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Review Article

Controversies in the management of early endometrial carcinoma: an update

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ABSTRACT

Endometrial carcinoma (EC) is the commonest genital tract malignancy in developing countries and is usually confined to the uterus at the time of diagnosis with excellent prognosis and high cure rates. But the management is associated with lot of controversies like in staging, best surgical approach, extent of lymphadenectomy, adjuvant therapy, fertility sparing surgery in young women etc. A thorough surgical staging is important to determine uterine and extrauterine spread and also understanding of the pathophysiology and management strategies to identify women who are at high risk and tailoring the adjuvant treatment if necessary without increasing the morbidity. This evidence based narrative review conducted by searching Medline (1994- 2015) and other online articles from Pubmed, Google scholar. Articles were selected based on their currency and relevance to the discussion they summarize the current literature to provide an approach to best practice management of early endometrial carcinoma.

Keywords: Adjuvant treatment, Endometrial carcinoma, Lymphadenectomy

INTRODUCTION

Endometrial carcinoma (EC) is the commonest genital tract malignancy in developing countries accounting for 50% of all new gynaecological cancers diagnosed but worldwide it is the second common cancer after carcinoma of cervix 75 to 85% occur in the sixth and seventh decades of life, and 95% of them over 40 years and 5% below 40 years.[1,2]

It is predominantly a disease of affluent obese women of low parity who are usually medically compromised and also in women with endometrial hyperplasia, unopposed estrogen therapy etc. In addition to 5% of EC are associated with Lynch Syndrome Type II, who has a life time risk of developing EC in 30-60% of cases. Use of combine oral contraceptive pills decreases the risk of EC both in premenopausal and perimenopausal women.[3] Patients who have high risk factors like advanced age, high tumor grade, aggressive histology and advanced stage presents a real challenge.

Histologically there are two subtypes of EC. Type I, most common, estrogen dependent, occurs in younger age, has a precursor lesion and typically localized. 75-80% are in early stage with 5-year survival rate of more than 90%. Type II, it usually occurs in older age women with no obvious risk factors, non-estrogen dependent and has high propensity for metastasis. Around 60% present in early stage.[4]

METHODS

This is an evidence based narrative review conducted by searching Medline (1994-2015) and other online articles from Pubmed, Google scholar by using terms like

endometrial carcinoma, controversies in endometrial carcinoma, screening, FIGO staging, management, lymphadenectomy, fertility sparing treatment and adjuvant therapy in early endometrial carcinoma and It included 33 articles. Articles were selected based on their currency and relevance to the discussion. We did not use statistical testing or concepts of statistical significance. No attempt was made to analyze any specific aspect of early endometrial carcinoma but we have highlighted the important existing controversies in early endometrial carcinoma.

Current article would provide an approach to best practice management of early endometrial carcinoma and also promote and facilitate a more educated, systematic and effective physician response.

Controversies in screening and diagnosis

Controversy is whether routine screening is required or screening only a high-risk woman. As there is no ideal screening test for EC like carcinoma cervix screening is recommended for women with high risk factors. Cervical cytology is abnormal only in less than 50% of cases.

Transvaginal ultrasound is a single noninvasive technique to determine endometrial thickness with a cutoff value of 5mm for postmenopausal women. Women with ≥5mm requires further evaluation. Endometrial biopsy is the first definitive step in evaluating postmenopausal women with bleeding, those with abnormal Pap smear showing endometrial cells in postmenopausal women or atypical glandular cells in premenopausal women or those on tamoxifen therapy with bleeding or thick endometrium. If finding is inconclusive and highly suspicious hysteroscopic guided biopsy is the best option.

Controversies in surgical staging

FIGO 1971 clinical staging, which was useful only to a small number of EC who will be treated primarily with radiotherapy (RT) or preoperative RT for high risk women based on fractional curettage and clinical findings, this was replaced by FIGO 1988 surgicopathological system, which emphasis both uterine and extrauterine spread, which is important for prognosis but it does not specify the role of lymphadenectomy, extent of the lymphadenectomy for complete staging.[5] FIGO 1988 surgicopathological staging differentiate low risk and high risk group who may require adjuvant treatment and also helps to determine the initial extent of the disease. But this is useful mainly in early stage EC, there is no benefit on survival in low risk group. Morbidity is increased with pelvic and paraaortic node sampling/removal as most of them are obese and medically compromised and it is not of much use in advanced stage. With advances in imaging technology most of the prognostic factors can be assessed preoperatively. In 2009, FIGO revised the surgical staging for EC.[6] The primary changes were stage IA and stage IB which were combined as stage I A with no or < 50% myometrial involvement, removal of prior IC as IB ≥50% myometrial invasion and tumor of any grade. This change was made due to the fact that there was no difference in survival between I A and IB with tumor grade 1 or 2.

