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Choice of treatment tactics in Stage IAG2 endometrioid endometrial cancer with invasion into the myometrium

Relevance. *The role of regional lymphadenectomy and adjuvant radiation therapy (RT) in the treatment of endometrial cancer (EC) is under discussion for more than 30 years. While the general principles of lymphadenectomy are currently known, the indications for adjuvant RT are still not clear. The discovery of new prognostic factors, such as lymphvascular space invasion, complicates the task of determining the need for adjuvant treatment.*

Purpose of the study *was to determine the optimal tactics of post-surgical support, and the method of adjuvant RT when indicated to patients with stage IAG2 EC with invasion into the myometrium based on the results of the retrospective and prospective randomized studies.*

Material and methods. *The retrospective study included patients suffering from stage IAG2 EC treated in Belarus in 2006- 2010. 1451 patients were diagnosed with endometrioid stage IAG2 EC with invasion into the myometrium. The prospective randomized study conducted in 2011-2015 in N.N. Alexandrov National Cancer Center of Belarus included 216 women with endometrioid EC stage IAG2 with invasion into the myometrium.*

Results and discussion. *According to the retrospective study, at the stage IAG2 with invasion into the myometrium, the 5-year survival was equal to: overall (OS) – 85.5% (95% CI 83.6-87.3%), cancer-specific (CSS) – 90.9% (95% CI 89.3-92.3%), and recurrence-free (RFS) – 89.0% (95% CI 87.3- 90.6%). Statistically significant differences in OS, CSS and RFS (p_{os}=0.0005, p_{css}=0.002, p_{rfs}=0.006) were obtained between the groups receiving surgical and combined treatment.*

In the prospective study, 5-year OS was 90.7% (95% CI 86.1-94.3%), CSS was 93.4% (95% CI 89.4-96.4%), and RFS was 92.2% (95% CI 87.7-95.4%). At that, RFS was statistically significantly higher (p_{rfs} = 0.020) in the group receiving adjuvant brachytherapy. The prognostic significance of lymphvascular space invasion was not proven (p_{os}=0.928, p_{css}=0.838, p_{rfs}=0.802).

Conclusion. *Simple hysterectomy with bilateral salpingo-oophorectomy and adjuvant brachytherapy can be considered as optimal treatment tactics for all patients with stage IAG2 EC with invasion into the myometrium regardless of lymphvascular space invasion.*

Keywords: *endometrial cancer, low risk, surgical treatment, adjuvant radiation therapy.*

Relevance. According to the Belarusian Cancer Registry, endometrial cancer (EC) ranks third in the cancer incidence among female population after skin tumours and breast cancer. 85.0% of all primarily diagnosed cases are early EC stages I-II [1].

Endometrioid EC stage IAG2 with invasion into the myometrium is traditionally referred to cancers with a low risk of development of loco-regional recurrences and distant metastases [2]. In low-risk EC, surgical treatment (ST) in the volume of simple hysterectomy with bilateral salpingo-oophorectomy (HE-BSO) is the main method of treatment according to the recommendations of the leading communities [3-5]. Discussions regarding adjuvant treatment, the role of radiation therapy (RT) and its type continue. However, it is not indicated what the clinician should do, which therapeutic tactics he should use in EC stage IAG2. I.e., the recommendations of the National Comprehensive Cancer Network (NCCN) suggest three tactics for post-surgical follow-up of patients with EC stage IAG2 with invasion into the myometrium: follow-up, adjuvant brachytherapy (BT), adjuvant external-beam radiotherapy (EBRT) on the pelvic region [3].

Recommendations of the Society of Gynaecologic Oncology (SGO) specify that adjuvant treatment in low-risk EC, that includes endometrioid carcinoma of IAG2 stage with invasion into the myometrium, in the form of radiation therapy (RT) reduces the frequency of relapses but does not affect overall survival (OS) [4]. The method of choice out of RT techniques is the post-surgical endovaginal brachytherapy (EBT).

