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Chapter 8

Past, Present and Future Perspectives on the Management of Endometrial Cancer— A Comprehensive Review

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Additional information is available at the end of the chapter

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1. Introduction

Endometrial cancer is the most frequent gynecologic malignancy in the United States and the sixth most frequent malignancy worldwide. The highest incidence of endometrial cancer is reported in North America, followed by Central and Eastern Europe. Conversely, the lowest incidence of endometrial cancer is reported in developing countries such as Central and Western Africa [1]. In the United States, roughly 47,000 new cases of endometrial cancer and 8,000 related deaths are recorded yearly [2]. The incidence of endometrial cancer has dramatically increased by 21% since 2008, and unfortunately, the mortality rate per 100,000 cases has increased by more than 100% over the last two decades, and by 8% since 2008 [3].

At the time of clinical diagnosis, it has been estimated that approximately 75% of endometrial cancer patients have early stage disease (FIGO stage I and II) with a 5-year overall survival of 80% to 90% [4, 5]. However, nearly 10% to 15% of patients with early-stage disease develop recurrences after the primary surgical treatment [6, 7]. Conversely, a very small group of patients are unlucky and present with advanced stage disease with unfortunate prognoses. The 5-year survival rates for regional disease (FIGO stage III) and distant disease (FIGO stage IV) are 57% and 19%, respectively [8].

Management of endometrial cancer can be very challenging, even for early-stage disease. The objective of the chapter is to comprehensively shed light on the past, present and future perspectives on the different treatment modalities employed in the management of endometrial cancer.

2. The role of surgery in management of endometrial cancer:

Despite the vast majority of patients diagnosed with endometrial cancer present to clinical attention with early stage disease limited to uterus, metastatic disease is recognized in a substantial proportion when comprehensive surgical staging is carried out [9]. In 1988, the International Federation of Gynecologists and Obstetricians (FIGO) officially suggested surgical staging as part of the primary management plan for endometrial cancer. Despite the recent amendments of the staging system in 2009, comprehensive staging (total hysterectomy, bilateral salpingooophorectomy, peritoneal cytology, intraoperative bilateral pelvic and para-aortic lymph node dissection) continue to be recommended [10-12].

The major advantages of comprehensive surgical staging are directly related to the diagnosis, prognosis, and proper categorization of patients who may benefit from adjuvant therapy. FIGO endometrial cancer staging is chiefly based on surgical pathology and comprehensive surgery permits accurate delineation of disease extent.

2.1. The role of laparotomy, conventional laparoscopy and robotic-assisted laparoscopy in management of endometrial cancer

Conventionally, laparotomy has been the primary mode for surgical staging in patients with endometrial cancer [10-12].

However, several studies examined the practicality of minimally invasive approaches such as laparoscopy for surgical staging of endometrial cancer [13,14].

Afterwards, randomized controlled trials endeavored to compare laparotomy versus conventional laparoscopic approaches. In Gynecologic Oncology Group Study (GOG) LAP2, more than 2000 patients with endometrial cancer were randomized to receive comprehensive surgical staging via conventional laparoscopy or laparotomy [15]. Conventional laparoscopic arm experienced fewer post-surgery complications (14% vs 21%, respectively; p=0.0001), shorter hospitalization rates over 2 days (52% vs 94%, respectively; p=0.0001), however, longer operating periods (204 minutes vs 130 minutes, respectively; p=0.001). The incidence of intraoperative adverse events was similar. Operative conversion from conventional laparoscopy to laparotomy happened in roughly 17.5% of patients with body mass index (BMI) of 25, and 26.5% of patients with BMI of 35 and above, mainly due to poor surgical exploration. Over the 6-week recovery period, the conventional laparoscopic arm patients articulated much higher scores on multiple quality-of-life aspects (less pain, more cosmetics, faster resumption of daily and social activities) [16].

A recently published meta-analysis of survival data compiling 3 randomized controlled clinical trials did identify survival differences between the surgical approaches in patients receiving the conventional laparoscopy and laparotomy for surgical staging of endometrial cancer [17]. A secondary survival analysis showed largely comparable 5-year overall survival rate (around 90% in both groups) and 3-year recurrence rate (around 11% vs 10% in conventional laparoscopy and laparotomy groups, respectively). Based on these findings, it was concluded that conventional laparoscopic approach was not inferior to laparotomy for surgical

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staging of endometrial cancer [15,18]. Rather, it was concluded that conventional laparoscopic surgical management of endometrial cancer is superior to laparotomy in terms of hospital stay and short-term safety with comparable overall survival and free-recurrence rates. Hence, conventional laparoscopy —whenever technically possible— should be considered as the recommended (primary) approach for comprehensive surgical staging in management of patients with endometrial cancer.

The daVinci Surgical System (Intuitive Surgical, Sunnyvale, CA) is widely used by many gynecologic oncologists and designed to facilitate robotic-assisted laparoscopy. Despite the many benefits (seated and long-distance operating setting, three-dimensional image of surgical field, tremor omission, etc), one of the major disadvantages is lack of haptic feedback [2].