Another change made in 2009 FIGO classification was stage IIIC is divided into C_1 with positive pelvic nodes and C_2 with positive paraaortic nodes as many studies revealed a worse survival pattern for patients with positive paraaortic lymphnodes.[7] (Table 1).

Controversy in the surgery of endometrial cancer

The surgical management of most of the patients affected by EC is through surgical exploration of the abdominal cavity with peritoneal cytology, total extrafasial hysterectomy with bilateral salpingo-oophorectomy as majority of women are in Stage I with well differentiated EC. Papillary, serous cell carcinoma and carcinosarcoma of the uterus requires comprehensive staging procedure which included TAH with BSO, peritoneal cytology, pelvic and paraaortic node dissection, omentectomy and biopsy and resection of any suspicious lesions.

For clinically obvious cervical involvement a radical hysterectomy with lymphadenectomy or preoperative radiotherapy followed by total extrafacial hysterectomy with BSO six weeks later.

Treatment planning must be tailored depending on tumor grade, depth of myometerial invasion, extension to cervical stroma or unfavourable histology. All these factors are directly related to the risk of regional lymphnodes and distant metastasis influencing overall prognosis. Laparotomy is the standard procedure but now a day with advances in technology laparoscopic or robotic surgery is coming into play. Vaginal hysterectomy has limited for high risk patients with co morbidities and with Stage I EC which contraindicates abdominal procedures. It has limitations of lack of exploration and cytological evaluation of the abdominal cavity, difficulty in performing salpingo-oophorectomy and inability to perform thorough evaluation of lymphnodes.[8]

Role of lymphadenectomy

The lymphadenectomy provides important information regarding the need for postoperative adjuvant treatment, in order to maximize the survival and minimize the morbidity of over-treatment and the risks of under-treatment leading to recurrence. Lot of controversy exists regarding lymphadenectomy. No consensus exists regarding role and extent of lymphadenectomy with primary surgical setting and more controversial in its therapeutic role. The risk of pelvic and or paraaortic nodal metastasis depends on histologic type, grade and myometrial invasion.

Table 1: Staging of endometrial carcinoma.

FIGO 1971 Clinical Staging	FIGO 1988 Surgico-Pathological Staging	FIGO 2009 New Minor Modification of 1988
Stage I: Confined to the corpus IA: Length of the uterine cavity is ≤8 cm IB: Length of the uterine cavity is >8 cm Stage I: further divided into G1, G2, G3	Stage I* IA: Tumour limited to Endometrium IB: Invasion to <50% of the myometrium IC: Invasion to >50% of the myometrium	Stage I*: Tumor confined to the corpus uteri IA: No or <50% myometrial invasion IB: Invasion to >50% of the myometrium
Stage II: Carcinoma involves the corpus and cervix	Stage II* IIA:Endocervical glandular involvement only IIB: Cervical stromal invasion	Stage II*: Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III: Carcinoma extends outside the uterus but not outside the true pelvis	Stage III* IIIA: Tumour invades serosa and/or adnexa and/or positive peritoneal cytology IIIB: Vaginal metastases IIIC: Metastases of pelvic and/or para-aortic lymph nodes	Stage III*: Local and/or regional spread of the tumor IIIA: Tumor invades the serosa and/or adnexae*** IIIB: Vaginal and/or parametrial involvement IIIC: Metastases to the pelvic and/or para- aortic lymph nodes IIIC1: Positive pelvic nodes IIIC2: Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV: Carcinoma extends outside the true pelvis or involves the bladder or rectum	Stage IV* IVA: Tumour invasion of bladder and/or bowel mucosa IVB: Distant metastases including intra-abdominal and/or inguinal lymph nodes	Stage IV*: Tumor invades bladder and/or bowel, mucosa, and/or distant metastases IVA: Tumor invasion of bladder and/or bowel mucosa IVB: Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes
Histologic subtypes of adenocarcinoma G1: Highly differentiated adenomatous carcinoma G2: Differentiated adenomatous carcinoma with partly solid areas G3: Predominantly solid or entirely undifferentiated carcinoma	* Either G1, G2, or G3	* Either G1, G2, or G3 ** Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II *** Positive cytology has to be reported separately without changing the stage.