Guidelines for adjuvant EC treatment of European societies, such as the European Society of Gynaecological Oncology (ESGO), the European Society of Medical Oncology (ESMO), the European Society of Radiotherapy and Oncology (ESTRO), called "ESGO-ESMO-ESTRO Consensus" indicate that in the absence of lymphvascular space invasion (LVSI-) in stage IAG2 EC with invasion into the myometrium belongs to the low-risk group, and adjuvant treatment is not required in this case [5]. In the presence of lymphvascular space invasion (LVSI+), EC stage IAG2 with invasion into the myometrium should be attributed to a high intermediate risk. In this case, if regional lymph nodes are removed, i.e., by pelvic lymphadenectomy (LAE), adjuvant EBT is necessary, or no adjuvant treatment is indicated. If the lymph nodes are not removed, adjuvant EBRT should be prescribed. And the question of chemotherapy (CT) of this cancer of high intermediate risk remains open till now since no study has proven its efficiency. That is, three methods of post-surgical support are recommended again, which the clinician should choose taking into account the status of LAE and the lymphvascular space invasion: observation, adjuvant EBT, adjuvant EBRT. At the same time, before receiving information on lymphvascular space invasion, stage IAG2 EC with invasion into the myometrium up to half of its thickness refers to a low risk, and the recommended amount of surgical intervention in this case is HE-BSO. Then there is a discrepancy in case after receiving a

histological response on the status of lymphvascular space invasion the risk group changes from low to high intermediate, but the pelvic LAE is not performed. Also, the pelvic LAE is not routinely recommended for all patients with stage IAG2 EC with invasion into the myometrium and can be an example of excessive treatment.

Thus, the decision-making on adjuvant treatment of stage IAG2 EC with invasion into the myometrium and its technique is a choice between the two options. First is the choice between follow-up and adjuvant treatment. Second is the choice between adjuvant BT or adjuvant EBRT option in case of adjuvant treatment selection.

Purpose of the study was to determine the optimal tactics of post-surgical support and the method of adjuvant RT when indicated to patients with stage IAG2 EC with invasion into the myometrium based on the results of retrospective and prospective randomized studies.

Material and methods. The retrospective study has assessed the outcome of patients with stage I EC treated in Belarus in 2006-2010. The inclusion criterion was EC stage I, the exclusion criterion was primary-multiple malignant tumours. 5025 women with primarily established EC stage I were treated in the mentioned period. 145 patients with primary-multiple tumours were excluded from the study, 4910 women were included in the study. Of them, 1451 patients aged 32 to 92 years (mean age – 61.3 ± 0.3 years, median age – 60 years) had endometrioid stage IAG2 EC with invasion into the myometrium.

Patients data was obtained from the Belarusian Cancer Registry; sub-stages of the disease, the histological type of the tumour, the degree of its differentiation, the volume of the operation, the treatment regimen, the volume and type of radiation therapy, the scheme and number of courses of CT, the start and end date of treatment, date of establishment of complete remission, fate of female patients were defined according to the case-records. Stages and sub-stages of EC were brought in line with TNM UICC and FIGO 2014 classification [6, 7].

4 treatment methods were used in the treatment of primary patients (Table 1):

- surgical treatment (ST group) receiving ST in the volume of HE-BSO or an expanded surgery in the volume of simple GS-SSR with pelvic LAE;
- combined treatment (CT group) receiving standard or extended surgery supplemented by RT;
- Radiation therapy (RT group) receiving RT only;
- Group receiving chemotherapy (WCT group) where surgery or combined treatment were supplemented with chemotherapy.

Table 1 – Methods of treatment of stage IAG2 EC with invasion into the myometrium in the retrospective study, 2006-2010.

Treatment methods	IAG2 with invasion into the myometrium
CT, including:	1161
PBT-ST	341
PBT-ST-EBRT	617
ST-EBRT	183
Other CT methods	20
ST	80
RT	75
WCT	135
Total	1451

In the CT group, radiation therapy was performed in the form of pre-surgical brachytherapy (PBT) or post-surgical EBRT.

The most common treatment regimens in CT group were: PBT-ST, PBT-ST-EBRT and ST-EBRT.

In all cases, the diagnosis was verified morphologically by the results of surgical intervention. In RT group with no surgery, histological diagnosis was established based on the results of curettage of the endometrium, and the depth of tumour invasion into the myometrium was refined according to instrumental methods.

Pre-surgical RT was conducted in the form of PBT in a single session in a single focal dose of 13.5 Gy on the eve of surgery, post-surgically – in the form of EBRT in usual fractions of 2 Gy to a total focal dose of 40-44 Gy in the pelvic region with the inclusion of regional zones (pelvic lymph nodes). Adjuvant ERBT was conducted 4-8 weeks post-surgery.

Medical records did not provide enough evidence to establish the reasons for prescribing chemotherapy during primary treatment of stage IAG2 EC with invasion into the myometrium.

