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Surgical Treatment of Endometrial Cancer

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ABSTRACT

Each year endometrial cancer is diagnosed in approximately 11.700 *women in Germany. Operation is the therapy of choice in the primary treatment of patients with endometrial cancer. The traditional abdominal approach, vaginal, laparoscopic and robotic-assisted methods are available for the surgical treatment of EC today. This article compares and evaluates these different treatment options. With rising incidence of obesity, number of patients with endometrial cancer will also increase. However, operations in obese patients are more challenging. Laparotomy as standard therapy in endometrial cancer patients stage I and II should be replaced by laparoscopic approaches. Laparoscopy is oncologically adequate to open procedures and offers many advantages to patients. Robotic surgery in the treatment of endometrial cancer is still under evaluation. Most controversial points of treatment today are indication and extention of lymphadenectomy in different stages. In advanced tumor stages, optimal debulking should be performed in order to improve effectiveness of adjuvant chemotherapeutic and/or radiation therapy.*

Keywords: *Endometrial Cancer, Operative Therapy, Laparoscopic Treatment, Robotic–assisted Hysterectomy, Fertility-preserving Therapy*

1. Introduction

Each year endometrial cancer (EC) is diagnosed in approximately 11.700 women in Germany. More than 80% are, fortunately, detected in the prognostic favourable stages I and II [1]. In comparison 41.200 women were diagnosed with EC in the United States in 2006, a substantial increased from 35.000 in 1987 [2]. The most important risk factors for the development of EC are obesity, postmenopausal status and unopposed estrogen use (Type I EC). Despite the lack of systematic data for the steady rise of overweight patients in Germany there seems to be a similar trend for the incidence of adiposity comparable to America (**Figure 1**). Fewer patients with EC are rather thin, have no history of exogenous estrogen exposure (Type II EC), are perimenopausal (20-25%) or younger than 40 years.

The average age of women with EC is 68 years. Therefore many patients are affected by additional relevant co-morbidities [3]. Combination of uterine corpus cancer with adiposity, hypertension, diabetes, coronary heart disease and/or other internal diseases increases surgical-anesthesiological risk is the major gynaecologic oncologic challenge in the current century. However, chronological age by itself is not a reason for higher perioperative morbidity and mortality [4].

In addition to the traditional abdominal approach, vaginal, laparoscopic and robotic-assisted methods are also available for the surgical treatment of EC today.

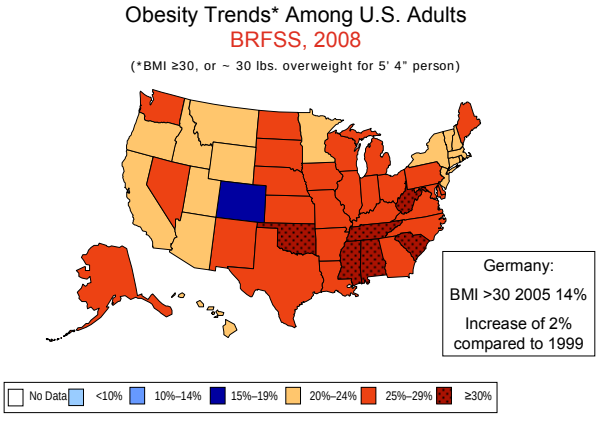

Figure 1. Obesity trend US 2008.

This article compares and evaluates these different treatment options.

2. Fertility Preserving Operation

Approximately 5% of the patients affected by EC are younger than 40 years. Some of them wish to preserve fertility. The decision for uterus conservation is complicated by the fact that in patients with EC stage IA grading 1 one can find in 10%-45% synchronous ovarian tumors. Additionally, in up to 10% of cases myometrial infiltration is histologically confirmed in spite of a negative MRI and a higher grading than in the D&C is detected in nearly 20% of cases. The accuracy of MRI to detect myometrial invasion is 70% [5]. Until today there are only a few case series or case reports available. All patients described in these publications were staged by imaging systems, even though PET-CT has been shown (in a small study) to have a sensitivity for detection of pelvic lymph node metastasis of only 67% [6].