Milan et al reported the risk of lymph node metastasis in low risk versus high risk patients from a secondary analysis of GOG study, which indicates only 8% of patients in the low risk group had nodal involvement there by suggesting avoidance of lymphadenectomy in those patients with very low risk for nodal metastasis.[9] Based on GOG study 33, the two most important factors in determining lymphnode involvement were depth of tumor invasion and grade of tumor. Creasman et al in their study of 621 patients with apparent Stage I EC reported only 22% of patients found to have extrauterine disease. Grade and depth of myometrial invasion were found to be related to the presence of extrauterine disease.[10] Results from Cochrane analysis showed no difference in recurrence free or overall survival of patients undergoing lymphadenectomy in EC confined to uterus clinically and found the risk of adverse events such as formation of lymphocyst or lymphedema was higher in lymphadenectomy group.[11] Lymphadenectomy improves the carcinoma related survival and recurrence in high risk endometrroid adenocarcinoma patients.[12] Conversely lymphadenectomy does not appear to benefit patients with grade 1 and 2 endometroid lesions with myometrial invasion <50% and primary tumor diameter <2cm. So, there is increased evidence against the need to perform systemic lymphadenectomy in low risk cases.[13] What is the extent of lymphadenectomy, whether paraaortic nodes has to be removed or not is controversial. Among patients

who underwent systemic pelvic and paraaortic lymphadennectomy 96.2% has negative paraaortic nodes when the pelvic nodes were negative but when pelvic nodes were positive 48% of them had positive paraaortic nodes so paraaortic lymphadenectomy is advised in all high-risk patients or in patients with two or more positive pelvic lymphnodes.[14] Lymphadenectomy could be important in determining prognosis and in tailoring adjuvant treatment.

In recent years, to reduced risk of perioperative complications compared to the systematic lymphadenectomy, the sentinel lymph node detection and dissection has emerged as viable option.

This is based on the theory that lymph drains away from the tumor in a specific centrifugal pattern, if the sentinel lymph node is negative for metastasis, then the chance that more distal nodes are involved by tumor is very low, and therefore the need for further lymphadenectomy is not necessary. Sentinel lymph node mapping could play an essential role in the identification of lymph nodes with micrometastases, especially in EC patients with early stage disease as mentioned in SENTI-ENDO study. Sentinel lymphnode identification in EC has been described with interesting preliminary results, needs investigation in properly designed clinical trials.[15]

Recommendations

Low risk disease

- Surgery may be limited to hysterectomy and salpingo oophorectomy as an acceptable alternative to stage I patients with grade 1 disease.
- Additional risk assessment can include preoperative or intraoperative evaluation of myometrial invasion. Adjuvant treatment depends on histopathologic stage and grade.

High risk disease

- In grade 2 or 3 adenocarcinomas, clear cell/ papillary serous carcinoma on biopsy, consideration should be given to perform pelvic and or paraaortic lymphadenectomy to facilitate accurate planning of adjuvant therapy which is often required postoperatively.[16]

Role of minimally invasive surgery

Laparoscopic staging combined with laparoscopic assisted vaginal hysterectomy can be recommended for treatment of endometrial carcinoma. It is less invasive with less intraoperative and postoperative morbidity. Walker et al in a large randomized trial (Lap II trail) from GOG compared laparoscopic hysterectomy with comprehensive surgical staging to the traditional laparotomy technique in 2616 patients of clinical Stage I to IIA uterine cancer. 920 patients were for open method and 1696 to laparoscopy group.

