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Type II Uterine Body Carcinoma (UBC), Pattern of the Disease in Egyptians, A Single Institutional Experience

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ABSTRACT

Background: UBC is 2nd common gynecological malignancy after cervix. It increases worldwide due to prolongation of life & obesity. Two main types exist (I & II); type II is more aggressive, occurs at older age, less common (20%), unrelated to estrogen, poorly differentiated and deeply invade myometrium. Main presentation is abnormal uterine bleeding, diagnosed by endometrial sampling either aspiration or blind D&C. LNs affection is most important prognostic factor. Pelvic radiation (RT)+/- brachytherapy is the

recommended adjuvant treatment. Multiagent chemotherapy (CTH) +/- RT improves disease free survival (DFS) & overall survival (OS) when using platinum/taxanes based regimen. *Aims:* to study clinicopathological features of all cases of type II UBC, pathological subtypes, management protocols, surgery, RT & CTH given & outcome 'DFS'& 'OS'. *Materials & Methods*: A single institution prospective analysis of all cases presented to NCI-Cairo University with type II UBC candidate for surgery over a period of 4 years from June 2016 until June 2020; 60 cases were included. Data collected then analyzed. *Results*: median age was 62 years with commonest age group was 60-70ys (34 cases, 56.6%). Main presentation was postmenopausal bleeding (52 cases, 86.6%). Dilatation & curettage (D&C) were done for (56 cases, 93.3%). Carcinosarcomas dominated the pathology (34 cases, 56.6%). Most cases surgically staged via open approach (54 cases, 90%) with minimal invasive techniques in 6 cases (10%). Only 32 cases (53.3%) underwent lymphadenectomy with positive LNs encountered in 14 cases (23.3%) and grade III predominate (26 cases, 43.3%). Post-operative positive margins found in 4 cases (6.6%). 63.3% (38 cases) were FIGO stage II. Adjuvant EBRTH (5000cGY/25Fr) was given to (36 cases, 60%), Brachytherapy (700cGY/3Fr) to (26 cases, 43.3%). (34 cases, 56.6%) received adjuvant CTH (platinum/taxanes based) + RT in advanced stage & high-grade tumors. *Conclusion*: Surgery is the primary treatment for early stages disease. In cases of irresectable tumors neoadjuvant combined RT/CTH is preferred. In advanced disease surgical debulking is justified. Pelvic RT +/- brachy therapy combined with multi-agent chemotherapy improves DFS and OS.

Keywords: Type II UBC, Outcome, NCI, EGYPT

1. INTRODUCTION

Worldwide, endometrial carcinoma or UBC constitute 9% of all cancers & 18% of female cancers. It ranks the 6th (4.8%) of all female cancers being 2nd commonest gynecological malignancy after the cervix. Endometrial carcinoma may be termed UBC to separate body uteri anatomically & pathologically from those tumors of cervix. It increases by ~2% annually with variation among different geographic. Incidence of UBC is continuously rising because of increased life expectancy & prevalence of obesity (Prat et al., 2007). The overall lifetime risk of developing UBC is 2.5%. most patients (95%) are over 50 in the 6^{th} & 7^{th} decades. 10,000 women are estimated to die from UBC in 2020 with an increased death rate by 1.9% annually. abnormal vaginal bleeding alerts patients to seek care (Prat et al., 2007; El- Bolkainy, 2013). Almost all UBC are adenocarcinomas with two main pathological types; Type I (endometrioid) carcinoma is the commonest (75-80%) having the typical risk factors & natural history of most endometrial carcinomas, thus termed "Endometrioid". They are indolent associated with hyperlipidemia, obesity & hyper-estrogenism (Felix et al., 2010).

Type II carcinomas are less common (20-25%) accounting for 40% of UBC deaths annually, unrelated to estrogen, poorly differentiated, appears at older age, deeply invade myometrium & spread into lymphatics, thus are more aggressive with poorer prognosis. They are derived frequently from carcinoma in situ (CIS) lesions in atrophic uteri with an unexplained linkage to dark colors. Cytogenetically, show ER or PR receptors activity loss, aneuploidy, decreased expression of E-cadherin, HER2-neu and p53genes mutations or over-expression. They include: papillary serous adenocarcinoma (10%), clear cell adenocarcinoma (1-6%), Carcinosarcoma (MMMT) [malignant mixed Mullerian tumor] (<5%), squamous cell carcinoma (<1 %), transitional cell carcinoma & undifferentiated carcinoma (<1%) (Brinton et al., 2013).