The range of described conservative therapy modalities is broad and comprises gestagen therapy, intrauterine insertion of MIRENA®, oral application of aromatase inhibitors, GnRH analoga or hysteroscopic resection of EC in combination with hormonal treatment. It is important to advise these patients carefully about individual treatment, thus high compliance and understanding are paramount. After informed consent has been obtained, following criteria must be fulfilled:

- grading 1 carcinoma
- no myometrial infiltration in MRI or sonography
- no detection of suspicious pelvic or paraaortic lymph nodes
- no evidence of adnexal tumos
- no contraindication for hormonal treatment
- agreement for close follow-up (curettage every 3 month)
- stage adjusted therapy after finishing desire for childbearing

Chiva *et al*. summarized data of 133 women with fertility preserving therapy in EC. 76% of patients responded to hormonally therapy. However, 34% of women developed recurrence after a mean of 20 months. In 24% of patients there was no response to hormonal therapy. 53 pregnancies occurred but also 4 treatment-related deaths [7].

It is advisable, that young patients with clinical stage IA G1 EC should undergo staging laparoscopy after informed counselling to exclude secondary ovarian neoplasia and lymph node metastases before starting hormonal therapy. After finishing family planning stage-adjusted operative (and radiation) therapy has to be initiated, frequently resulting in the discovery of higher tumor stages than initially diagnosed [8]. Ovarian preservation during surgical management of early stage endometrial cancer is still under debate and should be done only individually after extensive discussion and informed consent with the patient [9-11].

3. Operative Therapy Stage I Endometrial Cancer

The German Gynecologic Oncology Group's (AGO) guideline for surgical treatment of endometroid EC, in line with many international guidelines, includes an intraperitoneal cytology sample, total hysterectomy, bilateral adnexectomy and pelvic (at least 15 lymph nodes) and paraaortic (at least 10 lymph nodes) lymphadenectomy up to the renal vessels. In case of uterine papillary-serous carcinoma or clear cell carcinoma it is mandatory to extract multiple peritoneal samples as well as to perform omentectomy [12]. In clinical stages IA G1 and G2 and IB G1 and G2 lymphadenectomy is optional. In patients with relevant co-morbidities it is acceptable to omit lymphadenectomy, even in higher clinical stages. Systematic surgical staging, including simple hysterectomy with bilateral adnexectomy and pelvic and paraaortic lymphonodectomy is for most of the women affected by EC the baseline therapy and allows clear decision for stage-related adjuvant therapy. More extensive parametrial resection (radical hysterectomy) does not improve oncologic outcome in patients with stage I endometrial cancer [13]. However, definitive histologic grading, myometrial invasion and lymph node involvement differ in a substantial rate from intraoperative gross assessment (up to 15%) and frozen section result (up to 25%) [14,15]. Therefore decision on comprehensiveness of surgical treatment is challenging.

3.1. Abdominal Hysterectomy with Bilateral Salpingoophorectomy (BSO)

Most patients affected by histological proven EC today still undergo surgical treatment by abdominal approach. In most cases a midline longitudinal laparotomy is performed that starts above the pubic symphysis and (depending on the extension of the lymphadenectomy) expands until the xiphoid. Alternative ways of laparotomies are a wide Pfannenstiel incision (optionally with transsection of the Mm. recti) or laparotomy including a paniculectomy [16]. With increasing BMI rate of successful lymphadenectomies is however significantly decreasing. The estimated blood loss rises and duration of surgery extends [17]. In morbidly obese patients noninfectious wound breakdown occurs in up to 10% (**Figure 2**) [18].

Figure 2. Complete wound breakdown after surgical treatment of a patient with EC stage IIIc with a BMI of 56.