There was 26% conversion rate from laparoscopy to laparotomy more so in obese women. Frequency of positive lymph nodes were same in both groups (9%) while there was a statically significant higher paraaortic node dissection in laparotomy group (97% versus 94%). The rate of postoperative complications, median blood loss, median length of hospital stay was significantly lower in laparoscopy group despite the disadvantage of relatively higher conversion rate.[17]

Role of robotic surgery

Robotic surgery is particularly suitable for EC as they are obese and at greater risk for postoperative wound complication and will benefit with smaller incisions resulting in less risk of postoperative wound complications.

Operating difficulty is less in obese women. Gehrig et al in a retrospective study comparing laparoscopic approach with robotic assisted approach in obese and morbidly obese women found better surgical outcomes in women undergoing robotic surgery.[18]

Ovarian preservation in EC

There is a lot of controversy whether to reserve or retain ovaries during hysterectomy in young premenopausal women; ovaries are the site of occult metastatic disease and oophorectomy decrease the risk of recurrence or subsequent ovarian cancer.

Based on these facts traditionally BSO is done along with hysterectomy in the treatment of EC. Lie et al in their study of 175 women with EC whose median age was 38.5 years underwent hysterectomy without BSO and were followed up for 55 months and found that the overall survival was 93.3% with 7 patients developing recurrent disease in women with nonendometrial histology, deep myometrial invasion or in those with inadequate adjuvant treatment and found no recurrence in Stage IA disease.[19]

5% of patients with EC are less than 40 yrs and 14% of them were premenopausal. Preservation of ovaries is not the standard care. There are no preoperative predictors to predict the risk of ovarian disease. Genetic predictors may be useful.

Patients must be willing to come for follow up closely even then early detection of ovarian cancer may be missed.

Walsh et al in a retrospective analysis of 102 women with less than 45 years found synchronous ovarian tumors in 19%, metastatic disease in 3% and ovarian involvement in 25% of patients and advised strongly BSO.[20]

Based on various studies the recommendations are[21]

- Patients who are for fertility sparing surgery should be carefully evaluated with an endometrial sampling, MRI and other diagnostic modalities aimed at detecting advanced or high risk disease. (Level-A)
- Medroxy progesterone acetate (MPA) and megestrol acetate are most commonly used progestins in those women with early stage EC. (Level-A)
- Ovaries conservation at hysterectomy is feasible but should be individualized. (Level-C)
- BSO may be appropriate for women who have either HNPCC or a family history worrisome for genetic predisposition. (Level-B)

Fertility sparing treatment in EC

About 9% of women were diagnosed with EC in less than 44 years and 20% between 45-54 years. Even though it occurs in young it is not always low grade and early stage. It is very important to select suitable women for fertility sparing treatment.

Selection criteria for conservative treatment of EC[22]

- A well differentiated endometrial carcinoma with grade I
- No myometrial invasion
- No extrauterine involvement (no synchronus ovarian tumor or metastasis), suspicious retroperitoneal nodes.

Recommended method of assessment includes

- Dilatation and curettage, contrast enhanced MRI, office hysteroscopy (optional)
- Estrogen and progesterone receptors status
- Molecular prognostic factors such as P_{53}(optional)
- Laparoscopic staging (optional) or laparoscopic evaluation of adnexal involvement
- Strong desire for preserving fertility
- No contraindications for medical management
- Patient understand and accept that is not standard treatment
- Informed consent.

Progestin therapy

Commonly used progestin therapies are MPA and megestrol acetate. The other alternatives are progestin releasing IUCD. Combined OC pills, tamoxifen etc. Dose of MPA 200-800mg/day, megestrol acetate is 40-60 mg/day. The overall response rate was 68% with overall recurrence rate of 12% and 32% failed to respond. Duration of treatment was less than 6 months in 47% and less than 9 months in 17.3% and more than 9 months in 13%. The overall pregnancy rate was 35.7 % (78/218). Approximately 18% of women required assisted reproductive techniques.[23]

Risk stratification and adjuvant therapy

For women who are not surgical candidates primary RT may be recommended instead of surgery. Adjuvant therapy following surgery is associated with side effects so it is important to categorize them based on risk stratification in postoperative period who will need adjuvant therapy.