Main presentation is abnormal uterine bleeding. In addition to systemic, iatrogenic or hormonalage-related causes; endometrial polyps, submucousmyomas, hyperplasia & carcinomas are other causes leading to abnormal bleeding (Shobeiri et al. 2019; Toshniwal et al. 2020). Up to 8 years preceding menopause, women may have recurrent irregular anovulatory cycles which increases risk of type II UBC in 14 % of premenopausal women or the risk of its precursor hyperplasia with atypia (Sorosky, 2010). Less common presentations include; profuse discharge, hematuria, bleeding per rectum, pelvic pain (pyometra), pelvi-abdominal mass, distension duetoascites, backpain, or lymphedema of lower limbs in advanced stages. Also, may be accidentally discovered by routine Pap smear or thickened endometrium on transvaginal US (Munroe et al., 2011).

Diagnosis is done by endometrial sampling; office endometrial aspiration is relatively inexpensive, convenient & safe procedure preferred over blind D & C. Other diagnostics procedures include; transvaginal ultrasonography (TVUS), CT Scanning, MRI and FDG-PET CT (Dessole et al., 2006). 18F-FDG uptake in the endometrium can be physiological or pathological from benign & malignant causes. Therefore, FDG-PET CT main role is follow-up of treated cases & detection of local or systemic failure sites. It is most accurate in detecting adenopathy in pretreatment stage where it can detect metastasis in normal-sized nodes not evident by CT or MRI (Kitajima et al., 2010). Type II UBC is surgically staged according to 2010 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system. Complete formal surgical staging is the same as for ovarian malignancies including; thorough abdominal exploration, total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy with

omentectomy & peritoneal biopsies (AJCC, 2010). When ascites, peritoneal, ovarian disease, omental thickening or nodes are involved, maximal surgical debulking is recommended. If initially there is irresectable disease reaching vagina, parametrium, or infiltrating the bladder, bowel & rectum; combined radiotherapy (RT) & chemotherapy (CTH) are preferred initially over surgery (Creasman et al., 2006).

Pelvic lymphadenectomy involves removal of nodal tissue over distal commoniliac, around external iliac to the circumflex iliac veins with removal of nodes around internal iliac & obturator pad of fat over obturator nerve. Para-aortic nodes involvement occurs in 50% of women with positive pelvicnodes. Isolated para-aortic involvement (skip metastases) canoccur in 6% & suspected with higher grade, deepmyometrial invasion, cervix and lympho-vascular space invasion (May et al., 2010). Although lymphatic involvement remains the most important prognostic factor, controversy rises about therapeutic benefit of lymphadenectomy. The risk of having an affected lymph node increases mainly with higher grades & deeper myometrial invasion. It ranges from 3% in well-differentiated superficially invasive tumors to 30% in poorly differentiated deeply invasive malignancies (Bakkum-Gamez et al., 2011).

Pelvic external beam RT (EBRT) +/- brachytherapy is the recommended adjuvant treatment following surgery. It lowers cancer-specific deaths rate (18 % vs. 31.4 %), pelvic & vaginal recurrences (4.8 % vs. 19.6 %) as compared to brachytherapy alone. Prophylactic vaginal brachytherapy is considered after EBRT in cases of cervical involvement (stage II) (Aalders et al., 1980). A study from Dana-Farber Institute showed significant survival benefits with multiagent CTH plus RT throughout all stages (I to IV) where CTH improved DFS & OS using platinum/taxanes based protocols. Fader et al., 2009, studied (paclitaxel/carboplatin) +/- RT and their work was associated with improved recurrence rates (11%) compared to (50%) in those treated with RT alone or observation (P=0.013) while No patients with the CTH & RT regimen experienced recurrence in early follow up period (Viswanathan et al., 2011; Fader et al., 2009).

Aim is to study clinicopathological features of all cases with type II UBC, pathological types, management protocols, surgery, complications, Radiation (RT), Chemotherapy (CTH) given & outcome of treatments disease free survival (DFS) & overall survival (OS).

2. PATIENTS AND METHODS

This is a single institution prospective analysis of all patients diagnosed with type II UBC uterine body carcinoma presented to the National Cancer Institute, Cairo University, EGYPT. 60 cases were included throughout a period of 4 years from June 2016 until June 2020. Data were obtained from patients' files at statics department. Data included demographics (age, family history, history of smoking), presentation, complaint, preoperative radiographs (CT, MRI, ultrasonography, PET CT), biopsy, CA-125, type of surgery, histology, grade, LN state, TNM/FIGO stage, complications (intraoperative & early postoperative), hospital stay, CTH regimens, RT received & state of patients at the last visit.

