with superficially invasive neoplasms. Poorly differentiated cancers are six-times more likely to spread to the regional lymphatics than are well differentiated lesions.[4] The presence or absence of nodal disease and uterine risk factors affect the choice of adjuvant treatment for women with endometrial cancer. The importance of uterine risk factors and nodal metastasis was recognised in 1988, when the staging criterion for endometrial cancer was changed from a clinical to a surgical staging system. In 2009, the International Federation of Gynecology and Obstetrics further modified this classification system (table 1).[21]

Primary surgical treatment

Historically, hysterectomy was often preceded by intracavitary radiation but this approach has been replaced by initiatives to stage patients surgically to avoid unnecessary use of radiotherapy. Furthermore, traditionally almost all investigations were done via laparotomy whereas many operations worldwide are now done by minimally invasive techniques, where availability of technology allows. Vaginal hysterectomy is another option, but this approach restricts exploration of the abdominal cavity, peritoneal washing procurement, lymph-node dissection, and omentectomy as indicated. Issues of contention are the route and role of comprehensive staging, specifically whether and to what extent lymph-node dissection is necessary, and whether ovaries should be preserved in some patients. Many women with endometrial cancer are elderly and have several medical comorbidities. Therefore, both the primary surgical treatment and adjuvant therapy must be tailored accordingly.

Although the main route of spread for endometrial cancer is through lymphatic dissemination, the role of lymphadenectomy for women with early stage endometrial tumours is controversial. Some gynaecological oncologists advocate selective lymph-node sampling in women at high risk for nodal metastases (with high-grade or deeply invasive tumours) whereas others recommend routine systematic lymphadenectomy in all patients. Strategies using selective nodal assessment are potentially limited by the difficulty in prediction of the depth of tumour invasion and final tumour grade intraoperatively.[22,23] In a report of 181 patients with a preoperative diagnosis of grade 1 endometrial tumours, 19% of the tumours were upgraded and 18% of patients were upstaged on final pathology.[24] Proponents of

lymphadenectomy have argued that the procedure provides important diagnostic information that best selects optimum delivery of adjuvant therapy.[25]

Several studies have investigated the therapeutic potential of lymphadenectomy and its effect on survival. The necessary extent of nodal dissection is debated. Fotopoulou and colleagues[26] recorded high rates of metastasis in para-aortic nodes even above the level of the inferior mesenteric artery. Although results of retrospective reports suggest that survival is improved in women who undergo extensive nodal dissection,[27-29] results of two randomised trials[30,31] did not show a survival benefit for the procedure.[27-31] The multinational ASTEC (A Study in the Treatment of Endometrial Cancer) trial randomly assigned more than 1400 women to hysterectomy and salpingo-oophorectomy with or without lymphadenectomy. After surgery patients underwent a second randomisation into a radiotherapy trial. The investigators recorded no benefit for lymphadenectomy in either overall or recurrence-free survival.[31] Another study of more than 500 women reached similar conclusions.[30] Although critics have pointed out several methodological flaws of the studies such as the absence of quality control for the lymphadenectomy, findings from these studies have raised questions about the therapeutic role of lympha-denectomy in endometrial cancer.[32] Both trials reported small but statistically significant increases in the rates of perioperative complications and operative times with lymphadenectomy.[30,31] To decrease the morbidity of lymphadenectomy several studies have examined sen-tinel lymph-node dissection. Estimates of sensitivity and specificity for the detection of metastatic disease have varied widely and the technique is considered experimental.[33]

