Radiotherapy of endometrial carcinoma: Who needs to be irradiated?

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SUMMARY

Due to gynecological oncology general strategy and everyday aspiration for individual approach to malignant tumors, guidelines in treatment approach are not finally established, and they are controversial in some demands with age of the patients. If we look general treatment strategy approach to invasive endometrial cancer it is proved that operative treatment is priority and base line of treating endometrial carcinoma I and II clinical stage (FIGO) if there is general conditions for surgery, allowing complicated treatment in this age. Previous experience are showing that decision about application of therapy procedures in treatment of endometrial carcinoma every case have to has individual approach, regarding all known prognostic criteria: clinical stage, histologic type, myometrial infiltration, lymph-vascular space involvement, size of the tumor and its localization, depth of myometrial infiltration, invading of serosa, cervix and adnexa, present of hormonal tissue receptors, information about lymph node: number, size and size of the biggest metastases, data about both extra nodular expansion of tumor and peritoneal cytology. The use of postoperative radiotherapy should be limited to group of patients with highly enough risk of locoregional recurrence (15% and more) as risk warranty of morbidity connected to radiological treatment. Therefore, the goal of postoperative radiotherapy appliance is to achieve maximum locoregional disease control and survival without relapse. New Radiotherapy (RT) techniques, Conformal Radiotherapy (CFRT) and Intensity Modulated radiotherapy (IMRT), reduce the risk of complications, especially for patients with multimodal treatment.

Key words: *Radiotherapy; Endometrial Neoplasms; Health Planning Guidelines*

INTRODUCTION

Due to gynecological oncology general strategy and everyday aspiration for individual approach to malignant tumors, guidelines in treatment approach are not finally established, and they are controversial in some demands with age of the patients.

If we look general treatment strategy approach to invasive endometrial cancer it is proved that operative treatment is priority and base line of treating endometrial carcinoma I and II clinical stage (FIGO) if there is general conditions for surgery, allowing complicated treatment in this age.

Previous experience are showing that decision about application of therapy procedures in treatment of endometrial carcinoma every case have to has individual approach, regarding all known prognostic criteria: clinical stage, histologic type, myometrial infiltration, lymph-vascular space involvement, size of the tumor and its localization, depth of myometrial infiltration, invading of serosa, cervix and adnexa, present of hormonal tissue receptors, information about lymph nodes: number, size and size of the biggest metastases, data about both extra nodular expansion of tumor and peritoneal cytology.

General and following pathological conditions (extreme pathological obesity, diabetes and hypertension, and others) basically do not interfere with diagnose but they are crucial for the therapy selection.

Secondary main form of therapy endometrial carcinoma is radiotherapy which is used with endometrial carcinoma under following conditions: independent complete method of inoperable carcinoma of endometrial or accessory therapy method, with operative treatment and chemotherapy, vaginal brachytherapy and/or extreme irradiation.

Recommendations for adjuvant radiotherapy and chemotherapy with carcinoma of endometrial after complete surgery (NCCN Guidelines in Oncology) (1).

FIGO stage I

Basic treatment with FIGO stage of I endometrial carcinoma if there is no counter indications for operative treatment is total hysterectomy, bilateral salpyngo-oophorectomy (TAH/BSO) with pelvic and para-aortic lymph-nodal biopsy (sampling) and peritoneal cytology during surgical exploration. Indications for para-aortic lymph-nodal biopsy: enlarged common iliac lymph node, clear cell or papillary serosal carcinoma, enlarged para- aortic lymph node and adnexa. In all of these cases and omenectomy is indicated. Beginning of adjuvant radiotherapy is between 3 to 6 weeks after the surgery, not later than 2 months.

With FIGO stage IA (after the surgery) no matter for presence or absence of adverse risk factors (age > 60, presence of lymph vascular invasion, tumor size > 20 mm and infiltration of lower segment of uterus) with G1 and G2 regular observation of patient only, and with G3 and presence of adverse risk factors observation or vaginal brachytherapy with or without pelvic RT.

With FIGO stage IB (infiltration < 50%) in absence of adverse risk factors: with G1 tumor only observation, without additional treatment, with G2 and G3 tumor observation and vaginal brachytherapy is indicated. In cases of presence of adverse risk factors with G1 observations or appliance of vaginal brachytherapy, with G2 vaginal brachytherapy and/or pelvic RT and with G3 tumor pelvic RT and or brachytherapy are indicated (2-4).

With FIGO stage IC with presence of adverse risk factors on every grade appliance of pelvic RT and/or vaginal brachytherapy is indicated. In cases of absence of adverse risk factors with G1 and G2 vaginal brachytherapy is sufficient, and with G3 pelvic RT and/or vaginal brachytherapy is applied.

Patients who are candidates for RT only (presence of counter indications for surgery) with external irradiation are delivered therapy dosage 46-50. 4 Gy fractionated, with box technique of 4 fields or with appliance conformal RT and intracavital brachytherapy in HDR rating of exposure-5 fraction, 7 Gy by

fraction, once a week with a calculation of dosage on serosa* or in LDR rating (60-70 Gy on vaginal mucosa during 2 appliances).