Ethical Issues

This study posed no harm to patients & was submitted to our Institution Review Board (IRB) where it was reviewed & accepted. All data were anonymous to protect patient's privacy & confidentiality.

3. RESULTS

Hospital stay ranged (3-28 days) with median of 7days. Early recovery & discharge with fewer complications was noticed with minimally invasive surgery (all 6 cases discharged after 2 days).

Survival: overall survival (OS) was calculated from date of definitive treatment (surgery) to last date of follow up. Disease free survival (DFS) also was calculated from date of treatment to date of recurrence. Both were correlated with different prognostic factors. Data were coded & entered using statistical package SPSS (Statistical Package for the Social Sciences) version 23. Datas are summarized using mean, SD, median, minimum and maximum in quantitative data & using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using non-parametric Kruskal-Wallis and Mann-Whitney tests (Chan, 2003a). For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when expected frequency is < 5 (Chan, 2003b). P-values < 0.05 were considered as statistically significant (table 1-2, figure 1-3).

Table 1 Clinicopathological features of our patients (60 cases, 100%)

Age: median age at diagnosis was 62 years	
<40 years	4 cases,6.6%
>40 years [Commonest age group was between 60&70(34 cases, 56.6%)]	56cases, 93.4%

Main presentation:	
postmenopausal vaginal bleeding	52 cases, 86.6%
Others (pain, discharge & menstrual irregularities)	8 cases, 13.4%
Family history:	
Positive (for type I UBC with no specific age group)	10 cases, 16.6%
Irrelevant	50 cases, 83.4%
Comorbidity:	
Yes (triad syndrome of Hypertension, Diabetes & Obesity)	38 cases, 63.3%
No	22 cases, 36.7%
Pathological diagnosis:	
D&C	56 cases, 93.3%
Surgery without preoperative tissue diagnosis (life threatening vaginal bleeding)	4 cases, 6.4%
Hysteroscopy and biopsy	8 cases, 13.3%
Pathological types: (60 cases, 100%)	
Carcinosarcoma [MMMT]	34 cases, 63.3%
Papillary serous carcinoma	18 cases, 30%
Clear cell carcinoma	4 cases, 6.6%
Undifferentiated carcinoma	4cases, 6.6%
Radiological diagnosis:	
CT scanning (most common)	32 cases, 54.3%
TVUS→(endometrial thickening >1 cm, intrauterine ulcers or masses)	26 cases, 43.3%
MRI (3rdmost commonly used)	20 cases, 33.3%
FDG-PET CT	26 cases, 43.3%
CA125:	
++ (No association of this elevation with stage as these 6 cases were interestingly stage I)	14 cases, 23.3% 6 cases, 10%
Surgical staging:	
Open approach,	54cases, (90%)
Minimally invasive surgical techniques;	6cases, 10%
Laparoscopy	4 cases, 6.6 %)
Robotic	2 case 3.3%
Lymphadenectomy (pelvic and para-aortic)	32 cases, 53.3%
Complications:	
Intraoperative:	
Bladder Injury	8 cases, 13.3%
Small Bowel Injury	2 cases, 3.3%
Large Bowel Injury	2 cases, 3.3%
Intraoperative massive bleeding.	2 cases, 3.3%
Surgical site infection: not recorded in any of minimally invasive procedures	2 cases, 3.3% 12 cases, 20%
ICU admission (pulmonary embolism)	4 cases, 6.6%
Vesicovaginal fistula (after laparoscopic resection).	2 case, 3.3%
Postoperative Pathology:	
Grade:	
Grade III	26 cases, 43.3%
Grade II	18 cases, 30%
Grade I	16 cases, 26.6%
Resection margins:	
Positive	4 cases, 6.6%
Clear margins	56 cases, 23.4%

Positive lymph node: N1 N2 Staging (AJCC/TNM) & FIGO staging for endometrium. T3 T2 T1 T4 FIGO stage II FIGO stage III FIGO stage I FIGO stage IV & Tis were excluded from our study	14 cases, 23.3% 10 cases, 16.6% 4 cases, 6.6.% 38 cases, 66.6% 14 cases, 23.3% 6 cases, 10% 2 case, 3.3% 40 cases, 63.3% 14 cases, 23.3% 6cases, 10%
Adjuvant treatment: EBRTH (5000cGY/25Fr) Brachytherapy (700cGY/3Fr) to vagina CTH(platinum/taxanes based) plus RT in(advanced stage &high-grade tumors)	 36 cases, 60% 26 cases,43% 34 cases, 56.6%