There are multiple published retrospective case series studies that journeyed to explore the use of robotic-assisted laparoscopy for comprehensive surgical staging of endometrial cancer [19,20]. Primary results showed that robotic-assisted laparoscopy was feasible and safe (highly governed by hands-on surgical expertise). Unfortunately, robotic-assisted laparoscopy has not been prospectively compared in randomized controlled trials to conventional laparoscopy for evaluating the efficacy of endometrial cancer surgical staging, and hence data about survival, safety, and performance differences are lacking. Nevertheless, current literature data point out that robotic-assisted laparoscopy has advantages closely comparable to conventional laparoscopy. Moreover, over time, technical expertise can be simply acquired with robotic assistance as compared to conventional laparoscopy, and thus enabling the achievement of complete comprehensive staging of endometrial cancer in the obese and morbidly obese patients, as laparotomy possesses high potential adverse events in such populations [21]. For communities concerned about financial matters, cost differences between surgical approaches for staging endometrial cancer has been reported [22]. Laparotomy was the most expensive, followed by robotic-assisted laparoscopy, and followed by conventional laparoscopy.

Port-site tumor implantation taking place in patients undergoing minimally invasive laparoscopic techniques for gynecologic cancers is always a major concern for many patients and surgeons [10]. Generally speaking, the incidence of port-site tumor metastatic deposits following laparoscopic procedures in patients with malignant cancer is very minimal, and mostly takes place in the setting of already locally widely spread intra-abdominal disease or distant metastatic disease [23]. Precisely, the risks of port-site tumor implantation in patients with early-stage endometrial cancer following laparoscopic procedures (conventional or robotic-assisted approaches) are very low (less than 1%) [24]. Therefore, minimally invasive laparoscopic techniques can be used safely, to a greater degree, in patient with early-stage disease.

2.2. The role of lymphadenectomy in management of endometrial cancer

The issue of bilateral pelvic and para-aortic lymphadenectomy for surgical staging of endometrial cancer remains a topic of argument [10, 25-27]. Although lymphadenectomy is required for accurate staging, lymphadenectomy should generally be considered in patients with high risk for lymph nodal involvement [28-31]. Such risk factors include: tumor grade 3 (poorly

differentiated), more than 50% of myometrial invasion, lymphovascular space invasion, non-endometrioid histology (serous, clear cell, undifferentiated, small cell, anaplastic, etc), cervical stromal involvement, advanced FIGO stage (III and IV), and older age (above 60 years) [28].

Several randomized controlled clinical trials demonstrated no survival benefits from systematic lymphadenectomy in patients with early-stage and low-risk endometrial cancer. Benedetti Panici and colleagues [25] explored the effect of systematic lymphadenectomy in patients with stage I endometrial cancer and documented no difference in overall survival (90% vs. 86%) and disease-free survival (80% vs. 82%) rates between lymphadenectomy and no lymphadenectomy arms. Moreover, the ASTEC trial from United Kingdom [26] studied approximately 1400 patients with endometrial cancer limited to uterus, and showed no recurrence-free or overall survival benefits from pelvic lymphadenectomy in patients with early-stage endometrial cancer. Another randomized clinical trial from Italy [25] reported no difference in rates of survival or recurrence between patients who underwent lymphadenectomy versus who did not undergo lymphadenectomy for early-stage endometrial cancer. Furthermore, 2 cohort studies showed that patients with low-risk endometrial cancer disease (neoplasm size ≤2 cm, less than 50% myometrial invasion, grade 1 and 2 endometrioid neoplasms) had no lymphadenopathy at time of surgical staging and did not gain advantage from systematic lymphadenectomy [30, 31]. Collectively, these data suggest no therapeutic benefit of lymphadenectomy in patients with early-stage and low-risk endometrial cancer.

Bristow and associates [32] conducted a retrospective cohort study examining 41 patients with advanced stage IIIC endometrial cancer, and found statistically significant disease-specific survival benefit of 37.5 months versus 8.8 months (p=0.006) between patients who received optimal (completely debulked) lymphadenectomy and patients who received suboptimal lymphadenectomy groups. They concluded that patients with stage IIIC endometrial carcinoma, complete debulking of gross nodal disease and subsequent administration of combined adjuvant radiation therapy and chemotherapy are correlated with improved disease-specific survival.