Trocar placement(LAVH and TLH)

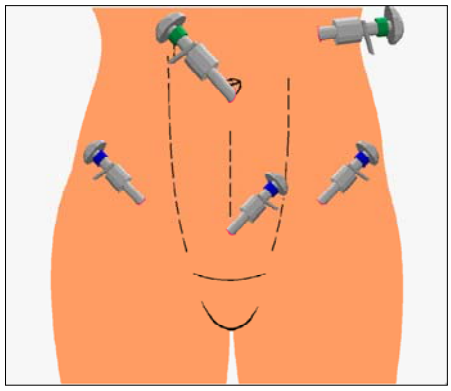

Figure 3. Scheme of trocar placement for conventional laparoscopic operations (laparoscopic assisted vaginal hysterectomy-LAVH and total laparoscopic hysterectomy-TLH) in patients with EC.

3.2. Vaginal Hysterectomy

In cases of considerable limited operability, vaginal hysterectomy is a feasible alternative to abdominal approach. Lelle *et al*. demonstrated in 60 patients with EC undergoing vaginal hysterectomy 5- and 10-year survival rates of 91% and 87%, respectively [19]. Despite refraining from bilateral adnexectomy in 50% of the women treated with vaginal hysterectomy, Chan *et al*. published similar oncologic results with respect to 5-year survival [20]. The disadvantage of the exclusive vaginal approach is the impossibility of performing a lymphadenectomy. A possible combination of vaginal hysterectomy and open extraperitonal lymphadenectomy was described by Massi *et al*., though without demonstrating oncologic results [21]. Dowdy *et al*. [22] successfully performed laparoscopic extraperitoneal paraaortic lymphadenectomy as second procedure in 90% of women with high risk endometrial cancer after previous vaginal hysterectomy.

3.3. Laparoscopic Assisted Vaginal Hysterectomy and Total Laparoscopic Hysterectomy

While laparoscopic approach is already the standard approach in treating benign gynecological diseases, it is only more recently used in gynecological oncology, including in the therapy of EC [23]. This was possible following secure ability to perform laparoscopic pelvic and paraaortic lymphadenectomy at the end of the last century [24,25]. The trocar placement is standardized (**Figure 3**). So far, the results of laparoscopic therapy of EC have been evaluated in about 50 prospective and retrospective, studies, predominantly designed as monocenter studies. More important data are available from 5 prospective randomized trials. One major argument against laparoscopic treatment of EC, occurrence of port-side metastasis, could be invalidated. Martinez *et al*. found after 1216 laparoscopic procedures, including 295 for EC, an incidence of trocar metastasis of 0.33%. Excluding patients with peritoneal carcinomatosis rate drops down to 0.16% [26].

All studies performing either laparoscopic assisted vaginal hysterectomy or total laparoscopic hysterectomy with or without lymphadenectomy report similar and consistent results, demonstrating that laparoscopic approach is a safe and oncologic adequate way of surgical treatment in patients with EC stage I. Laparoscopic staging in EC provides substantial benefits for the patients:

- less blood loss
- less transfusion rate
- reduced duration of hospital stay
- faster recovery to normal daily activity
- less postoperative demand on analgetics
- higher or equal number of removed lymph nodes
- less complications.

Disadvantages are the longer duration of surgery, especially when lymphadenectomy is performed, and the overcoming of the learning curve [27-38]. Conversion rate in the randomized studies varies between 7-20%. Nevertheless it could be shown that particular older patients with additional co-morbidity [39] and obese patients [40] benefited mostly from laparoscopic approach. The advantages lasting at least six months [41].