Hysterectomy and bilateral salpingo-oophorectomy are the foundation of treatment of endometrial cancer. The method by which this operation is done has changed substantially during the past decade in most parts of the world as both laparoscopic and robotic approaches have been shown to be feasible. In 1993, Childers and colleagues[34] reported the feasibility and safety of laparo-scopic or laparoscopic-assisted approaches including lymphadenectomy. The results have been confirmed in other studies.[35-37] Prominent among these studies was the Gynecologic Oncology Group LAP-2 trial,[37] a randomised comparison of conventional abdominal hysterectomy plus lymphadenectomy with laparoscopic assisted vaginal hysterectomy plus lymphadenectomy in more than 2600 patients with clinical stage I or IIA endometrial cancer. The laparoscopic approach was associated with longer operating times but a shorter hospital stay than laparotomy. Laparoscopy was initiated in 1682 patients and completed without conversion in 1248 (74·2%). The main advantage of these minimally invasive approaches compared with laparotomy has been faster recovery, shorter hospital stay, and lower morbidity overall in patients with endometrial cancer, many of whom have

significant comorbid disorders. The median number of lymph nodes removed was 24 (IQR 16–34) for laparoscopy and 25 (16–33) for open surgery.[37] However, laparoscopy was associated with only small improvements in quality of life.[38] Follow-up to establish the effect of laparoscopy on recurrence and survival is continuing.

Robotic-assisted surgical staging and treatment of endometrial carcinoma has been suggested as a useful alternative to open or laparoscopic surgery.[39] Reported advantages of robotic hysterectomy over conventional laparoscopy include three-dimensional imaging, greater range of motion, a shorter time to learn the technique, and possibly improved feasibility of lymphadenectomy in obese patients.[40] In one retrospective cohort study[39] comparing robotic, laparoscopic, and open hysterectomy, the robotic approach was associated with the highest lymph-node yield, shortest hospital stay, and lowest blood loss. Despite the potential advantages of robotic hysterectomy, the substantial resources needed and cost of use are greater than with laparoscopic surgery.[41]

Although most women with endometrial cancer are postmenopausal, about 20% of endometrial cancers occur in premenopausal women. For young women, ovarian preservation has been advocated in carefully selected patients who undergo surgery.[42-44] Although ovarian preservation prevents surgical menopause, patients are at risk of synchronous and metasynchronous ovarian neoplasms. For women who have not completed child-bearing, uterine preservation by medical treatment with a progestational agent can be considered. Results of several small observational studies[45] have suggested that as many as three-quarters of women with well differentiated endometrial cancer will respond to progestagen-based therapy. Careful follow-up is mandatory in these patients because recurrences are common.[45] The ideal progestational agent and duration of therapy are unknown.

	Grade 1	Grade 2	Grade 3
Stage IA			
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 with or without pelvic radiotherapy	Observe or vaginal brachytherapy with or without pelvic radiotherapy
Stage IB			
Adverse risk factors not present	Observe or vaginal brachytherapy	Observe or vaginal brachytherapy	Observe or vaginal brachytherapy with or without pelvic radiotherapy
Adverse risk factors present	Observe or vaginal brachytherapy with or without pelvic radiotherapy	Observe or vaginal brachytherapy with or without pelvic radiotherapy	Observe or pelvic radiotherapy with or without vaginal brachytherapy with or without chemotherapy

Potential adverse risk factors include age older than 60 years, lymphovascular space invasion, tumour size, and lower uterine (cervical or glandular) involvement.

Table 2: National Comprehensive Cancer Network recommendations for the adjuvant treatment of endometrial cancer, 2011[46]

Adjuvant treatment for low-risk and intermediate-risk endometrial cancer

The adjuvant treatment of women with low-risk and intermediate-risk endometrial cancer is one of the most controversial topics in gynaecological oncology. Table 2 shows the US National Comprehensive Cancer Network treatment recommendations for stage I and II endometrial cancer.[46] Women with grade 1 and 2 tumours confined to the endometrium have an excellent prognosis and are considered low risk. In one analysis[47] the 10-year recurrence risk for this subset of patients was only 3%. In view of this favourable prognosis, adjuvant therapy is usually withheld.[48–51]