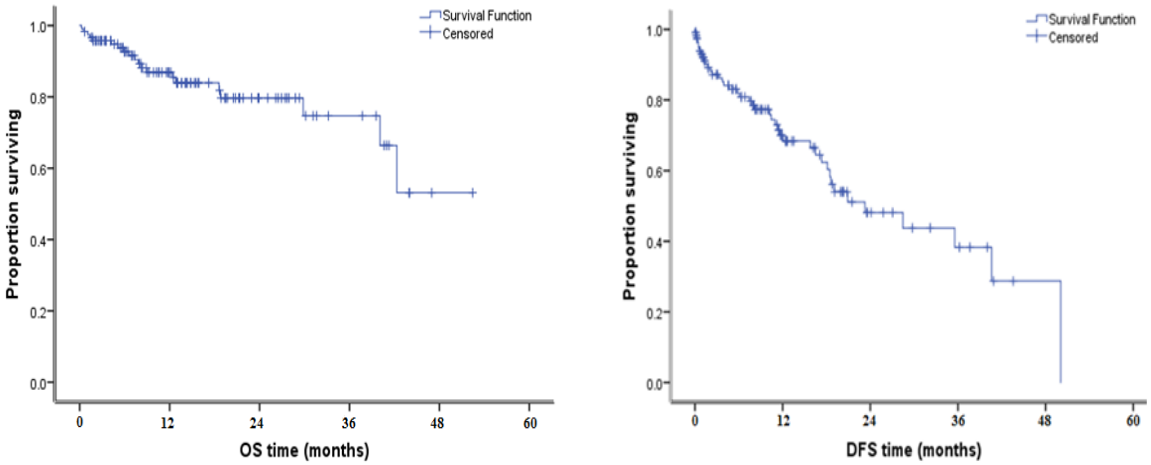

Figure 1 Overall Survival curve (left) &Disease Free Survival curve (right) in months

Table 2 Factors independently affected DFS

Variable	Hazard Ratio (HR)	95.0% Confidence interval(CI) for HR		
		Lower	Upper	P-value
Stage: (T1,T2 vs T3&T4)	 2.95	 1.47	 5.92	 0.002
Grade: Grade I vs II Grade I vs III	 1.07 2.82	 0.37 1.14	 3.10 7.01	0.020 0.906 0.025
Adjuvant RT& CTH:	0.34	0.17	0.67	0.002

Risk of relapse or metastasis (DFS) was 2.28 times more for stages T3, T4 than T1& T2 & was 2.82 times more for grade III than grade I tumors. The median OS in our cohort was 6.1 months ranging (0.1- 52.2). Risk of death was 6.48 times more for grade III than grade I and was 76% less among those received CTH & RT than those who did not.