More importantly, oncologic results (OS, DFS) of the laparoscopic surgery are equivalent to conventional abdominal surgery. This has been shown with the highest evidence level in 5 prospective randomized studies and related meta-analyses [42-48]. Unfortunately these 5

studies include only 238 patients in the groups that underwent laparoscopic surgery. If the results of further randomized studies like the Dutch multicenter trial NTR 821 and GOG LAP II should confirm these results, every patient affected by EC stage I should be offered a laparoscopic surgical therapy, and abdominal approach should only be chosen and accepted in cases of severe contraindications [49,50].

3.4. Robotic-assisted Hysterectomy

With approval of the DaVinci® Surgical System by the FDA in 2005, a new era of laparoscopic technique in gynecology began. This technique will potentially be able to overcome prejudices and resistances against laparoscopic oncological surgery.

Robotic-assisted laparoscopy offers substantial advantages such as a three-dimensional vision system, improved precision of instruments combined with potentially more degrees of freedom, tremor-free manipulation, an advanced ergonomic positioning of the surgeon and a faster learning curve, which is helpful in particular in complex gynecological procedures. The disadvantages of robotic-assisted surgery are the absence of tactile feedback, the large size of robotic equipment, the lack of vaginal access and larger skin incisions for inserting trocars [51-55]. Moreover, costs for robotic staging of EC patients are significant higher, approximately 1300$ per operation, due to longer operating room time and disposable instruments compared to traditional laparoscopy [56]. After passing the learning curve of about 20 operations [57] many authors consider robotic-assisted surgery to be an ideal combination of the advantages of abdominal and laparoscopic approach [58-60]. This new method of surgery is advantageous in comparison to the conventional abdominal approach and might even perform better than the conventional-laparoscopic surgery in relation to operative times, blood loss and postoperative hospital stay [61-63] which has however still to be confirmed by further studies. De Nardis *et al*. compared 2008 the surgical morbidity of 56 patients affected by EC clinical stage I after undergoing robotic-assisted laparoscopic hysterectomy with lymphadenectomy with a group of 106 patients who underwent abdominal approach. Three (5.4%) originally planned robotic-assisted operations needed to be converted to abdominal approach. Intraoperative blood loss, rate of perioperative complications (3.6% vs. 20.8%) and duration of hospital stay were significantly favorable in the DaVinci-group, but operative times were substantially longer. The lymph node yields were comparable. These results have to be interpreted cautiously because of differences in the characteristics of the groups of patients, with the group achieving robotic-assisted surgery containing younger and slimmer women with less co-morbidities and earlier clinical stages of EC [64].

Veljovich *et al*. performed a similar study and compared 118 patients after robotic operations with 131 women undergoing an open abdominal surgery and could demonstrate longer operative times for robotic surgery but also a significantly lower blood loss and a considerably shorter hospital stay. The lymph node yields were as well comparable [65]. Boggess *et al.* compared three possible ways to performing an extensive EC staging: abdominal approach (n = 138), conventional laparoscopic (n = 81) und robotic-assisted (n = 103). The blood loss was lowest in the DaVinci-group, the lymph node yields were significantly higher and the hospital stays shortest. The operative times were comparable in the robotic-assisted and conventional laparoscopy, but longer than by laparotomy. Boggess inserted five trocars for his operation (**Figure 4)**; a placement, that is now used by many other centres.

The complication rates of the robotic-assisted operations were significantly lower than in the laparotomy group (5.9% vs. 29.7%). There was no difference in the conversion rates between conventional and robotic- assisted laparoscopy [66]. Analyzing the subgroup of obese and morbid obese patients, there is an considerable advantage in using the robot compared to conventional laparoscopy, including shorter operative times, less blood loss and higher lymph node yields [67]. Comparable favorable results were demonstrated by Seamon *et al*. 2008. Only 12.4% of the originally planned 105 rbotic-assisted operations had to be converted, especially in morbid obese patients. The mean operative time was 242 minutes, the blood loss 99 cc, the lymph node yields 29. 24 hours later most of the patients were in the condition to get dis-