There are continuing disputes regarding whether to perform complete bilateral para-aortic lymphadenectomy in all patients. Positive para-aortic lymph nodes can occur in the absence of pelvic lymphadenopathy [30, 33]. Abu-Rustum and colleagues [33] identified 1.6% rate of para-aortic lymphadenopathy in 734 patients with negative pelvic lymphadenopathy and low- and high-grade endometrial cancer. As such, the current practice is to perform pelvic lymphadenectomy, in addition to para-aortic lymphadenectomy, or to propose sentinel lymph node mapping [34, 35]. Khoury-Collado and partners [34] evaluated a sum of 266 patients with endometrial cancer for lymph node mapping. Sentinel lymph node recognition was positive in 223 patients (84%). The utility of sentinel lymph node mapping may surface as a plausible suggestion to decide whether patients with early stage endometrial cancer will get advantage from pelvic and/or para-aortic lymph node evaluation.

Other studies recommend that para-aortic lymphadenectomy should be offered to patients with advanced stage and high-risk histopathological endometrial cancer [29-32]. Mariani and colleagues [30] explored 281 patients who had lymphadenectomy at the time of endometrial cancer staging and identified that approximately 22% of high-risk patients had lymph node

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invasion. Of these, roughly 33% had isolated pelvic lymphadenopathy, 16% had isolated para-aortic lymphadenopathy and 51% had both pelvic and para-aortic lymphadenopathy.

Although straightforward disease-free survival and overall survival benefits of pelvic and para-aortic lymphadenectomy have not been solidly reported, the procedure of lymphadenectomy offers accurate staging of endometrial cancer, and recognizes node-positive patients who may benefit from adjuvant treatment.

2.3. The role of "Cytoreduction" in management of recurrent endometrial cancer

Around 25% of endometrial cancer related mortality is primarily due to recurrent disease [6, 36, 37]. More than half of patients with endometrial cancer experience recurrence following the initial surgical treatment [38]. Recurrence rates can be as low as 15% in early-stage disease and benign pathology, and as high as 50% in late-stage disease and aggressive pathology [39-41]. Prognosis of patients with recurrent disease and peritoneal metastasis is very graving (median survival less than 12 months) [42, 43]. Optimal Surgical debulking (whenever feasible), even with multiple recurrences, is the standard of care followed with adjuvant radiotherapy, chemotherapy or hormonal therapy [43].

Bristow and associates [44] reported a cohort of 61 patients undergoing cytoreduction for recurrent endometrial cancer. Optimal cytoreduction (no gross residual disease) was achieved in 66% of patients and yielded longer median recurrence-free survival rates of 39 months as opposed to patients with suboptimal cytoreduction of only 13 months ($p=0.0005$).

Awtrey and partners [45] reported a cohort of 27 patients undergoing cytoreduction for recurrent endometrial cancer. Optimal cytoreduction (no gross residual disease) and suboptimal cytoreduction (less than 2 cm residual disease) was achieved in roughly 56% and 67% of patients, respectively, and, yielded longer median survival rates (43 months vs. 10 months, respectively; $p< 0.05$).

In the above-mentioned two studies, the absence of residual disease was correlated with improved disease-free survival and overall survival rates [44, 45]. Collectively, Barlin and colleagues [46] conducted a meta-analysis and showed that optimal cytoreduction to no macroscopic disease was correlated with overall survival benefits ranging from 9 to 25 months in patients with recurrent endometrial cancer.

2.4. The role of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in management of recurrent endometrial cancer

The utilization of hyperthermic intraperitoneal chemotherapy (HIPEC) has yielded significantly substantial improvements in disease-free survival and overall survival rates in patients with peritoneal recurrence from pseudomyxoma peritonei [47], colon cancers [48], gastric cancers [49] and ovarian cancers [50]. Its use in management of recurrent endometrial cancer is minimal and has not gained much popularity.

Bakrin and colleagues [43] studied the combination of cytoreduction and HIPEC in 5 patients with recurrent endometrial cancer. Optimal cytoreduction was achieved in all patients. HIPEC

was carried out with mitomycin C and cisplatin. Intraoperative and postoperative adverse events were uneventful. Two patients developed early recurrences at 2 and 10 months and both died afterwards. The remaining three patients were alive and disease-free at 7, 23 and 39 months with fair performance status.

Abu-Zaid and colleagues [51] studied the combination of cytoreduction and HIPEC in 2 and 4 patients with primary advanced and recurrent endometrial cancer, respectively. Optimal cytoreduction was achieved in 5 patients. HIPEC was carried out with doxorubicin and cisplatin. Intraoperative and postoperative adverse events were uneventful. All patients received adjuvant chemotherapy (carboplatin and paclitaxel). Despite optimal debulking, one patient with an aggressive histology (clear cell carcinoma) relapsed within 6 months and died 5 months later because of metastatic spread to liver and pelvis. One patient with suboptimal cytoreduction (more than 2 cm residual disease) developed liver recurrence within 3 months and was still alive with disease at a follow-up of 6 months. The remaining patients were alive and disease-free without recurrence at follow-up at 35, 34, 19, and 7 months.

Another study done in France [52] included 13 patients treated with cytoreduction and HIPEC for management of endometrial cancer with peritoneal metastases. One patient was lost to follow-up. Following HIPEC, three patients died before the first year, and two patients approximately died at first year and first year and half, respectively. Three patients were alive with disease, and 4 patients were alive without disease, between approximately 2 and 125 months period.