FIGO stage II

Reference treatment with FIGO stage II is a Wertheim operation with nodal dissection and postoperative radiotherapy. FIGO stage IIA: when myometrium infiltration is < 50% with G1 tumor observation or vaginal brachytherapy, G2 observation or vaginal brachytherapy with or without pelvic RT, and with G3 strictly vaginal brachytherapy with or without pelvic RT. If FIGO IIA infiltration of myometrium is > 50% with G1 and G2 vaginal brachytherapy with or without pelvic RT is indicated, while with G3 strictly vaginal brachytherapy with pelvic RT (5).

On FIGO stage IIB with G1, G2 and G3 pelvic RT and vaginal brachytherapy is indicated. For patients who are candidates for RT only (presence of counter indications for operation) procedure is similar to stadium I (6).

FIGO stage III

Individualistic treatment approach in this stadium is conditioned with histological extension of the very tumor. New FIGO classification includes patients with serose or adnexal extension or positive peritoneal cytology (IIIA) and with vaginal extension (IIIB) or with metastasis in pelvic and/or para-aortic lymph nodes (IIIC).

On FIGO stage IIIA (after complete surgery staging of disease): when is positive only peritoneal cytology, and tumor is limited on fundus of uterus on G1and G2 of tumor is following only observation, and with G3 tumors observation or vaginal brachytherapy or pelvic RT with or without vaginal brachytherapy. On subclinical intraperitoneal extension is suggesting installation P32 (15mCi) or abdominal pelvic radiotherapy.

With rest of FIGO IIIA stage (serosa or adnexal extension) all grade (G1, G2, G3) RT is indicated directly on tumor with chemotherapy or chemotherapy with or without RT, or pelvic RT with or without vaginal brachytherapy or abdominal pelvic radiotherapy with or without vaginal brachytherapy.

On FIGO stage IIIB is indicated pelvic (directly on tumor) RT with or without chemotherapy.

On FIGO stage IIIC (positive pelvic, common iliac or para- aortal lymph nodes) is necessary pelvic RT with expanded field to aortal bifurcation with chemotherapy.

At the patients which are candidates for pelvic RT only therapy dose is 50.4Gy with brachytherapy boost dose on vaginal magetna. At abdominal pelvic RT therapy dose is 30 Gy at all abdomen (protection of renal field) then we add boost to pelvis to 50.4 Gy. Para aortal region is treated with 45-50 Gy on CTV by box technique or CFRT. With inoperable patients the selection treatment presents pelvic RT (with open field -40 Gy) and additional boost on lateral pelvic walls (50-60 Gy) combined with brachytherapy in LDR or HDR regime up to 80 Gy. Optimal pelvic dosage is 64 Gy (7).

FIGO stage IVA and IVB (debulking, without big residues, or presence of subclinical intraperitoneal extensions) chemotherapy with or without RT, or RT with or without vaginal brachytherapy. If performance status (medical operable) satisfies with infiltration of urinal bladder or rectum without fixation on to pelvic wall, pelvic exenteration or abdominopelvic irradiation with or without vaginal brachytherapy, or chemotherapy and irradiation is indicated.

Palliative radiotherapy: "short" technique is priority method of palliative irradiation with patients who suffer from extreme pain or profuse vaginal bleeding. It is carried out fractionated with total dosage of 20 Gy, 4 Gy by therapy. Treatment is repeatable after two weeks. Symptoms of distant metastasis (pathological bone fracture) can be treated with single fraction 8 Gy, 5 fractions by 4 Gy, or 10 fractions by 3 Gy.

WORLDWIDE SITUATION

In recent years, special attention of most eminent international scientists is given to issue of justification of postoperative radiotherapy appliance with endometrial carcinoma FIGO stadium I. Dozens of expert analysis and three major randomized studies have been published: PORTEC study (Postoperative Radiotherapy Of Endometrial Carcinoma), Norwegian study (Alders and assoc.), GOG 99 study (Kays and assoc.)

PORTEC study (1) is multicentre prospective randomized study, completed in 2002., time of observation 73 months, 19 radiology-oncology centers included. Study involved sum of 715 patients with endometrial carcinoma, G1 and G2 IC stadium, IB G2 and G3 stadium after the surgery: abdominal hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy. Goal of PORTEC study: to evaluate validity of postoperative pelvic RT with endometrial carcinoma FIGO stadium I (grade 1 with ≥ 50% myometrium infiltration, grade 2 regardless of myometrium infiltration depth, and grade 3 with superficial (< 50%) myometrium infiltration, locoregional control, presence of recurrence, appearance of distant metastasis and overall patient survival. Conclusion of PORTEC study: postoperative pelvic RT significantly reduces presence of local recurrence (4%), contrary to patients only surgically treated (16%), overall 5-years survival in both groups is similar, (81% vs. 85%), as and presence of distant metastasis (8% vs. 7%), but associated surgical-radiological complications in radiotherapy group are more often (25% vs. 6%) with surgery only treated. Postoperative pelvic RT is not indicated in FIGO I stadium of endometrial carcinoma with patients under 60 years old and with grade 2 tumors with superficial invasion myometrium (8).