The prospective, randomized study was conducted in 2011-2015 in N.N. Alexandrov National Cancer Center of Belarus. A total of 798 women were included in the study. Of them, 216 women aged 37 to 80 years (mean age – 58.7±0.6 years, median age – 59 years) had endometrioid stage IAG2 EC with invasion into the myometrium. Randomization was made using a computer random number generator. The patients were randomized in three groups: Group 1.1 – only surgical treatment (ST) in the volume of simple hysterectomy with bilateral salpingo-oophorectomy (Table 2), Group 1.2.1 – PBT in the same volume conducted before surgery, Group 1.2.2 – EBT sessions conducted after simple HE-BSO. PBT method was the same as in the retrospective study. EBT method was used in our country for the first time in an original technique when two EBT sessions at a single focal dose of 8.5 Gy, a total focal dose of 17 Gy (equivalent to 36 Gy), were conducted with an interval of one week. Adjuvant EBT was conducted 4-6 weeks post-surgery.

Table 2 – Methods of treatment of stage IAG2 EC with invasion into the myometrium in the prospective randomized study, 2011-2015.

Group number, treatment regimen	Number of patients
1.1. ST	82
1.2.1. PBT-ST	64
1.2.2. ST-EBT	70
Total	216

All diagnoses were histologically verified. The histological type of tumour, the depth of invasion into myometrium, and the presence/absence of LVSI was established according to the results of post-surgical definitive histological response (Table 3).

Table 3 – Presence of lymphvascular space invasion in stage IAG2 EC with invasion into the myometrium in the prospective randomized study, 2011-2015.

Presence of lymphvascular space invasion (LVSI)	IAG2 with invasion into the myometrium (%)
LVSI +	81 (37.5)
LVSI -	135 (62.5)
Total	216 (100)

Calculations started from the date of commencement of treatment and from the date of verification of complete remission. The primary endpoint in the study was the time before the occurrence of outcome; the overall survival (OS), cancer-specific survival (disease-specific, onco-specific, adjusted) (CSS), and the recurrence-free survival (RFS) by Kaplan-Meier were calculated. Confidence interval was calculated by Wilson method. Log-ranking was used to assess the statistical significance. Univariate analysis was performed using the regression method of Cox proportional hazards. Calculations were made using Statistica StatSoft software package (v. 10.0).

Results and discussion. According to the retrospective study, the 5-year OS at the stage IAG2 with invasion into the myometrium was: 85.5% (95% CI 83.6873%), CSS – 90.9% (95% CI 89.3-92.3%), RFS – 89.0% (95% CI 87.3- 90.6%).

In stage IAG2 EC with invasion into the myometrium, the leading method of treatment was CT, and almost in 10% of cases the treatment was accompanied by chemotherapy.

This group was the only one at low-risk EC with OS, CSS and RFS in CT statistically significantly higher than in the ST group (Fig. 1) (p_{os}=0.0005, p_{css}=0.002, p_{rfs}=0.006). Also, statistically significant differences were obtained for OS, CSS and RFS indicators between CT and WCT groups (p_{os}=0.004, p_{css}=0.00009, p_{rfs}=0.00001). There were no statistically significant differences between the ST and WCT groups (p_{os}=0.144, p_{css}=0.775, p_{rfs}=0.736). RT demonstrated extremely unfavourable long-term results as an independent method of treatment with a 5-year OS at 50%, as well as CSS and RFS – about 70%.