In the above-mentioned studies, disease-free survival and overall survival rates were largely affected by degree of peritoneal cancer index, cytoreduction completeness and tumor pathology [43, 51, 52].

Despite promising results, almost all the existing studies are limited by their retrospective study designs, lack of randomized controlled trials, short follow-up periods and small sample sizes. This is an interesting arena for research and further studies are needed.

The logic for using HIPEC is chiefly attributed to the straightforward temperature-improved cytotoxicity of the intraperitoneal chemotherapeutic agents [53, 54]. Moreover, HIPEC aims to deeply penetrate the residual microscopic deposits [53, 54]— the primary source of surgical failure and early recurrence rates [43, 51, 52, 55, 56] in recurrent endometrial cancer. Moreover, HIPEC avoids the needless chemotherapy-related systemic toxicities while maximizing the local concentrations [57]. The most frequently used HIPEC agents include cisplatin [58] doxorubicin [59] and mitomycin C [60].

Generally, morbidity and mortality of cytoreduction and HIPEC are greatly influenced by the surgeons' expertise and learning curve [61]. A recent systematic review by Chua and colleagues [62] demonstrated that the morbidity rate associated with cytoreduction and HIPEC range from approximately 12% to 52%, whereas mortality rate range from 1% to 6%.

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3. The role of adjuvant radiation therapy in management of endometrial cancer

The role of radiation therapy in management of endometrial cancer is still under investigation with inconsistent findings and there are no solid conclusions. Improvement in disease-free survival rates is noted only.

3.1. Pelvic external beam radiation therapy (EBRT)

The efficacy of adjuvant external beam radiotherapy (EBRT) was studied in five randomized clinical trials [40, 41, 63-69]. Only ASTEC/EN.5 clinical trial included a substantial percentage of patients with aggressive serous or clear cell histology (6.5%) [64]. Conversely, in all the other remaining trials, endometrioid adenocarcinoma was the most predominant histology. All trials demonstrated advantages of EBRT in terms of loco-regional control (disease-free survival) only, but failed to yield any survival benefits. Furthermore, at a median follow-up of 21 years, an update of Oslo trial demonstrated that patients under 60 years of age who were administered adjuvant EBRT experienced lower overall survival rates and higher risks of harboring secondary malignancies, as high as 30% [69]. Moreover, in the PORTEC trial, patients who received EBRT had worse quality of life as opposed to the observation patients [68]. The EBRT toxicities commonly involved the urogenital and gastro-intestinal tract systems and included urinary leakage and urgency, in addition to frequent diarrheal attacks and stool incontinence. These findings were endorsed in two recently published meta-analyses [70, 71]. Subgroups analyses were completed and demonstrated that EBRT had improved disease-free survival in patients with high risk of recurrence ($p=0.03$), however, EBRT had harmful outcomes on overall survival in patients with low or intermediate risk of recurrence ($p=0.03$) [70]. Therefore, it can be concluded that adjuvant EBRT should be largely employed for management of high-risk patients with primary advanced or recurrent endometrial cancer. Moreover, long-term related toxicities of EBRT should be considered wisely when adjuvant EBRT is selected for younger patients. EBRT should be selected in patients with high-risk histological features, positive lymph nodes or primary advanced stage disease (III/IV) [28]. The suggested histopathological features for determining high-risk disease include: tumor grade 3 (poorly differentiated), more than 50% of myometrial invasion, lymphovascular space invasion, non-endometrioid histology (serous, clear cell, undifferentiated, small cell, anaplastic, etc), cervical stromal involvement, advanced stage disease (FIGO stage III and IV) and older age (more than 60 years) [28].

3.2. Vaginal brachytherapy

The efficacy of adjuvant vaginal brachytherapy (VB) was evaluated in two randomized clinical trials [72, 73]. Patients with serous or clear cell histology were exempted from the studies and only patients with endometrioid adenocarcinomas were included. In low-risk patients with endometrial cancer (stage IA−B, grades 1–2), vaginal brachytherapy did not add benefit over observation [72]. However, in PORTEC-2 clinical trial, in high-intermediate risk patients, vaginal brachytherapy was demonstrated to be non-inferior to EBRT and provided comparable

loco-regional control (less than 2% at 5-year period for both arms), disease-free survival and overall survival [63, 73]. Vaginal brachytherapy is associated with considerably fewer gastrointestinal tract toxicities (less diarrheal attacks and stool incontinence) and a better functioning social quality of life [72-74]. Sorbe and colleagues [63] compared combination of EBRT and brachytherapy versus brachytherapy alone: there was no 5-year overall survival benefit (89% and 90%, respectively; p=0.548). However, the 5-year pelvic and loco-regional recurrences were much more common in the vaginal brachytherapy alone group (1.5% and 5%, respectively; p=0.013). It was concluded that combined radiation therapy (EBRT and vaginal brachytherapy) should possibly be reserved for high-risk patients, whereas vaginal brachytherapy alone should be reserved for purely medium-risk patients.