There are risk categories in EC.[24]

- Low risk - Stage I endometrioid, (G1and G2), <50% myometrial invasion, LVSI negative
- Intermediate risk-stage I endometrioid, (G1and G2), ≥50% myometrial invasion, LVSI negative
- High-Intermediate risk-stage I endometrioid, (G3), <50% myometrial invasion, regardless of LVSI status or Stage I endometrioid, (G1and G2), LVSI unequivocally positive, regardless of depth of invasion
- High risk-tage I endometroid type, (G3), ≥50% myometrial invasion, regardless of LVSI status, Stage II, Stage III endometroid, all stages with nonendometroid type.

Adjuvant therapy can be RT in the form of brachytherapy or external beam therapy, chemotherapy or hormonal therapy depending on risk factors.

Low and low intermediate risk patients may not require postsurgical therapy however molecular risk factors such as P_{53} mutation etc may impact the disease. Those of high intermediate and high risk require post-surgical treatment with RT to reduce local recurrence based on the fact that 75% of recurrences are in the pelvis. Large prospective randomized trials have demonstrated that postoperative pelvic RT decrease local recurrence but have no overall impact on survival.[25] The next controversy that arises is whether to use pelvic radiation or vaginal brachytherapy. Long term follow up studies of PORTEC-1 and PORTEC-2 have shown that urinary and bowel dysfunction were less with vaginal brachytherapy than pelvic radiation.[26,27] Vaginal brachytherapy has been shown to be equivalent to whole pelvic RT in achieving local control and providing reasonable disease specific and overall survival in patients with high intermediate risk EC and also it is associated with less gastrointestinal side effects and better quality of life. In low risk EC chances of recurrence are very low and so follow up and observation advised. In well-defined intermediate and high risk, vaginal brachytherapy gives similar results in relation to recurrence and 5-year survival as pelvic RT.

Recommendations for adjuvant therapy.[24]

Stage I low risk

As risk of recurrence is low in this group no further treatment should be given after definite surgery. Regular

or follow up should be performed to monitor for symptoms and signs of recurrence.

Stage I, Intermediate risk EC

- Adjuvant brachytherapy is recommended to decrease vaginal recurrence, (Level-B)
- No adjuvant treatment is an option, especially for patients aged <60 years (Level-C)

S*tage I, High-intermediate risk EC*

Surgical nodal staging performed, node negative

- Adjuvant brachytherapy is recommended to decrease vaginal recurrence, (Level-B)
- no adjuvant therapy is an option (Level-C)

No surgical nodal staging

- Adjuvant EBRT recommended for LVSI unequivocally positive to (Level-B) decrease pelvic recurrence,
- Adjuvant brachytherapy alone is recommended for G 3 and LVSI (Level-B) negative to decrease vaginal recurrence

Systemic therapy is of uncertain benefit; clinical studies are encouraged. (Level-C)

Stage I, High risk

Surgical nodal staging performed, node negative

- Adjuvant EBRT with limited fields should be considered to decrease local regional recurrence, (Level –B)
- Adjuvant brachytherapy may be considered as an alternative to decrease vaginal recurrence, (Level-B)
- Adjuvant systemic therapy is under investigation. (Level-C)

No surgical nodal staging

- Adjuvant EBRT is generally recommended for pelvic control and relapse-free survival, (Level- B)
- Sequential adjuvant chemotherapy may be considered to improve progression free survival and cancer specific survival, (Level-C)
- There is more evidence to support giving chemotherapy and EBRT in combination rather than either treatment modality alone. (Level-B)

Chemotherapy

Endometrial cancer is a relatively chemo-sensitive disease, with anthracyclines, platinum-based drugs and taxanes shown to be the most active agents. Role of adjuvant chemotherapy in patients with I or II EC not been well established. The benefits of adjuvant chemotherapy in addition to adjuvant RT especially in surgically Stage I and II patients with high risk features are not clearly defined. Hormone therapies in the form of progestins are usually advised in young women for fertility sparing, in advanced stages and in recurrent and metastatic disease. An Italian randomized study comparing 5 cycles of cisplatin, doxorubicin, and cyclophosphamide with external pelvic radiation in patients of FIGO stage IC grade 3 or stage IIA–IIB grade 3 with 50% or more myometrial invasion or stage III disease, they observed no difference between therapies in terms of progression-free or overall survival.[28] Similarly Japanese GOG study on comparing chemotherapy with radiotherapy in patients with stages IC to IIIC endometrioid adenocarcinoma concluded that chemotherapy had no benefit progression-free or overall survival over RT.[29]

Published phase III studies have shown the efficacy of chemotherapy with cisplatin and doxorubicin or carboplatin and paclitaxel in advanced uterine cancer.[30] The results of two additional GOG studies 249 and 258, examining the role of adjuvant chemoradiotherapy in the treatment of endometrial carcinoma are awaited by 2017.