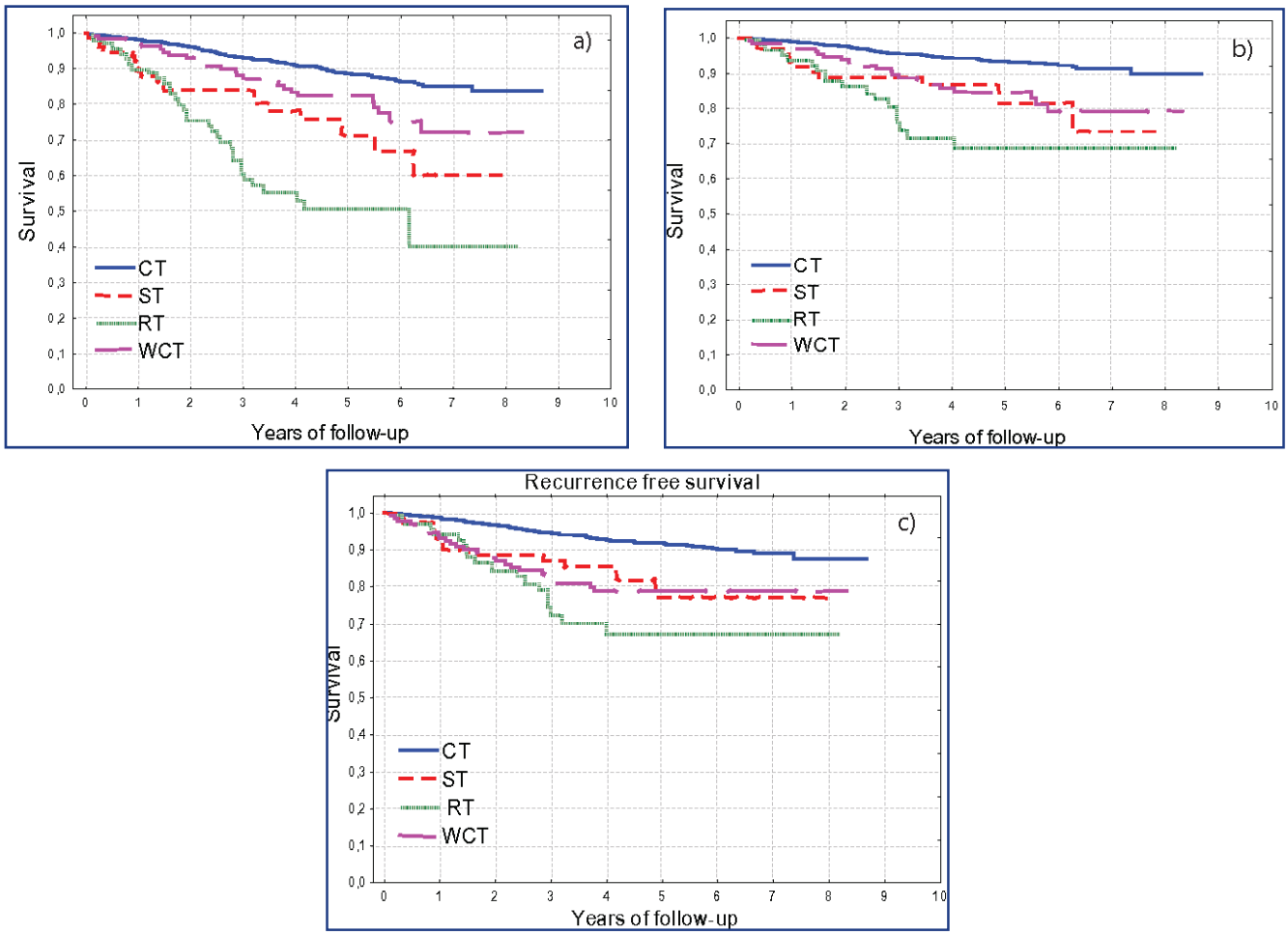

Figure 1 – Overall (a), specified (b) and recurrence-free (c) survival in stage IAG2 EC with invasion into the myometrium, depending on the method of treatment

Therefore, it is necessary to avoid the prescription of RT as an alternative to chemotherapy in stage IAG2 ECwith invasion into the myometrium. Also, chemotherapy reduces the life expectancy of patients in this group, and while CT is not more efficient than ST. Therefore, there are no grounds for the prescription of chemotherapy. Besides, taking account the difference in survival, ST shall be supplemented with RT.

When ST was compared with the used CT methods in which standard surgery was supplemented with PBT, or with PBT and adjuvant EBRT, the OS, CSS and RFS were found to be higher in the subgroups receiving contact RT (BT). No significant increase in survival was obtained in the group where ST was supplemented only with adjuvant EBRT (Figures 2-4).