In conclusion, vaginal brachytherapy, to a certain degree, effectively decreases the risk of vaginal recurrence in patients with risk factors while minimizing the radiation-related toxicities. In patients with early-stage endometrial cancer, vaginal brachytherapy should the adjuvant treatment of choice over EBRT.

4. The role of adjuvant chemotherapy in management of endometrial cancer

The role of adjuvant chemotherapy has been studied in patients with early-stage intermediate-to-high risk endometrial cancer, as well as patients with primary advanced, inoperable or recurrent late-stage endometrial cancer [39, 75-81]. The efficacy of postoperative chemotherapy was studied in a total of nine randomized clinical trials [39, 75-81]. The following trials included a substantial percentage of patients with the aggressive serous or clear cell histology: NSGO-EORTC (37%), GOG122 (25%), GOG184 (18%) [39, 78, 81]; the vast majority of patients had endometrioid adenocarcinoma histology.

Three clinical trials compared chemotherapy schedules with radiotherapy [39, 75, 76]. Two randomized clinical trials compared between one group of patients receiving cyclophosphamide–doxorubicin–cisplatin, and one group of patients receiving pelvic EBRT. There were no benefits between both groups with respect to 5-year progression-free survival and overall survival rates [75, 76]. Conversely, GOG122 trial demonstrated statistically significant 5-year progression-free survival (50% and 38%, respectively; p=0.007) and overall survival (55% and 42%, respectively; p=0.004) rates between one group of patients receiving doxorubicin–cisplatin, and one group of patients receiving EBRT. All patients studied in COG122 study had advanced stage disease (III/IV) with less than 2 cm residual disease post-surgery [39].

Four clinical trials explored the advantage of adding a chemotherapy regimen to EBRT [77-79]. Three clinical trials (MaNGO ILIADE-III, Kuoppala and GOG34) demonstrated no progression-free survival or overall survival benefits of combined treatment (chemotherapy plus radiotherapy) versus EBRT alone. However, the NSGO-EORTC trial showed that postoperative chemotherapy was correlated with an improved 5-year progression-free survival rate (79% and 72%; p=0.004), but not overall survival benefits [77]. There are discrepancies for the reported results among studies and these can be attributed to the variances of treatment

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methods such as: percentage of patients with advanced stage disease (stage III–IV) and choice of chemotherapy regimens. Therefore, such studies must be interpreted with caution.

However, overall, a recently published meta-analysis covering a total of nine clinical trials showed that adjuvant chemotherapy was correlated with a statistically significant overall survival benefit (HR=0.74 [95% CI: 0.62–0.89]; p=0.0009), associating with an absolute difference of 3% in 5-year survival rate [80].

Two clinical trials endeavored to compare chemotherapy regimens and the superiority of either of them in terms of progression-free survival or overall survival rates failed to take place [81, 82]. Fujimura and colleagues [81] considered one group of patients with cyclophosphamide–doxorubicin–cisplatin, and one group of patients with etoposide–cisplatin. Homesley and colleagues (the GOG184 trial) [82] considered one group of patients for doxorubicin–cisplatin–placitaxel, and one group of patients for doxorubicin–cisplatin. In this study, the addition of paclitaxel to a cisplatin–doxorubicin regimen was accompanied with substantial chemotherapy-related side effects, mainly neurologic and hematologic [82].

There is an ongoing randomized clinical trial GOG209 phase III (paclitaxel–carboplatin versus paclitaxel–doxorubicin–cisplatin for management of recurrent/advanced endometrial cancer) [83]. Preliminary findings demonstrated that carboplatin–placitaxel combination was not inferior to doxorubicin–cisplatin–placitaxel with respect to progression-free survival (comparable median of 13-14 months; $p > 0.05$) and overall survival (32 versus 38 months, respectively; no statistical significant difference: $p > 0.05$) and was associated with reduced toxicity: peripheral neuropathic toxicity grade 2 or higher (19% versus 26%), thrombocytopenia (12% versus 23%), metabolic imbalances (8% versus 14%), vomiting (4% versus 7%) and diarrhea (2% versus 6%) [10]. However, in consideration of the paclitaxel–doxorubicin–cisplatin associated toxicity, the combination of paclitaxel–carboplatin probably stands as the most preferred utilized chemotherapy regimen, and its administration is supported by the GOG209 trial above [83] and many other retrospective studies [51]. More studies are needed.

Previous studies have demonstrated that neoadjuvant chemotherapy with subsequent optimal cytoreduction for patients presenting with primary advanced endometrial cancer yielded no residual disease in 79% to 100% of all patients treated [84, 85]. Additional studies are needed.

