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REVIEW ARTICLE

Surgical treatment of high stage endometrial cancer: current perspectives

Salvatore Giovanni Vitale[1] · Gaetano Valenti[2] · Ferdinando Antonio Gulino[2] · Pietro Cignini[3] · Antonio Biondi[2]

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Abstract Endometrial cancer is now the most common gynecologic malignancy. We investigate on new scientific evidences in endometrial cancer, particularly underlined updates in advanced endometrial cancer. Early stage endometrial cancer is the most frequent presentation; however, advanced endometrial cancer that occurs in 3–13 % of cases has bad prognosis. There are two types of endometrial cancer different in molecular pattern, therapeutic strategy and prognosis. Type I endometrial cancers develop in an environment of unopposed estrogen and often arise out of endometrial hyperplasia, characterized by mutations in the PTEN gene, K-ras, and microsatellite instability inception. Type II cancer is not an estrogen-related cancer, occurs predominantly in postmenopausal women, shows typical mutations in p53 and HER2/neu and has a poor prognosis. Preoperative characterization of the type's disease is an essential step for a right diagnosis and treatment. All patients should undergo to surgical staging, except those who are inoperable, according to FIGO recommendation. Surgical debulking, neoadjuvant chemotherapy and interval debulking can be strategy options.

Keywords Advanced endometrial cancer · Histology · Diagnostic evaluation · Staging · Molecular pattern · Treatment strategies · Surgical debulking

✉ Salvatore Giovanni Vitale
vitalesalvatore@hotmail.com

[1] Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Via Consolare Valeria 1, 98125 Messina, ME, Italy

[2] Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy

[3] Department of Gynecologic Ultrasound Imaging, Altamedica Fetal Maternal Medical Centre, Rome, Italy

Introduction

Endometrial cancer (EC) is now the most common gynecologic malignancy in the US, with an estimated 43,470 new cases in 2010 and 7950 deaths [1]. The number of deaths per year has been increasing despite a relatively stable number of new cases [2]. Early stage endometrial cancer is the most frequent presentation among affected women and has a favorable prognosis. However, 3–13 % of new cases occur such as advanced endometrial cancer when tumor extending outside of the true pelvis or with invasion of the bladder or rectal mucosa. Patients with stage IV disease have a 5 years survival of 10–20 %. Treatment strategies for these patients have evolved from hormonal therapy with progestational agents [3–5], to radiation [6–8] and chemotherapy [9]. The role of surgical cytoreduction in patients with advanced EC has also been reviewed in retrospective studies [10–14]. This strategy shares many aspects with the management of ovarian cancer (OC) implementing aggressive surgical cytoreduction followed by adjuvant chemotherapy. Both relative paucity of patients with advanced EC and different presentation in metastasis involvement have resulted in limited prospective data available to guide clinicians in the optimal management of these patients, and at present, there is no consensus as to the most effective treatment. The aim of this review is to collect the newest evidences and multidisciplinary approach in advanced endometrial cancer in order to steer physicians along the management options.

Discussion

Endometrial cancer is a malignant neoplasm of the epithelial portion of the endometrium. The combination of uterine corpus cancer with obesity, hypertension, diabetes, coronary heart disease, and/or other internal diseases and the increase surgical and anesthesiological risk justify that advanced EC is the major gynecologic oncologic challenge of the current century.