Although definitions vary in individual studies, the remainder of women with stage I and II tumours are considered intermediate risk. So far, no study of adjuvant treatment has convincingly shown survival benefit in this subgroup of women. In patients who have undergone comprehensive staging, survival is favourable even without further therapy.[52] Radiation has been the most frequently prescribed treatment; however, two studies[53,54] have examined the use of chemotherapy either alone or in combination with radiation for intermediate-risk patients. Radiation reduces the risk of local, pelvic recurrence but does not improve survival in women with stage I or II endometrial cancer (table 3).[55–59] Investigators for the Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC)-1 trial randomly assigned 715 patients with stage IB grade 2–3 tumours or stage IC grade 1–2 tumours to either observation or whole pelvic radiotherapy. After 10 years of follow-up survival did not differ between groups but pelvic radiation reduced the risk of vaginal recurrence from 15% to 4%.[55] A Gynecologic Oncology Group trial[56] done in the USA in women with early-stage disease who had undergone lymphadenectomy as part of their treatment had similar findings.

The inability of adjuvant pelvic radiotherapy to improve survival stems partly from the fact that many recurrences occur at the vaginal cuff and can be salvaged with radiotherapy at the time of recurrence. However, the results from these trials must be interpreted with caution because many patients included in the studies were at low risk of death from endometrial cancer.[55–58] These trials might therefore not have the power to identify a survival advantage for early-stage patients at greatest risk.

In view of these limitations, investigators have attempted to identify subgroups of patients with early-stage endometrial cancer who might benefit from radiotherapy. An analysis of more than 21 000 patients in the US National Cancer Institute's Surveillance, Epidemiology, and End Results database showed that radiation improved survival for women with stage IC tumours.[60] Results of two meta-analyses[61,62] have suggested that radiation is associated with improved survival for patients with stage IC, grade 3 neoplasms.

Pelvic radiotherapy, especially after lymphadenectomy, can be associated with pronounced adverse effects.[55,56] 25% of 354 patients in the radiotherapy group of PORTEC-1 had late complications.[55] To decrease the morbidity associated with pelvic radiotherapy while attempting to preserve the benefits of decreasing locoregional recurrences, vaginal brachytherapy is now widely used for intermediate-risk endometrial cancer.[62] Vaginal brachytherapy is administered in the outpatient setting with a vaginal cylinder. With high-dose rate schedules, three fractions of 7 Gy each are delivered at 1 week intervals. A randomised trial comparing[59] whole pelvic radiotherapy and vaginal brachytherapy for intermediate-risk endometrial cancer (PORTEC-2) showed no difference in survival between the two methods. The investigators noted that although the vaginal recurrence rate was 1·8% for brachytherapy compared with 1·6% for external beam radiation, pelvic recurrences were more frequent with brachytherapy (3·8% vs 0·5%).[59]

Endometrial cancer was previously thought to spread predominantly through lymphatic dissemination, but clinicians now recognise that even women with tumours

	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=NS
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=0·31
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=0·55
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=0·31
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=0·66

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

that seem confined to the uterus are at risk of distant disease. A study of women with high-grade, deeply invasive tumours who all received pelvic radiotherapy showed that nearly a third developed distant metastases.[63] The high rate of systemic failure and the success of chemotherapy for advanced-stage endometrial cancer provide strong rationale for the investigation of adjuvant chemotherapy in women with uterine-confined disease.[53,54,64] The Japanese Gynecologic Oncology Group compared pelvic radiotherapy and chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in a cohort of women with stage IC–IIIC endometrial cancer. Although survival was equivalent for the two methods overall, the investigators noted a survival advantage in the group of women whom they described as high-to-intermediate risk (stage IC, >70 years of age, or grade 3; or stage II or positive cytology with >50% myometrial invasion).[53]