5. The role of hormonal therapy in management of endometrial cancer

Many endometrial cancers express estrogen (ER) and progesterone (PR) receptors, and hence hormonal therapy can be applied as reasonable therapeutic choice in patients with hormone receptor-positive endometrial cancers. The presence of ER and PR receptors largely provides a powerfully predictive value in evaluating therapeutic response to hormonal therapy.

Primary hormonal therapy (without surgical intervention) to preserve fertility in child-bearing women with endometrial cancer has shown some degree of success, although the vast majority of patients ended up receiving the definitive therapy (that is, total abdominal hysterectomy) [86, 87]. As opposed to adjuvant radiotherapy, chemotherapy or combined radio-chemother-

apy, hormonal therapy is hardly ever considered as one of the "primary" adjuvant treatment regimens in management of patients with endometrial cancer [86, 87]. Currently, hormonal therapy is largely employed for management of patients with poor performance status or recurrent/advanced/metastatic endometrial cancers, with the advantages of low morbidity, few drug-related side effects and relatively suboptimal therapeutic response [86, 87].

The most frequently employed hormonal agents for management of endometrial cancer include: progesterone/progestin, selective estrogen receptor modulators (SERMs), gonadotropin-releasing hormone (GnRH) agonists, and aromatase inhibitors [86-90].

5.1. Progesterone/progestin

Progesterone/progestin has been proven to be an effective inhibitor (suppressor) of endometrial carcinogenesis mediated through estrogen exposure [91, 92].

Many retrospective studies and clinical trials have been conducted to evaluate the role of multiple progestin-based hormonal therapy regimens in management of patients with recurrent endometrial cancer. The most commonly used regimens are megestrol acetate (MA) and medroxyprogesterone acetate (MPA).

In 1996, a meta-analysis of 6 randomized trials comprising a sum of 3339 patients with endometrial cancer failed to produce any survival benefits when adjuvant progesterone/progestin therapy was administered [93]. Moreover, a successively reported randomized clinical trial recruiting more than 1000 patients with endometrial cancer also failed to produce any survival benefits when adjuvant progesterone/progestin therapy was administered [94]. Furthermore, in 2011, a recently published Cochrane meta-analysis demonstrated no survival benefits of adjuvant progesterone/progestin in 4556 patients with endometrial cancer [95]

5.2. Selective estrogen receptor modulators (SERMs)

The expression of ER in endometrial cancer justifies the use of selective estrogen receptor modulators (SERMS), such as tamoxifen and raloxifene [96]. The tamoxifen-induced increased risk of developing endometrial cancer is a well-known adverse effect and must always be considered in mind [97], as opposed to raloxifene that is not associated with any endometrial cancer risk.

Thigpen and partners [98] used adjuvant tamoxifen (2 doses of 20 mg/day) in management of patients with recurrent and advanced endometrial cancer. The response rate was 10%. The median progression-free survival and overall survival rates were roughly 2 and 9 months, respectively. Raloxifene produced equally unsatisfactory results.

Arzoxifene is a modified drug of raloxifene. Two phase II clinical trials by McMeekin et al. [99] and Burke et al. [100] explored the role of adjuvant arzoxifene (20 mg/day) for management of patients with recurrent, metastatic and advanced endometrial cancer. The response rates were 25% and 31%, respectively. The median response periods were approximately 19.3 and 12.9 months, respectively.

Rendina and associates [101] compared the efficacy of adjuvant tamoxifen versus MPA in patients with recurrent endometrial cancer, and response rates were roughly 53% and 56%, respectively.

Pandya et al. [102] randomized 20 patients and 42 patients with endometrial cancer to receive MA (standard progestin) and combination of MA plus tamoxifen, respectively. The response rates were 20% (1 complete and 3 partial responses) and 19% (1 complete and 7 partial responses), respectively. It was decided that the combination of MA plus tamoxifen did not yield clinical benefits over MA alone in management of patients with advanced endometrial cancer.

Whitney et al. [103] in a phase II trial of MPA (200 mg/week) plus tamoxifen (40 mg/day) in patients with advanced and recurrent endometrial cancer demonstrated a 33% response rate (13 partial and 6 complete responses among a total of 58 patients). The median progression-free survival and overall survival were 3 month and 13 months, respectively. It was concluded that daily tamoxifen (40 mg/day) and alternating weekly MPA (200 mg/week) constitutes an effective therapeutic regimen in management of patients with recurrent and advanced endometrial cancer.

5.3. Gonadotropin-releasing hormone (GnRH) agonists

Gonadotropin-releasing hormone (GnRH) agonists can effectively suppress estrogen production levels by ovarian cells — a process mediated by down-regulation of GnRH receptors [87]. Multiple studies in the United Kingdom explored the usefulness of GnRH agonists in the management of patients with recurrent endometrial cancer [104, 105]. In a phase II clinical trial, 6 out of 17 patients (35%) experienced a response rate at a median of 20 months without drug-related toxicities [104]. A long-term follow-up study, five years afterwards, the same research team documented that the response rate was 28% in 32 patients with recurrent endometrial cancer [105]. The response rate was higher in the previously irradiated regions (35%) versus non-irradiated regions (28%) of relapse. The study concluded that utilization of GnRH agonists greatly exhibit beneficial anti-cancer outcomes in patients with recurrent and advanced endometrial cancer, particularly in those patients who received previous radiation therapy.