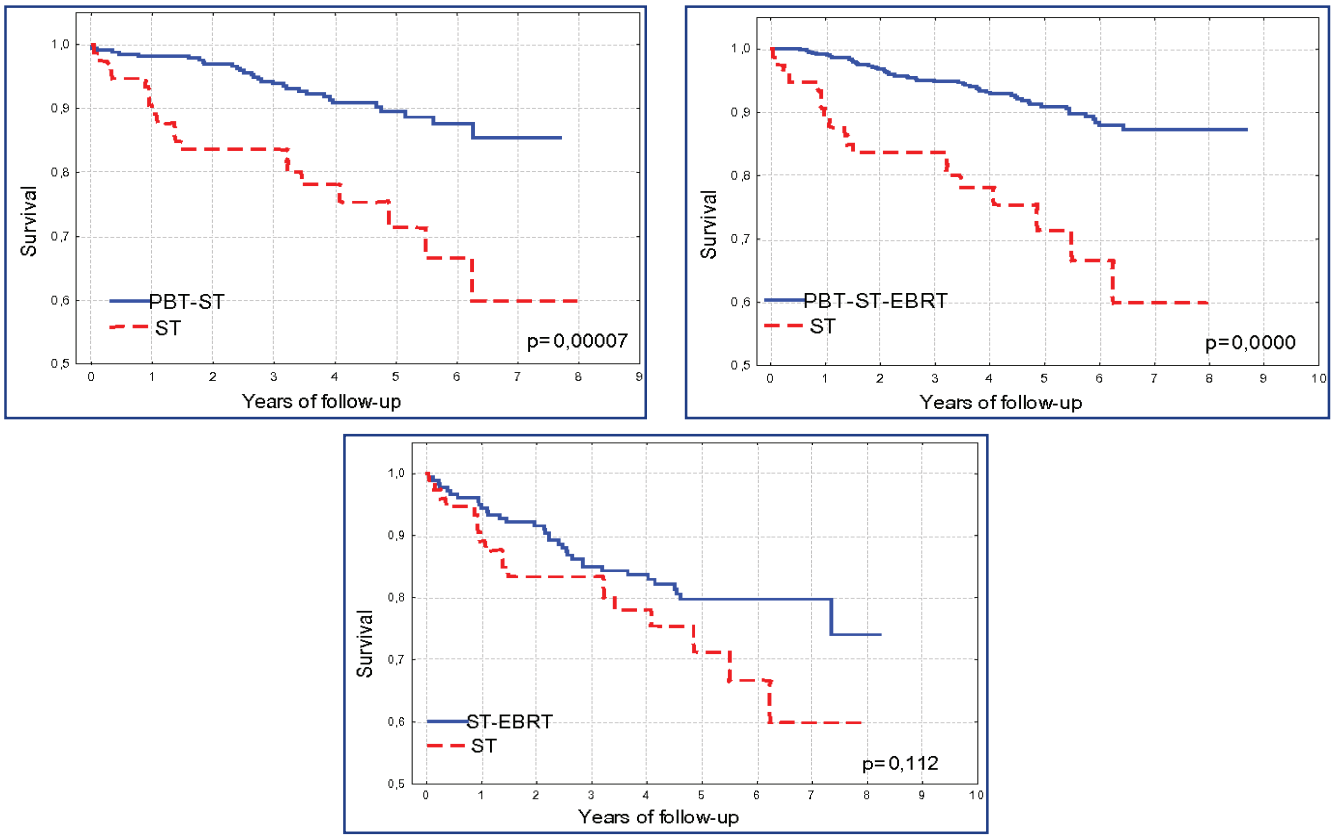

Figure 2 – Comparison of overall survival in stage IAG2 EC with invasion into the myometrium between surgical treatment and various methods of combined treatment