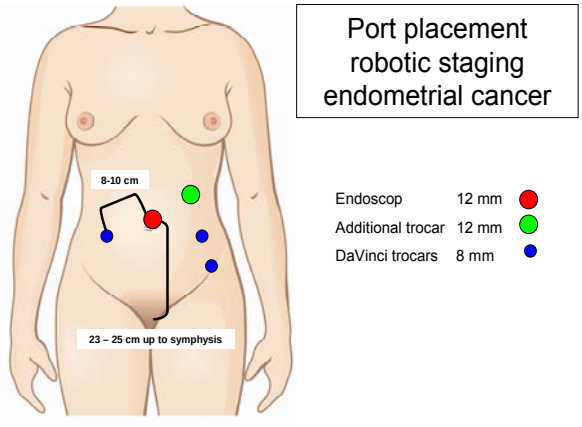

Figure 4. Schematic demonstration of the port-placement in robotic-assisted operation for endometrial carcinoma.

Robotic-assisted operations in

Autthor/Year	n	OR-time	Blood loss	Lymph nodes	follow-up
Bell 2008	40	184 min	77 cc	17	n.s.
Denardis 2008	56	177 min	105 cc	19	n.s.
Boggess 2008	103	191 min	75 cc	33	n.s.
Seamon 2008	105	242 min	100 cc	21	n.s.
Veljovich 2008	25	283 min	67 cc	-	n.s.
Denardis 2008	56	177 min	105 cc	19	n.s.
Hoekstra 2009	32	195 min	50 cc	17	n.s.
Lowe 2009	405	170 min	88 cc	16	n.s.
Jung 2010	28	193 min	n.s.	21	n.s.
Cardenas 2010	102	237 min	109 cc	22	n.s.
Peiretti 2009	80	182 min	n.s.	24	n.s
Cardenas 2010	102	237 min	109 cc	22	n.s..

Figure 5. Summary of operative data for robotic staging in endometrial cancer patients.

charged [68]. More recently Cardenas-Goicoechea and co-workers demonstrated similar results by analyzing 102 patients with EC after robotic-assisted staging (**Figure 5**) [63].

Up to now there are no oncologic follow up date after robotic assisted staging in EC patients available. Ultimately, the 5-year survival rate must be the decisive oncologic criterion for robotic surgery [69].

4. Lymphadenectomy Yes or No?

The role of pelvic and paraaortic lymphadenectomy is currently the most controversial and internationally most inconsistently used element of the surgical approach to endometrial carcinoma. Following FIGO women with histological confirmed EC requires comprehensive staging that includes total hysterectomy, bilateral salpingoovarectomy, peritoneal washing and locoregional lymphadenectomy. This is the only way stage IIIc (nodal positive) can be identified and the appropriate radiation therapy can be subsequently initiated or avoided. In addition,systematic lymphadenectomy seems to have a therapeutic effect in women with EC [70-72]. However, extend (sampling or complete) and level (only pelvic, pelvic and paraaortic-inframesenteric/ intrarenal) of lymphadenectomy and are not mandatorily defined.

Guidelines for surgical treatment of EC vary between countries. German recommendation is to perform comprehensive pelvic and paraaortic lymphadenectomy up to the renal vessels in all patients except stage IA G1[12]. In stages IB G1, IA G2 and IB G2 lymph node dissection is optional, an all other cases obligatory according to retrospective Mayo data, that demonstrated a high percentage of pelvic and (sometimes isolated) paraaortic lymph node metastasis [73].

These results could, however, not be confirmed in other analysis. In the current FIGO - report 2006 pelvic lymph node metastases are detected in stage I EC in 1.4-37.2% of patients and paraaortic lymph node metastases in 0.3-12.6% (in correlation to grading and myometrial invasion) (see **Figures 6** and **7**) [74]. A similar distribution of lymph node metastases in 349 patients was found by Chi at al. 2008 in a retrospective monoinstitutional analysis [75]. All together one can expect lymph node metastases in 10-12% of women affected by stage I endometrioid endometrial carcinoma [73-75].