Histology

According to histological feature, adenocarcinomas representing approximately the 80 % of endometrial cancers. 60–65 % of them are endometrioid cancers. Serous and clear cell adenocarcinomas represent the last 20 % and mixed type about 10 % of there. Rare forms of endometrial cancer are mucinous adenocarcinoma, endometrioid cancer with squamous metaplasia, small cell neuroendocrine carcinoma, squamous cell carcinoma, transitional cell carcinoma, and sarcomas [15]. The most common histological type of endometrial cancer, adenocarcinoma, is associated with the increasing rate of obesity in the population. Several recent studies correlate increasing body mass index (BMI) with increased endometrial cancer risk and implicate pathways not limited to unopposed estrogen but also involving obesity-related insulin resistance and hyperinsulinaemia, that works as independent risk factor in the pathogenesis of endometrial carcinoma [16–18]. The histological classification of endometrial cancer can be broken down into two major types. Type I endometrial cancers develop in an environment of unopposed estrogen and often arise out of endometrial hyperplasia. Type I grows slowly and has a good prognosis. Both menopausal and pre-menopausal women can be affected. A typical genetic pattern can be showed in endometrioid EC, characterized by mutations in the PTEN gene, K-ras, and microsatellite instability inception [19]. Estrogen exposure can originate from exogenous sources such as hormone replacement therapy or endogenous factors such as excessive obesity and anovulation. Other causative pathways in obesity-related endometrial cancer arise from insulin resistance, hyperglycaemia and compensatory hyperinsulinaemia, which can lead to increased insulin growth factor (IGF) bioavailability, which promotes endometrial proliferation by IGF-1 receptor signaling. Recently it was demonstrated that metformin inhibited endometrial cancer cell growth in vivo [20, 21]. Furthermore EC is strongly correlated with chronic inflammatory and oxidative background [22]. Not all patients have the same risk factors for developing an endometrial cancer. Genetics play a main role in individual's susceptibility to disease development and progression. Recent data demonstrated that APOE overexpression, lipoproteins with antioxidant, anti-inflammatory, and antiatherogenic properties, was associated with advanced grade and stage or more aggressive low differentiated cancer. APOE has several isoform and E2 isoform is associated with endometrial hyperplasia and EC [23]. Type I represents approximately 75 % of endometrial malignancies, endometrioid is the most common histological presentation and is characterise by low Istological atypia pattern (G1). Also, they are liable to hormonal therapy thanks to their estrogen and progesterone receptors. Type II endometrial cancer histologies include clear cell and papillary serous, and often arise in an atrophic environment. Tamoxifen use has also been associated with increased risk of both low- and high-grade endometrioid uterine cancers as well as non-endometrioid histologies and sarcomas [24]. Type II cancers most often present in postmenopausal women and at more advanced stages that carry a poorer prognosis. Type II cancer is not an estrogen-related cancer, occurs predominantly in post menopausal women, growing on an atrophic endometrium and shows a early invasion, getting lymph node involvement much easier than type I. It also has a poor prognosis. Type II shows typical mutations in p53 and HER2/neu [19]. A meticulous preoperative characterization of the disease severity by ultrasonography, MRI, instrumental biopsy specimen is an essential step for a right diagnosis and treatment. However, there are some evidences that the histo-type and grade change between the endometrial biopsy and surgical specimen. This discordance diagnosis has an unpleasant impact on overall survival, disease-specific survival and recurrence-free survival that are significantly lower in the high-risk EC patients who were preoperatively evaluated by endometrial biopsy compared with patients with an appropriate preoperative histological diagnosis [25]. Types 1 and 2 showing different molecular pattern of mutations also have difference in the use of currently target drugs, that have great potential to give benefit in both type of EC. For example, Temsirolimus was evaluated in recurrent or metastatic endometrial cancer patients showing a probable efficacy combined with classical chemotherapy and currently is under evaluation advanced EC by Gynecologic Oncology Group (GOG). Oral mTOR inhibition such as Everolimus and Ridaforolimus achieved encouraging result in short and long-term clinical benefit. Also in EC angiogenesis plays a main role in tumor growth process. Bevacizumab, a monoclonal antibody targeting VEGF-A, shows good results in several trials. Fibroblast growth factors (FGF) are also involved in tumorigenesis and the presence of activating mutations in FGFR-2 gene makes this a potential therapy target. Phosphatidylinositol-3-kinase (PI3K)/AKT, that play a central role in cell survival, is often constitutively activated in EC and presents one of the most promising targets for EC. Furthermore, potential

biomarkers were discovered to predict response to therapy such as PIK3CA, PTEN, AKT, as well as overexpression of phosphorylated mTOR and phosphorylated AKT (pAKT) [26]. While most endometrial cancers are sporadic, the hereditary non-polyposis cancer syndrome (Lynch syndrome) genetic mutation is associated with 2–5 % of endometrial cancers [27].