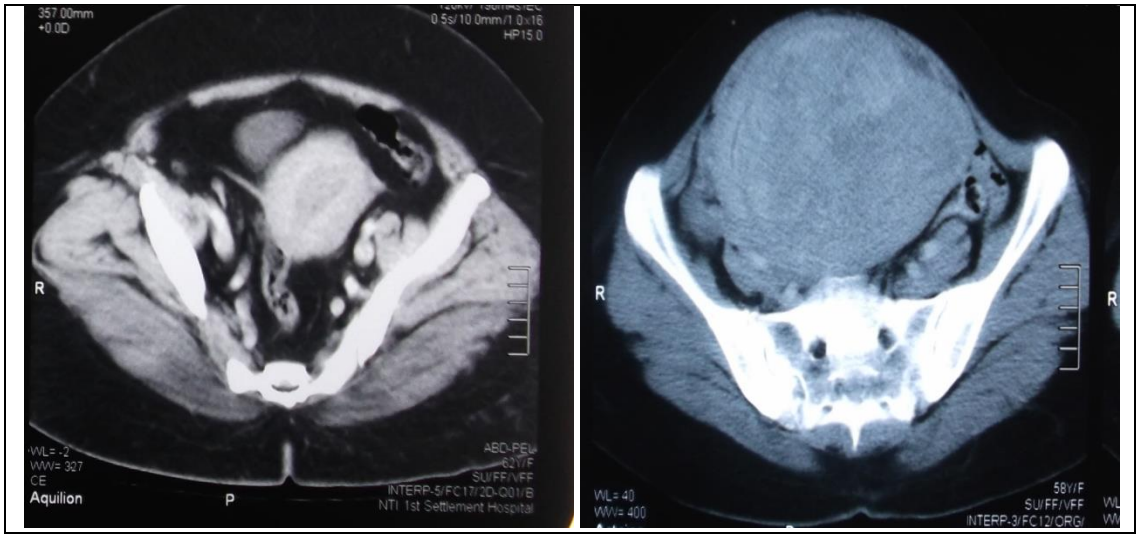

Figure 2 CT scanning of 2 of our patients (axial views) showing endometrial thickening (left) & large necrotic uterine body mass (Rt).

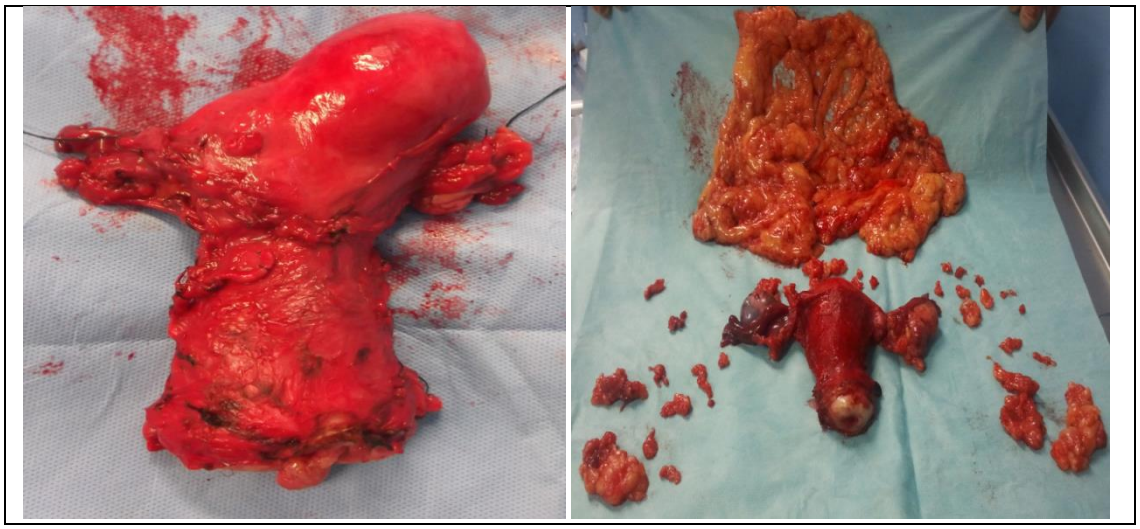

Figure 3 post-operative specimens of 2 of our patients showing TAH (Right) & complete formal surgical staging procedures (left).

4. DISCUSSION

In Egypt, UBC comes the 13thamong female cancers representing 1.6%. It is considered commonest female genital tract malignancy, accounting for 40 % of all new diagnosed gynecological cancers (El- Bolkainy, 2013; Torre et al., 2015). Type II UBC is typically a disease of postmenopausal women. In our study vast majority were post-menopausal. Commonest age group was between 60 & 70ys (34 cases, 56.6%) with median age at diagnosis (62years). This came close to latest SEER registry where median age at diagnosis was 63 years. In this cohort age was not a significant variable of outcome which was the same as most studies showed insignificance of age as a prognostic factor) El-Bolkainy, 2013; Creasman et al., 2006). 90% of patients present with post-menopausal vaginal bleeding; in concordance to our work (52 cases, 86.6%). Other complains as abdominal pain, vaginal discharge and menstrual irregularities accounted for (8 cases, 13.4%). There was an obvious association of triad syndrome of (Hypertension, Diabetes and Obesity) in these groups of our patients (38 cases, 63.3%), (Sorosky, 2010; Munroe et al., 2011; Zhang et al., 2013).