Several groups are investigating chemotherapy in combination with radiation for intermediate-risk endometrial cancer.[65,66] The European Organisation for Research and Treatment of Cancer and Nordic Society of Gynecological Oncology reported results of a trial[67] comparing adjuvant radiation to chemotherapy (various regimens) and radiation in patients with stage I–IIIC endometrial cancer. The hazard ratio for progression-free survival was 0·64 (95% CI 0·41–0·99) in favour of the combination regimen. 27% of 186 patients in the chemotherapy group did not complete treatment.[67] The Gynecologic Oncology Group's protocol for the adjuvant treatment of high-intermediate-risk endometrial cancer compares whole pelvic radiotherapy with the combination of vaginal brachytherapy and carboplatin and paclitaxel (Gynecologic Oncology Group protocol 249). The PORTEC-3 trial compares pelvic radiotherapy with radiation plus chemotherapy for women with high-intermediate-risk and high-risk disease. Future trials will probably continue to explore the role of chemotherapy for intermediate-risk endometrial cancer. The Japanese Gynecologic Oncology Group is doing a randomised trial to establish the most feasible chemotherapy regimen without radiotherapy for women with intermediate-risk endometrial cancer.[68]

Adjuvant treatment for advanced-stage disease

Adjuvant chemotherapy is now the mainstay of treatment for women with stage III and IV endometrial cancer. A trial[69] of whole abdominal radiotherapy versus chemotherapy with cisplatin and doxorubicin in patients with stage III and IV disease showed the superiority of chemotherapy to radiation. 5-year survival was 53% in patients given chemotherapy compared with 42% for the radiation group.[69] On the basis of these findings, chemotherapy was rapidly incorporated into the care of women with advanced-stage endometrial cancer.

As in the treatment of intermediate-risk endometrial cancer, clinicians frequently use multimodality therapy for women with advanced-stage disease.[70,71] Multimodality therapy combines the systemic effects of chemotherapy with the improved local control provided by radiation.[70,71] The subgroups of patients most likely to benefit from combination therapy, the optimum chemotherapeutic agents, and the ideal sequencing are under active investigation. The Gynecologic Oncology Group prospectively examined radiation in combination with doxorubicin and cisplatin with or without paclitaxel in the adjuvant treatment of women with stage III and IV endometrial cancer. The addition of paclitaxel had no effect on survival but was associated with increased toxic effects.[72]

Recurrent disease

Women with recurrent endometrial cancer are a highly heterogeneous population, ranging from patients affected by an isolated vaginal relapse amenable to curative therapy to women presenting with widespread disease in whom palliation constitutes the mainstay of treatment. As such, treatment is highly individualised. Surgery, radiation, chemotherapy, and hormonal therapy are all used for recurrent endometrial cancer.

Radiation is the treatment of choice for women who have a relapse at the vaginal cuff after surgery.[73,74] 2-year survival after an isolated recurrence at the vaginal cuff is as high as 75%.[56,73,74] Patients with vaginal recurrences who have previously received radiotherapy are candidates for surgical resection. Selected patients with large pelvic recurrences might also be candidates for surgery or radiotherapy. Other radical surgical approaches such as secondary cytoreduction, pelvic exenteration, or laterally extended endopelvic resection might be considered in highly selected patients with locally advanced disease and good performance status in whom cure might be possible.[75]

Endometrial cancer is hormonally responsive, and several endocrine therapies have been examined for women with recurrent disease. Progestagens and tamoxifen are the most commonly used agents; aromatase inhibitors and gonadotropin-releasing hormone analogues have also been assessed but have shown less antitumoral activity.[76–79] Progestagens have shown response rates of 15–30%, with median overall survival of 7–11 months. Most responses are partial and of short duration. Response rates tend to be higher in women with well differentiated tumours and in those with neoplasms that express the progesterone receptor than in other types of tumour.[77,80] In the Gynecologic Oncology Group's series, 17 of 46 (37%) women with progesterone-receptor-positive tumours responded to progesterone compared with only seven of 86 (8%) of those with progesterone-receptor-negative neoplasms.[77] Several trials have examined various dosing regimens and endocrine combinations: low-dose progestagen regimens seem to be as effective as higher-dose regimens, but are associated with fewer toxic effects; and the combination of tamoxifen with a progestagen does not seem to confer

benefit to progestational therapy alone.[77,81-85] Endocrine therapy is especially attractive in women with medical comorbidities because it is typically well tolerated and has a favourable side-effect profile.