Diagnostic evaluation and staging

Uterine bleeding in a postmenopausal woman is the main presenting sign of endometrial carcinoma. Pre- or perimenopausal women with acyclical bleeding should also undergo thorough diagnostic evaluation, particularly if they have risk factors for endometrial carcinoma. Targeted screening examinations for early detection, with endovaginal sonography followed by endometrial biopsy, may be reasonable for women at high risk (e.g., those with Lynch syndrome); yet, even for these women, there is no evidence to confirm the benefit of screening. Women with abnormal bleeding of the types described should undergo the following studies:

- Gynecological examination to localize the source of bleeding and determine its physical extent; transvaginal ultrasonography for evaluation of the endometrium and adnexa. In postmenopausal patients with uterine bleeding, an endometrial thickness exceeding 5 mm is considered suspect. In contrast, no reliable cut off has been reported in pre- or perimenopausal women, as well as in postmenopausal women taking hormone replacement therapy or tamoxifen.
- Hysteroscopy and fractionated uterine curettage [28, 29].

The surgical staging of endometrial carcinoma according to the classification of the *Fédération Internationale de Gynécologie et d'Obstétrique* (FIGO) has been obligatory since 1988. A modified classification was issued by the FIGO on 1/1/2010 (Table 1). As a rule, all patients should undergo surgical staging, except those who are inoperable because of other accompanying diseases. Complete surgical staging can also be omitted for premenopausal women with early type I carcinoma that still wish to bear children (i.e., the uterus and adnexa are left in place). In such cases, contrast-enhanced magnetic resonance imaging (MRI) of the uterus and adnexa combined with diagnostic laparoscopy may be a reasonable fertility preserving approach, although it affords less diagnostic certainty than complete surgical staging. For patients who undergo surgical staging—consisting of open abdominal exploration, hysterectomy, bilateral adnexal removal, and pelvic and para-aortic lymphadenectomy (in the modified FIGO classification, peritoneal lavage cytology is no longer considered in tumor staging)—the following presurgical studies are recommended:

- a thorough physical examination (including the supraclavicular lymph nodes);
- a chest X-ray (postero-anterior and lateral views);
- abdominal ultrasonography to rule out urinary obstruction and metastasis to the upper abdominal organs;
- (optionally) cystoscopy and rectoscopy to rule out FIGO stage IVA disease [30].

Surgical debulking for advanced-stage disease

Multiple retrospective reviews have provided data supporting the role of cytoreductive surgery in the management of endometrial cancer [10–12]. In 2010, Barlin et al. [31] reviewed the published data on surgical cytoreduction in uterine cancer. In a univariate analysis combining data from 14 retrospective studies of advanced and recurrent uterine cancer, these investigators reported a relationship between complete cytoreduction and improved median survival, with borderline significance. The data came from a heterogeneous group of studies with variable definitions of optimal cytoreduction and there was not sufficient power for multivariable analysis. Thus, it is difficult to determine the true strength of the findings. The morbidity associated with more aggressive surgical techniques was not addressed. Complete cytoreduction has also been shown to increase median survival in advanced stage uterine papillary serous carcinoma (UPSC). In a retrospective study of 70 patients with stage IIIC or IV UPSC who underwent surgery, the median overall survival in patients with microscopic disease was 51 versus 14 months in patients optimally reduced and 12 months in those who were sub optimally cytoreduced. This finding remained significant when examined only in patients with macroscopic tumor at the start of surgery. Findings were similar regardless of whether or not aggressive surgical techniques were required to reach complete cytoreduction, although the study was underpowered for that comparison. Once again, data on surgical complications were not included [9]. Many studies downplay or ignore the complications associated with cytoreduction [31, 32]. In some situations, complete cytoreduction requires more aggressive surgical techniques, which are associated with increased morbidity and mortality. In a study that treated 47 cases of stage IV endometrial carcinoma, perioperative mortality was 7 % [10]. Although this is an overestimation of the true perioperative mortality, we know from the ovarian cancer literature that the morbidity and mortality associated with cytoreduction is significant [33]. The data on the role of surgical cytoreduction in uterine cancer, all of which are retrospective, are severely limited by selection bias,