Another GOG clinical trial explored the influence of Goserelin acetate (GnRH agonist) in 42 patients with advanced and recurrent endometrial cancer. A total of 5 patients (11%) experienced a response rate. The median progression-free survival and overall survival rates were roughly 2 and 7.3 months, respectively [106].

5.4. Aromatase inhibitors (AIs)

Aromatase inhibitors (AIs), such as anastrozole and letrozole, directly block the aromatase enzyme, and subsequently decrease the estrogen production and suppress its estrogen-driven neoplastic endometrial proliferation [87].

A phase II clinical trial by Rose and colleagues [107] studied the efficacy of anastrozole (1 mg a day for 28 days) in 23 patients with advanced or recurrent endometrial cancer. The response

rate was 9% and progression-free interval ranged from 1 to 6 months. Despite the drug-related adverse events were well-tolerated, it was concluded that anastrozole does not offer any survival advantages.

Another multi-center phase II clinical trial by Ma and colleagues [108] studied the effect of letrozole in 28 patients with metastatic or recurrent endometrial cancer who previously received progestin-based and/or chemotherapy regimens. One patient (3.6%), two patients (7.1%) and eleven patients (39%) experienced a complete response, a partial response and a median 6.7-month stable disease, respectively. The median time to progression and overall survival were approximately 4 and 9 months, respectively. The most frequently encountered drug-related adverse events in a descending order were: hot flashes, grade I and II (28%), followed by fatigue and anemia

In short, it can be concluded that AIs greatly failed to offer survival benefits in management of patients with endometrial cancer

6. The role of molecular-target therapy in management of endometrial

As opposed to conventional cytotoxic drugs, molecular-targeted cytotoxic drugs are able to differentiate between normal cells and cancerous cells, and therefore specifically damage only the cancerous cells by inhibiting the cellular molecules/pathways associated with neoplastic proliferation and metastasis [109].

6.1. Mammalian target of rapamycin (mTOR) inhibitors

PTEN genetic mutations are associated with reduced apoptosis and are implicated in more than 80% of endometrioid cancer of the uterus [109]. The effects of PTEN genetic mutations can be decreased by utilizing mammalian target of rapamycin (mTOR) inhibitors (for example, temsirolimus, ridaforolimus, everolimus, and AP2357) by interrupting phosphoinositide 3-kinase◎AKT◎mTOR pathway [109, 110]. In a phase II clinical trial of temsirolimus in previously chemotherapy-untreated patients with recurrent endometrial cancer, 26% and 63% of patients experienced partial response and stable disease, respectively [111]. In a phase II clinical trial of temsirolimus in previously chemotherapy-treated patients with recurrent endometrial cancer, 7% and 44% of patients experienced partial response and stable disease, respectively [112].

In a phase II clinical trial of ridaforolimus as a single agent in patients with advanced endometrial cancer, a total 29% of patients experienced clinical beneficial response in the form of complete response, partial response or prolonged stable disease for more than 16 weeks [113].

In a phase II clinical trial of everolimus as a single agent in patients with recurrent endometrial cancer, 21% of patients experienced confirmed clinical beneficial response in the form of complete response, partial response or prolonged stable disease at 20 weeks after therapy [114].

There is an ongoing randomized controlled trial single-agent temsirolimus versus a combination of temsirolimus and hormonal therapy [109]

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6.2. Human Epidermal Growth Factor Receptor (EGFR) Inhibitors

Epidermal Growth Factor Receptor (EGFR) is frequently expressed in normal endometrial tissues; however, its overexpression is correlated with advanced endometrial cancer and poor prognosis [110]. Examples of EGFR inhibtors include erlotinib and gefitinib, both of which are low-molecular weight tyrosine kinase inhibitors.

In a phase II clinical trial of erlotinib in 23 patients with recurrent endometrial cancer, only one patient (4.3%) experienced partial response [115]. In a phase II clinical trial of gefitinib in 29 patients with recurrent endometrial cancer, only one patient (3.4%) experienced complete response [116].

Cetuximab is a monoclonal antibody targeted against EGFR. A phase II clinical trial of cetuximab in management of recurrent endometrial cancer is still ongoing [110].

Trastuzumab belongs to human EGFR type 2 (HER-2)-related inhibitors [110]. HER-2 overexpression is implicated in the development of advanced endometrial cancer and poor prognosis [117, 118], and specifically found in up to 20-30% of patients with serous endometrial cancer [119]. A phase II clinical trial of trastuzumab in 33 patients with HER-2 amplified recurrent/advanced endometrial cancer did not result in any clinical beneficial response [120]

Lapatinib is an inhibitor targeting EGFR and HER-2 receptors. A phase II clinical trial of lapatinib in management of recurrent endometrial cancer is still ongoing [110].