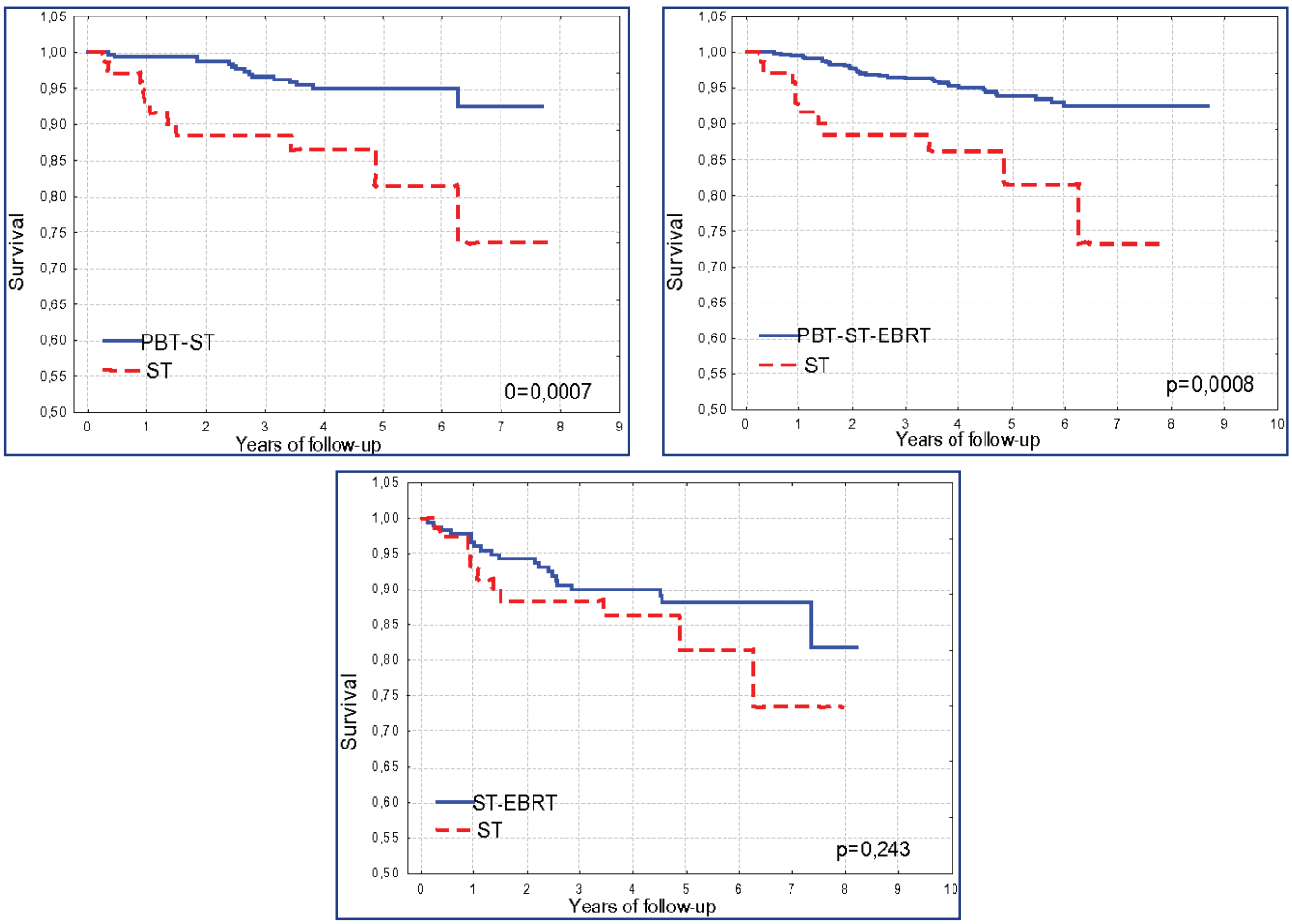

Figure 3 – Comparison of cancer-specific survival in stage IAG2 EC with invasion into the myometrium between surgical treatment and various methods of combined treatment

Thus, in CT group survival was statistically significantly higher than in ST group. The resulting difference in survival indicated that in stage IAG2 EC with invasion into the myometrium, CT was the optimal method of treatment since RT was to be prescribed for all patients with stage IAG2 EC with invasion into the myometrium without exception as an addition to the surgery. That is, if the final diagnosis was confirmed RT was prescribed routinely.

Of the three main CT methods, survival was statistically significantly higher in case of methods that included PBT (Figures 5-7).