Chadha and associates present the treatment results of postoperative vaginal brachytherapy only of patients with negative pelvic lymph nodes: 5-years survival rate is 93%, local control 100% and without toxic G3 and G4 complications. Chadha recommends only vaginal HDR brachytherapy without pelvic RT in total dosage sum of 21 Gy (3 fractions by 7 Gy) at: "high risk" stadium IB grade 3, and at stadium IC (G1, G2, G3), at negative pelvic lymph nodes and lymph vascular invasion absence. All patients with clear cell and serose type are excluded (9).

Rittenberg and associates has tried to answer if the pelvic RT can be safely excluded at IC stadium if the nodal status is known. He emphasizes that up to 1995, on patient with endometrial carcinoma stadium I, with myometrium infiltration >50% he applied "vault" brachytherapy in combination with pelvic RT in spite of negative nodal status. Since1995 patients are treated only with vault brachytherapy in HDR regime of exposure with total dosage sum of 1680 cGy during three fractions, (equivalent to dosage of 4000 cGy in LDR). Treatment results are similar: there were no statistically significant differences in recurrence presence (5.7% vs. 3.6%) and when pelvic RT is applied. Rittenberg and assoc. decided: that pelvic RT can be excluded with certainty with FIGO IC endometrial carcinoma if the nodal status is known (10).

In Norwegian study (Alders and assoc.) randomize trial 540 women with clinical stage I endometrial cancer after TAH/BSO and brachytherapy vs. brachytherapy + pelvic RT (8). Study shows that adjuvant pelvic radiotherapy

*There are defined dosimetric points (sum of 5) in coordinate system of corpus uteri which are in function of region of interest (ROI) and they allow therapy reproduction and maximal constant dosage in multifractional rating of exposure. Coordinate inception presents cervix estuary, y-axis is established craniocaudal and also presents the depth of cavum uterus: points X_1 and X_2 are defined as 20mm away from centre of coordinate system on y-axis, and for 20 mm each lateral distance on x-axis. Points Y_1 and Y_2 are defined as 5/6 of cavum uteri distanced points and 40mm away lateral from y-axis. Point Z lies on Y-axis and is 15 mm away from the headmost applicator pod.

in clinical stage I of endometrial carcinoma does not show survival benefit (89% vs. 91%) but better locoregional control is achieved (1.9% vs. 6.9%). Larson and assoc. reports (8) that at 123 high-risk patients with grade 3 and > 50% myometrium infiltration after surgery radiotherapy is not applied. During the 5-year observation there was no pelvic recurrence (node of negative patients), survival was 91%, 4 lung and 4 vagina metastasis are recorded.

The results of the randomized study of the GOG-99 are published by Keys and assoc. in the GOG-99 study compares postoperative pelvic radiotherapy at medium risk of FIGO stage I of endometrial carcinoma vs. no additional treatment (surgery alone) (11). It is the 3-rd multicentre randomized study, after Norwegian and PORTEC studies, which investigates this topic - pelvic radiotherapy at I stage of endometrial adenocarcinoma. It was conducted in period of 8 years (1987-1995). Study included 448 random selected patients. Results of this study show necessary information's which finally resolve any perplexity about indication for pelvic RT and range of surgical endometrial carcinoma treatment.

In the GOG-99 surgery is combination of total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), perioneal cytology, and in contrast to other studies, pelvic and para-aortal lymphadenectomy.

CONCLUSION

The use of postoperative radiotherapy should be limited to group of patients with highly enough risk of locoregional recurrence (15% and more) as risk warranty of morbidity connected to radiological treatment. Therefore, the goal of postoperative radiotherapy appliance is to achieve maximum locoregional disease control and survival without relapse.

With low risk patients (stage IA and stage IB grade 1 and 2): not indicated lymphadenectomy and adjuvant pelvic radiotherapy. These patients should be only observed after TAH-BSO, and RT can be used as very effective treatment of patients with vaginal relapse.

With medium risk patients (IR): stage IB grade 3 and IC grade 1 and 2, stage II (occult) grade 1 and 2, 60 years and more old, exclusion of RT would expose patients to the significant risk of vaginal or pelvic recurrence disease genesis.

Rittenberg and Chadhe recent information suggest that appliance of vaginal brachytherapy reduces vaginal relapse risk, with lesser morbidity and consequentially results with better life quality. These are arguments of PORTEC-2 trials which are underway and randomize between pelvic RT and vaginal brachytherapy.

With high risk patients (HIR): age along in years (> 70 years old), tumor grade 2 and 3, deep myometrial invasion, presence of lymph-vascular space, pelvic radiotherapy continues to be most effective adjuvant treatment (in cause of good pelvic control and overall survival of patients - GOG 99 results).

Lymphadenectomy is indicated at high risk grade, indicates need of expanded exposure field and appliance of adjuvant chemotherapy.

Further inquiry is necessary in order to define optimal treatment for high risk and progressed disease patients with specially combined appliance of radiotherapy and chemotherapy, considering both life quality and cost-benefit analysis.

Conflict of interest

We declare no conflicts of interest.

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