6.3. Angiogenesis Inhibitors

Vascular Endothelial Growth Factor (VEGF) plays central roles in angiogenesis and overexpression is a feature in advanced endometrial cancer and correlated with poor prognosis [110, 121].

In a phase II clinical trial of single agent bevacizumab (a recombinant humanized immunoglobulin monoclonal antibody targeted against VEGF) in 52 patients with recurrent endometrial cancer, only 7 patients (around 14%) showed complete/partial response at 6 months following treatment. The median progression-free survival and overall survival were roughly 4 and 11 months, respectively. The adverse side effects were tolerated [122]. Wright and colleagues [123] studied the role of bevacizumab in 10 patients with recurrent endometrial cancer. Only two (20%) and three (30%) patients responded to treatment and experienced stable disease, respectively. A GOG 229-E phase II clinical trial of single-agent bevacizumab, and GOG 229-G phase II clinical trial of a combination of bevacizumab and temsirolimus in management of patients with metastatic endometrial cancer are still ongoing [109, 110].

Aflibercept is a fusion protein with high-affinity against VEGF receptors [110]. In a phase II clinical trial of single agent Aflibercept in 44 patients with recurrent endometrial cancer, only 3 patients (around 8%) experienced partial response. Moreover, 18 patients (41%) experienced progression-free survival of 6 months; however, of these, 8 patients had to withdraw aflibercept secondary to drug-related adverse events. The median progression-free survival and overall survival were roughly 3 and 15 months, respectively [124].

Thalidomide possesses anti-angiogenetic action [110]. In a phase II clinical trial in 24 patients with chemotherapy-unresponsive recurrent endometrial cancer, 3 patients (12.5%) experienced partial response and 2 patients (8.3%) had a progression-free survival of more than 6 months. The median progression-free survival and overall survival were roughly 1.7 and 6.3 months, respectively [125].

Sunitinib is a multi-kinase inhibitor with an anti-angiogenetic action. It is currently under investigation in clinical trials to assess its effectiveness in management of patients with recurrent endometrial cancer [109, 110].

The existing response rates to molecular-targeted regimen as single-agent treatment are largely insignificant and additional randomized clinical trials are necessary, probably with a combination of currently available treatments and an exploration for elements influencing molecular targeted drug sensitivity.

7. Conclusion

- Management of endometrial cancer is challenging.
- Endometrial cancer is primarily treated with surgical staging.
- Comprehensive surgical staging for endometrial cancer is recommended (total hysterectomy, bilateral salpingooophorectomy, peritoneal cytology, intraoperative bilateral pelvic and para-aortic lymph node dissection). It allows accurate delineation of the extent of the disease and subsequently allows identifying patients who may benefit from adjuvant therapy.
- The extent of lymph node dissection (bilateral pelvic and/or para-aortic) in surgical staging of patients with endometrial cancer, regardless of FIGO staging, remains controversial.
- As opposed to laparotomy, conventional laparoscopy —whenever technically possible— should be considered as the recommended (primary) approach for comprehensive surgical staging in patients with endometrial cancer
- For patients with recurrent endometrial cancer, optimal cytoreduction (even if multiple) is associated with increased disease-progression survival.
- For patients with recurrent endometrial cancer and peritoneal metastasis, the role of hyperthemic intraperitoneal chemotherapy is still experimental. Despite initial promising results, additional studies are needed.
- For high-risk patients with endometrial cancer, adjuvant treatment (radiation therapy, chemotherapy, or both) is recommended, and appropriate selection of patients for adjuvant therapy is critical.
- For high-risk patients with endometrial cancer, adjuvant pelvic external beam radiation therapy is recommended over vaginal brachytherapy. Conversely, in low-risk patients with

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endometrial cancer, adjuvant vaginal brachytherapy, and not external beam radiation therapy, should be primarily used (if deem necessary by treating physicans). Radiation therapy can improve disease-free survival.

- For high-risk patients with endometrial cancer, carboplatin—placitaxel adjuvant chemotherapeutic regimen is recommend over the standard doxorubicin—cisplatin (with or without placitaxel) chemotherapeutic regimen, due to its well-tolerated drug-related adverse effects and non-inferiority to the standard chemotherapeutic regimen. It is associated with improved disease-free survival.
- For high-risk patients with endometrial cancer, a combination therapy of radiation therapy and chemotherapy could probably decrease the disease progression and overall death.
- Hormonal therapy is not recommended, and its use should be restricted to clinical trials.
- Molecular-targeted therapy is not recommended, and its use should be restricted to clinical trials.
- Long-term follow-up of patients is necessary.
- Further randomized controlled clinical trials are needed.

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