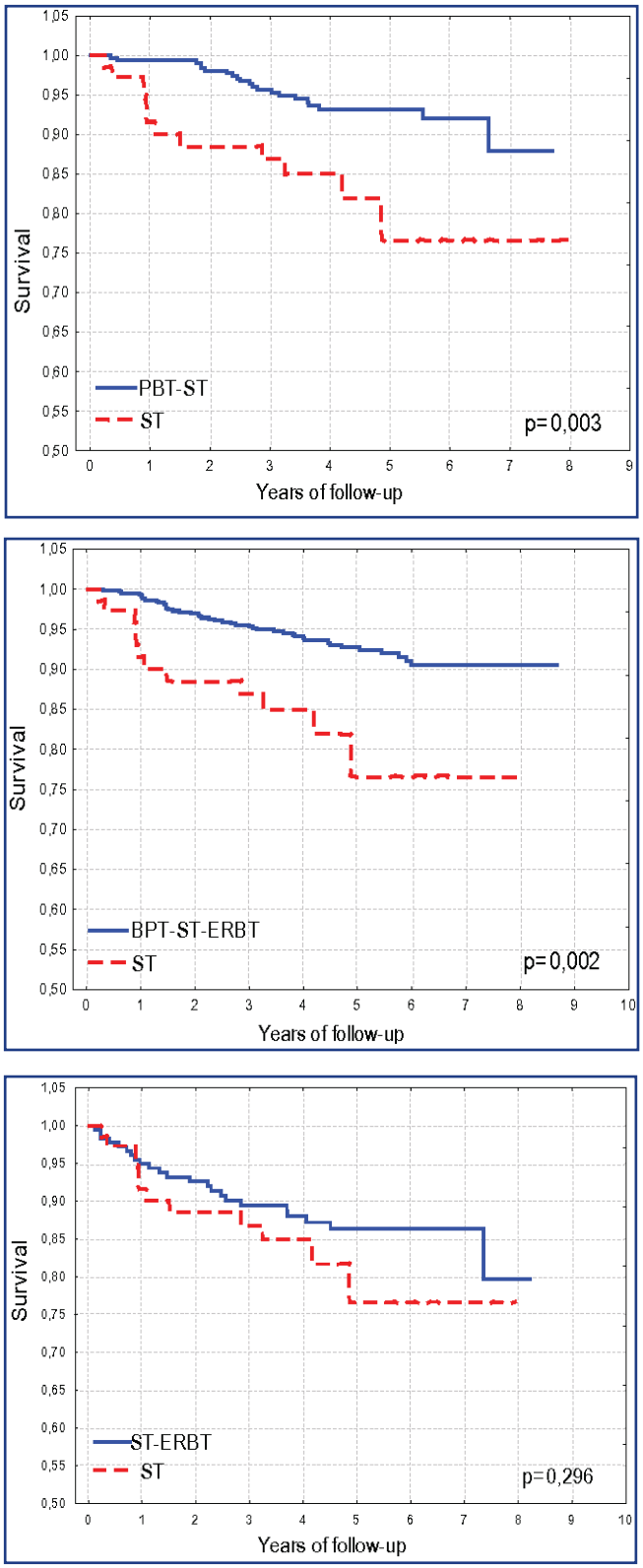

Figure 4 – Comparison of recurrence-free survival in stage IAG2 EC with invasion into the myometrium between surgical treatment and various methods of combined treatment