Cytotoxic chemotherapy is frequently given to women with systemic disease. Although several chemotherapeutic agents have been assessed, doxorubicin and cisplatin have traditionally been regarded as the most active single agents. Response rates for single-agent doxorubicin are reported to range from 17% to 25%.[86-89] Although the response rate for the combination of doxorubicin and cisplatin is better than that for doxorubicin alone, survival is much the same for the combination regimen and single-agent treatment.[88,90]

Interest has also focused on the incorporation of paclitaxel into the treatment of recurrent endometrial cancer. Combinations of paclitaxel with a platinum analogue, cisplatin or carboplatin, have shown response rates of more than 40%.[91,92] The Gynecologic Oncology Group investigated doxorubicin in combination with paclitaxel as an alternative to doxorubicin and cisplatin.[93] The two combinations showed similar response rates and survival.[93] The same group compared doxorubicin and cisplatin with a three-drug regimen consisting of doxorubicin, cisplatin, and paclitaxel.[94] The objective response rate was improved from 34% to 57% with the three-drug regimen and overall survival was improved from 12·3 to 15·3 months. The triple regimen was associated with substantial toxic effects—more than a quarter of patients assigned to doxorubicin, cisplatin, and paclitaxel had grade 2 neuropathy, and 12% had grade 3 neuropathy.[94] In view of the substantial side-effect profile of doxorubicin, cisplatin, and paclitaxel, many clinicians treat elderly women who have recurrent endometrial cancer with carboplatin and paclitaxel or a less toxic doxorubicin-containing doublet. The Gynecologic Oncology Group is doing a phase 3 trial comparing doxorubicin, cisplatin, and paclitaxel with carboplatin and paclitaxel (Gynecologic Oncology Group protocol 209).

Preliminary data for several molecularly targeted agents for endometrial cancer are emerging. The PI3K/Akt/mTOR pathway is frequently upregulated in women with endometrial cancer because of loss of the tumour suppressor gene *PTEN*.[95] Inhibitors of the mammalian target of rapamycin (mTOR) have shown promising early results.[96,97] The mTOR inhibitor temsirolimus was associated with a 26% response rate in chemotherapy naive patients.[98] In patients with previous treatment, investigators noted a 4% (one of 25 patients) response rate with disease stabilisation in 48% (12 of 25).[97] Although epidermal growth factor receptor is frequently expressed in normal endometrium and in endometrial cancer, use of erlotinib, an inhibitor of the receptor, was associated with a response rate of only 13%.[99,100] Similarly, although HER-2/neu is frequently overexpressed or amplified in endometrial cancer, no responses to the monoclonal

anti-HER-2/neu antibody trastuzumab were reported in a phase 2 trial.[101,102] Angiogenesis and vascular endothelial growth factor signalling also seem to have a key role in endometrial cancer progression.[103,104] Although a phase 2 trial of the oral, multitarget tyrosine kinase inhibitor sorafenib showed disappointing results, several trials of the antivascular endothelial growth factor monoclonal antibody bevacizumab are continuing.[105]

Conclusions

The past decade has witnessed several remarkable advances for endometrial cancer. An improved understanding of the molecular biology of endometrial cancer, the introduction of less morbid minimally invasive surgical approaches, and the more routine use of chemotherapy have all improved the outcomes of women with endometrial cancer. Further trials to refine adjuvant treatment strategies and to establish the efficacy of target therapeutics are underway and will probably improve the treatment of endometrial cancer.

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