Additionally, pelvic and infrarenal paraaortic lymphadenectomy in patients with relevant co-morbidities and obesity is often associated with increased rate of early and late postoperative complications or cannot be performed at all [76]. Furthermore, lymph node metastases of endometrial carcinoma are often not macroscopical enlarged [77].

In contrast there are the results of two prospective randomized studies including more than 2000 patients that could not demonstrate an oncological advantage (OS, DSF) comparing patients that had a pelvic lymphadenectomy with those having not [76,78]. Though these two studies (with a high evidence level) reach identical conclusions, the results have to be interpreted carefully. In both studies only pelvic lymphadenectomy was performed. In the ASTEC study the mean lymph node yield was just 12 lymph nodes. A systematic paraaortic

Incidence of pelvic lymph node metastases

	G1(%)	G2 (%)	G3 (%)
Endometrium T1a	1,4	7,2	16,1
Myometrium < 50 % T1b	2,1	6	9,7
Myometrium > 50 % T1c	10,7	21	37,2

FIGO 2007Report on the Results of Treatment in Gynecological Cancer

Figure 6. Incidence of pelvic lymph node metastases in correlation to tumor stage und grading in patients with EC.

Incidence of para-aortic lymph node metastases

	G1(%)	G2 (%)	G3 (%)
Endometrium T1a	0,4	2,4	5,4
Myometrium < 50 % T1b	0,3	1,8	4,3
Myometrium > 50 % T1c	2,2	5,9	12,6

FIGO 2007Report on the Results of Treatment in Gynecological Cancer

Figure 7. Incidence of paraaortic lymph node metastases in correlation to tumor stage und grading in patients with EC.

lymph node dissection was not required. The adjuvant therapy was inconsistent (due to a lack of definition) and the participating centers had discretion in choosing the right adjuvant therapy. In addition, statistical assumptions are justifiable to only a limited extent.

Therefore the possible spectrum of lymph node staging comprises no lymphadenectomy, exclusive pelvic lymph node sampling, additional inframesentric paraaortic sampling and complete pelvic and infrarenal paraaortic lymphadenectomy. The incidence of isolated paraoartic lymph node metastasis in case of negative pelvic nodes is very low (**Figure 8**) [79].

In summary it can be said, therefore, that these differing research results might rather increase the level of confusion than clarifying the evidence for performing pelvic and paraaortic lymphadenectomy in patients with endometrioid endometrial cancer stage I and II. Further research, in particular prospective randomized studies are required to evaluate the significance of systematic paraaortic lymphadenectomy in correlation to pelviclymph node status as part of surgical treatment of endometrial carcinoma to be able to indicate appropriate adjuvant therapy [80-83]. Outside of studies lymphadenectomy is not adequate in low and intermediate risk EC patients because risk-benefit balance seemsrather in favor of not performing surgical staging. In contrast high-risk patients seem to profit from complete pelvic and paraaortic lymphadenectomy [84].

6. Operation for Stage II Endometrial Cancer

In case of confirmed infiltration of the cervix uteri (stage pTIIb) in an endometrial carcinoma the few available studies demonstrate an increased survival rate when performing a radical hysterectomy (**Figure 9** and **10**) so that the parametrics also should be resected as the guidelines recommend [11]. Sartori *et al*. retrospectively compared 135 patients receiving a simple hysterectomy to 68 patients undergoing radical hysterectomy in stage pTIIb. They detected a significant difference in the 10 - year-survival in favor of radical hys terectomy (94% versus 74%), while adjuvant radiation was without effect [85]. Almost the same results were demonstrated by Cohn *et al*. They retrospectively evaluated 162 patients affected by endometrial cancer stage II. 75% were treated with simple hysterectomy and 25% with radical hysterectomy. 5-year-survival-rate was 94% in the radical hysterectomy group and 76% (p = 0,05) in the simple hysterectomy group [86]. However, other study groups demonstrated only marginal differences in survival rate [87].