Table 1 FIGO classification (2010)

Stage	Criteria
Staging for endometrial cancer	
–	Primary tumour cannot be assessed
–	No evidence of primary tumour
0	Carcinoma in situ
I	Tumour confined to uterine body
IA	Tumour limited to endometrium or involves <50 % of myometrium
IB	Tumour invades ≥50 % of endometrium
II	Tumour invades cervical stroma, does not extend beyond uterus
III	Local and/or regional spread of tumour
IIIA	Tumour invades serosa of uterine body and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with/without positive pelvic lymph nodes
IV	Tumour invades bladder mucosa and/or bowel mucosa and/or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-umbilical metastases and/or inguinal lymph nodes

including performance status, histologic subtype, and the use of various postoperative treatment modalities. Although in general the data available support an attempt at complete cytoreduction in patients with advanced endometrial cancer and a good performance status, the decision to perform cytoreductive surgery and how aggressive to be is an individual one that takes into account the patient's comorbidities, her performance status, her symptoms, and surgical risks. Intraoperatively, it can be difficult to distinguish between advanced uterine and advanced ovarian cancer. Optimal cytoreduction is strongly associated with improved survival in prospective and retrospective studies of women with ovarian cancer [33, 34]. As stated earlier, it is less clear for uterine cancer. Thus, whenever there is doubt on frozen section analysis regarding the origin of the pelvic malignancy, be it ovarian, tubal, or primary peritoneal, there is greater reason to risk morbidity to ensure an optimal cytoreductive procedure.

Neoadjuvant chemotherapy and interval debulking

The data in support of neoadjuvant chemotherapy and interval debulking in endometrial cancer lag behind those in ovarian cancer [33]. Surgical cytoreduction is useful only when it is used in conjunction with effective chemotherapy. Data have shown that chemotherapy is effective in advanced endometrial cancer [9], although not nearly so effective as it is in ovarian cancer [30]. Identifying patients responsive to chemotherapy could assist in triaging which patients might benefit from extensive cytoreduction. This is an area deserving of further investigation.

Unresectable disease because of patient factors or extent of disease

In patients in whom cytoreductive surgery is deemed impossible or inappropriate, it is often beneficial to perform a palliative hysterectomy using the least invasive approach. Unresected uterine tumor outgrows its blood supply and becomes necrotic, emitting a foul odor and causing bothersome drainage. Tumor can erode into vasculature, causing bleeding and eventually hemorrhage. Pelvic tumor can also be painful, much like advanced cervical cancer. Although many of the same symptoms can occur with pelvic or vaginal recurrence, the likelihood is theoretically higher with the uterus in situ [35].

Conclusions

Endometrial cancer (EC) is now the most common gynaecologic malignancy in the US. Advanced endometrial cancer had undergone several changes in treatment. Recently, interest in molecular pathways has steered in novel treatment strategies using hormonal therapy and molecular agents. The cornerstone is aggressive surgical cytoreduction followed by adjuvant chemotherapy that ensure a superior overall survival outcome despite the value of lymphadenectomy that is currently discussed. Several kinds of therapies can be used in association with surgery approach such as primary or adjuvant radiotherapy, hormonal and target agent therapy. Particularly the last evidences in this field could improve the personalised treatment of EC based on specific genetic characterization.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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