Diagnosis was done pathologically & radiologically. Pathology was confirmed by D & C (56 cases, 93.3%). CT scanning remained imaging modality used for preoperative evaluation & staging (32 cases 53.4%). $^{FDG-PET}$ CT was used liberally in our work in both diagnosis & follow up assessment (26 cases, 43.3%), (Dessole et al., 2006; Kitajima et al., 2010; Rha et al., 2003). CA-125 as a prognostic factor was studied by Espino-strebel and Luna in 90 patients. They concluded that CA 125 was significantly correlated to deep myometrial invasion, adnexal metastasis, node involvement & recommended routine CA-125 estimation. In this cohort CA-125 was not routinely requested (only 54 cases, 90%) with 36 cases only (60%) showed elevation (Espino-strebel & Luna, 2009). Treatment of type II UBC is mainly through formal surgical staging via thorough exploration of peritoneal cavity, peritoneal washing, hysterectomy, bilateral salpingo-ophorectomy & bilateral pelvic and para-aortic LNs dissection. This is followed by adjuvant either

RT or combined RT/CTH according to stage. In our study, surgery was done to all cases (60 cases, 100%) through open approach (54 cases, 90%), (Teng et al., 2014).

Laparoscopic & Robotic approaches are now used more frequently and have been found to be therapeutically feasible and beneficial. Potential advantages include rapid recovery & short hospital stay. In this cohort only in (6 cases, 10%) minimal invasive techniques were performed [laparoscopy (4 cases, 6.6%) & robotic (2 cases, 3.3%)]. All showed smooth postoperative course, rapid recovery & short stay (2 days). Two cases (3.3%) only developed vesico vaginal fistula after 3 weeks of laparoscopy & was successfully managed conservatively (Fader et al., 2012; He et al., 2013). Still lymphatic affection is the most important prognostic factor. Despite this fact controversy raises concerning therapeutic benefit of lymphadenectomy. Some claims its role only in staging and this information again could be accurately obtained through PET CT, while other described its role for improvement of both DFS & OS (Torre et al., 2015; SGO et al., 2014).

In our work lymphadenectomy was not routinely done for all cases (only 32 cases, 53.3%) with positive nodal deposits in (14cases, 23.3%) of them. This meant that about 43.7 % of resected nodes patients were found positive and thus improper staging was done for rest (28 cases, 46.7%) as there was LNs status was provided. Sentinel lymph node mapping (SLNM) has high sensitivity and detection rate in early staged disease with advantage in diminishing the neurovascular injuries, blood loss, bacterial infection and lymphedema. However, it is not used routinely in our institute (Frumovitz et al., 2007).

In our study there was significant relationship between histopathological type and DFS. The 4 years DFS markedly dropped to 1.6% with undifferentiated tumors with p-value (0.012) which was comparable to other studies that showed that type II UBC tumors are more aggressive, less differentiated and carry dismal prognosis (Sorbe, 2012). The current study showed significance for tumor grade & DFS where the 4 years DFS for grade I was (69.7%), grade II was (74.2%) which dropped to (20.1%) for grade III which were significant with DFS p-value (<0.001). Also, this work showed significance for tumor grade & OS for grade I (96.4%), grade II (82.4%) which dropped with grade III to (61.8%) which were significant OS p-value (0.004). In our study, patients with high grade had significant lower DFS rates (p-value<0.001) and OS rates (p-value 0.004) than in literature where 5-year survival for stage III was 29% (Loizzi et al., 2014). FIGO stage was a significant prognostic factor for survival. 5-year OS rates for stage I type were 80-85%, and dropped to 29% for stage III disease. Similarly, in our study patients with advanced stage had significantly lower rates of DFS (p=<0.001) and OS (p=0.001) (AJCC, 2010; Teng et al., 2014; Torre et al., 2015).

A review by Society of Gynecologic Oncology (SGO) summarized major randomized controlled trials investigating role of adjuvant EBRT in early stage UBC which showed that pelvic EBRT improves local control rates (DFS) but not OS. In our study there was a statistical significance of offering adjuvant EBRT or brachy therapy on DFS with p-value (0.009) and also on OS with p-value (0.008) for both early and late stages (SGO et al., 2014). Most of the data reporting survival benefit of Adjuvant CTH for advanced stage & high-grade tumors were derived from retrospective studies. A meta-analysis by Park et al. Suggested that CTH could probably improve DFS & OS in advanced stages. In the current study, there was improvement noted in OS with p-value (0.144) & DFS with p-value (<0.001) when offering adjuvant CTH alone, however this improvement did not reach statistical significance (Park et al., 2013).

5. CONCLUSION

Surgery is the primary treatment for early stages disease. In cases of irresectable tumors neoadjuvant combined Radiation/Chemotherapy is preferred. In advanced disease surgical debulking is justified. Pelvic raiation +/- brachytherapy combined with multi-agent chemotherapy improves both DFS and OS.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of national cancer institute/Cairo University.

Data and materials availability

All data associated with this study are available upon request to the corresponding author.

Peer-review

External peer-review was done through double-blind method.

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