Incidence of isolated para-aortic lymph node metastases with negative pelvic lymph nodes

	G1(%)	G2 (%)	G3 (%)	All grades
Endometrium T1a	0,0	1.6	0.0	0.6
Myometrium < 50 % T1b	0.31	0.32	2.34	0.62
Myometrium > 50 % T1c	0.37	0.84	2.87	1.56

Boronow RC. Gynecol Oncol. 2008 Oct;111(1):3-6.

Figure 8. Incidence of isolated paraaortic lymph node metastasis in patients with negative pelvic lymph nodes correlated to tumor stage und grading.

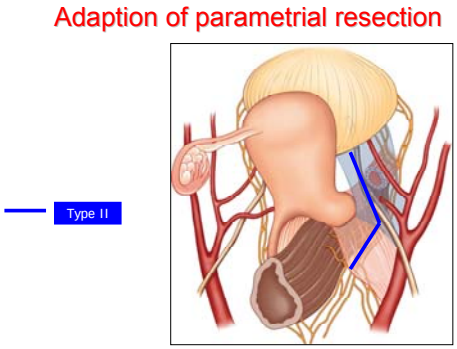

Figure 9. Schematic graph of parametrial resection in radical hysterectomy type II as operative treatment of stage IIb EC[1].

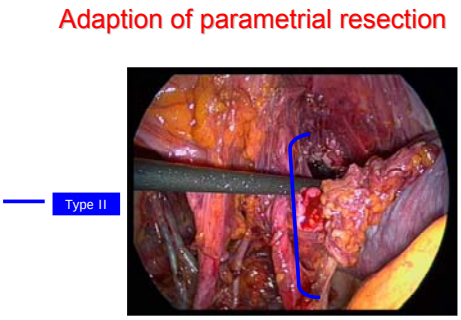

Figure 10. Intraoperative situs as described in Figure 9.

7. Value of Operative Therapy in Advanced Cancer Stages

Prognosis of patients with an advanced endometrial cancer is unfavorable. The few available studies nevertheless demonstrate a significant survival benefit if maximum tumor debulking could be achieved. Bristow *et al*. detected in 65 patients in stage IVb a survival of 34 months after reducing tumors to below 1 cm. If remaining tumor were larger than 1 cm the survival was only about 11 months irrespective of adjuvant radiation and/or chemotherapy [90]. Similar results were demonstrated by Ay-

han *et al*. in 37 patients in stage IVb. If tumor could be reduced below 1 cm survival was 25 months. In case of no macroscopic residual tumor survival was even 48 months. In contrast women who did achieve only suboptimal tumor reduction survived only 13 months [90]. In advanced stages maximum tumor debulking should thus be performed in order to improve effectiveness of adjuvant chemotherapeutic and/or radiation therapy [12]. Combination of maximum cytoreductive surgery and adjuvant use of radiation and chemotherapy sequentially or concomitant seems to be the most potential treatment in patients with advanced endometrial cancer [91-93].

8. Conclusion

Operation is the therapy of choice in the primary treatment of patients with endometrial cancer. With rising incidence of obesity number of patients with endometrial cancer will also increase. However, operations in obese patients are more challenging. Laparotomy as standard therapy in endometrial cancer patients stage I and II could be replaced by laparoscopic approaches. Laparoscopy is oncologic adequate to open procedures and offers many advantages to patients–less blood loss, lower complication rate, shorter hospital stay and better quality of life, especially those with relevant co-morbidity. Robotic surgery in the treatment of endometrial cancer is still under evaluation. Most controversial points of treatment today are indication and extend of lymphadenectomy in different stages. In advanced tumor stages, optimal debulking should be performed in order to improve effectiveness of adjuvant chemotherapeutic and/or radiation therapy.

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