Role of HRT following treatment of endometrial cancer

Benefits of HRT must be weighed against the risk of stimulating growth and recurrence. According to current opinion hormone therapy for Stage I and II is still considered as an option and continuous combined estrogen and progestin replacement therapy would be recommended. So far only observational and nonrandomized studies have been reported which did not show an increased rate of recurrence or mortality. With progestin only therapy increased risk of breast cancer has to be taken in to account. Alternative therapies like tiblone, raloxifen, phytoestrogens or pschyotherapeutic drugs such as venlafoxene should be considered for relief of menopausal symptoms. In the absence of well-designed studies, the choice of hormone therapy after treatment of EC should be based on prognostic indicators including depth of invasion, degree of differentiation and cell type.[31] Consider estrogen replacement for patients who are low risk for tumor recurrence. Initiating the therapy should be individualized and discussed with the patient. There should be a 12-month waiting period before initiation of HRT. Estrogen therapy in postmenopausal women has been shown to reduce or reverse the signs and symptoms of hypoestrogenism.[32]

Management of undiagnosed EC who has undergone hysterectomy and incidental diagnosis of EC

There is a lot of controversy whether to observe, reoperate or do imaging studies. A comprehensive pathological review is needed to know the histologic type, grading, depth of myometerial invasion, tumor size and for the presence of lymphovascular space invasion (LVS).

Features like small tumor volume, endometrial histology with grade 1 and 2 tumors and superficial myometrial invasion is associated with low risk of extrauterine disease and recurrence. There is no need for surgical staging. If they have intermediate or high risk factors like nonendometroid histology, grade 3 tumors, deep myometrial invasion, extensive LVS involvement etc than surgical staging is indicated which will help to avoid unnecessary adjuvant therapies or guide such therapies.[32]

Those who are not surgically staged should be evaluated by diagnostic imaging techniques like CT, MRI and occasionally PET CT to evaluate for extrauterine disease so that necessary adjuvant therapy can be given.

Recommendation[21]

Women found to have EC incidentally after hysterectomy should have the risk of extrauterine disease and potential for disease recurrence. They should be evaluated based on age, histologic type and uterine tumor features. Individualized treatment plans can be based on the findings. (Level-C)

Management of women with synchronous endometrial and ovarian carcinoma

Women with synchronous tumors are usually young these tumors tend to be low grade and in early stage with good prognosis. Synchronous endometroid tumors are frequently associated with endometriosis and have a better prognosis than other histologic types of cancer.[33] incidence of Lynch Syndrome (HNPCC) was low unless there is a family history of HNPCC associated cancers.

Five-year survival rates in early stages

At diagnosis 75% of women have disease confined to uterus (Stage I) with a 5-year survival rates of almost 98% in low grade tumors. If the cancer is diagnosed and is still only in the area started called local the 5-year survival rates are about 95%, if there is a spread regionally it is 68% and if spread is distant sites it is 17%.[34]

Follow up

Patients treated for EC should be followed up for both recurrence and late toxicity. Early detection of recurrence helps to cure or improve survival benefit. The National Comprehensive Cancer Network (NCCN) guideline recommends physical examination which includes general, speculum, pelvic and rectovaginal examination and evaluation of any possible symptoms associated with recurrence like vaginal bleeding, pelvic pain, weight loss or lethargy every 3-6 months for 2 years and every 6 months or annually thereafter. Vaginal cytology and annual chest X-ray are done to detect recurrence. CT, MRI, PET scan is indicated only if there is a suspicion of recurrent disease. During surveillance, the risk of cancer of breast ovary and colon in patients with EC should be kept in mind.[35]

CONCLUSION

Endometrial carcinoma is the commonest genital tract malignancy in developed countries with good survival rates as majorities are in Stage I. Surgery is the main stay of treatment with adjusted RT depends on risk stratification. Fertility sparing is possible in highly selected patients. Follow up is essential to detect early recurrence and metastasis.

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