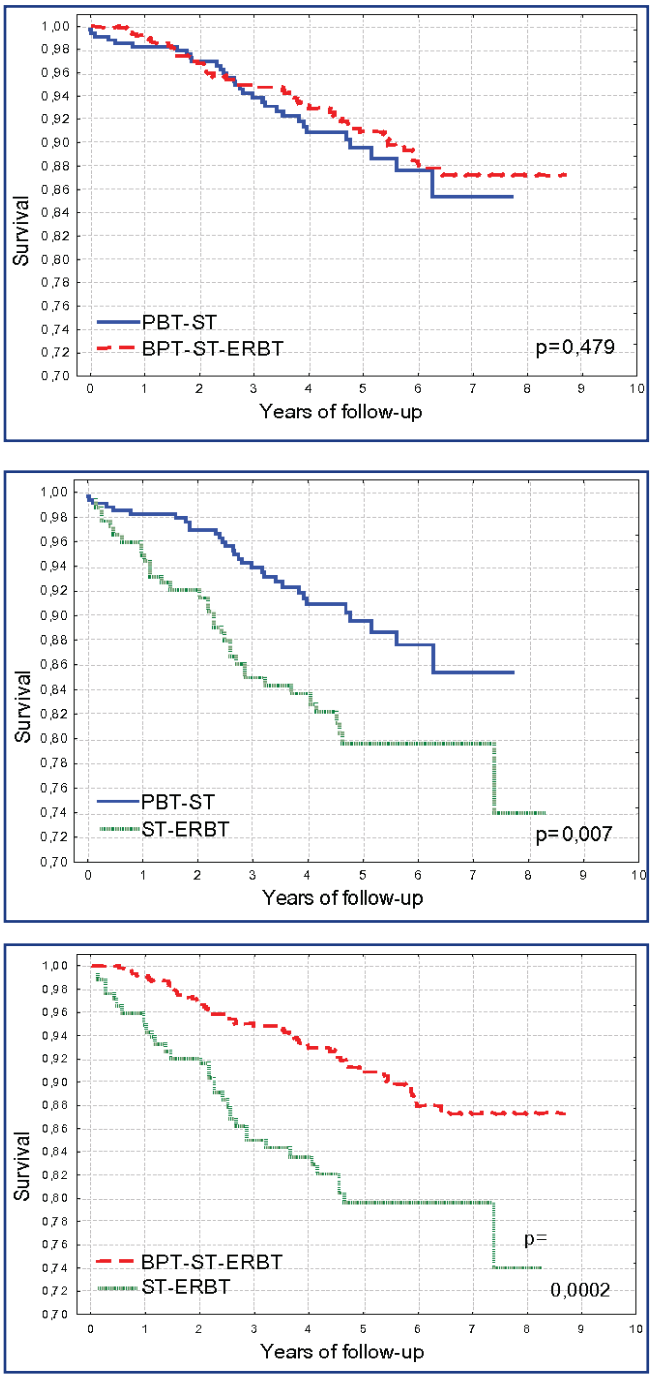

Figure 5 – Comparison of overall survival in stage IAG2 EC with invasion into the myometrium when using different methods of combined treatment

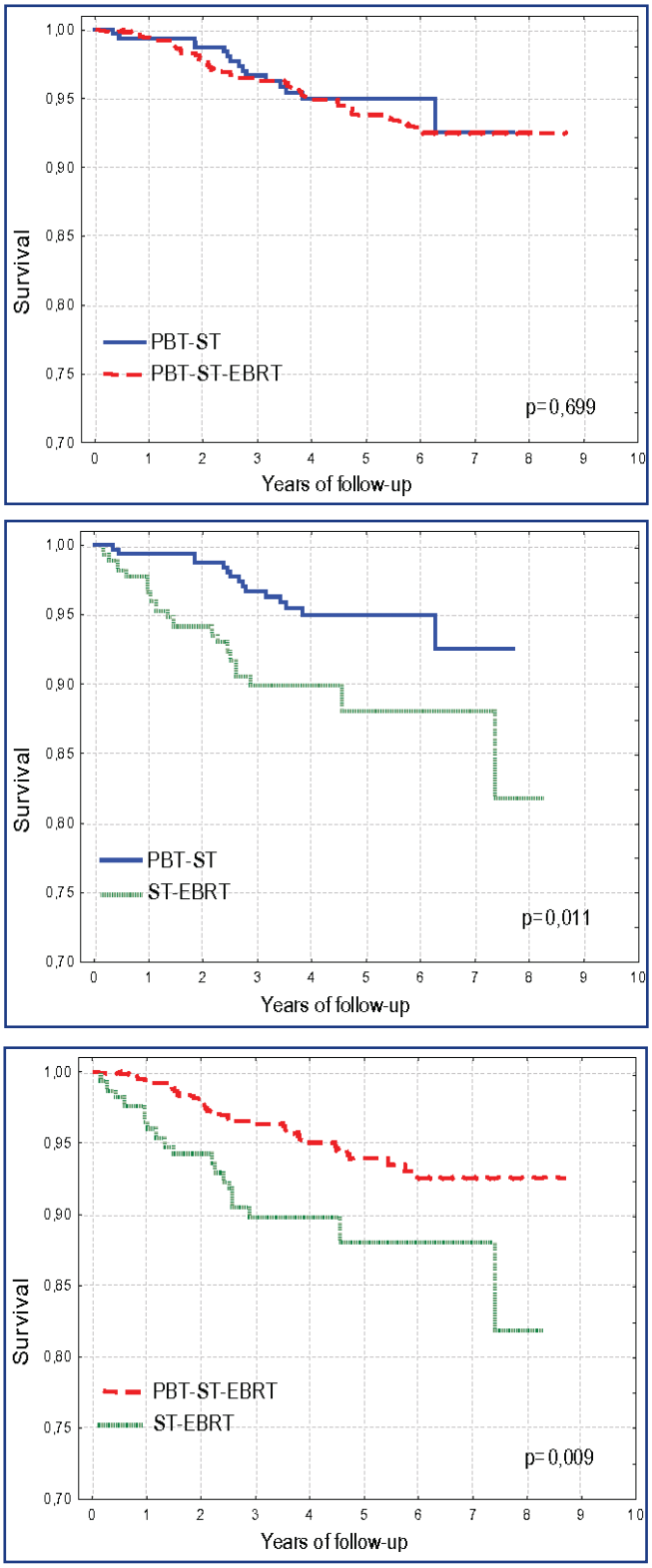

Figure 6 – Comparison of cancer-specific survival in stage IAG2 EC with invasion into the myometrium when using different methods of combined treatment

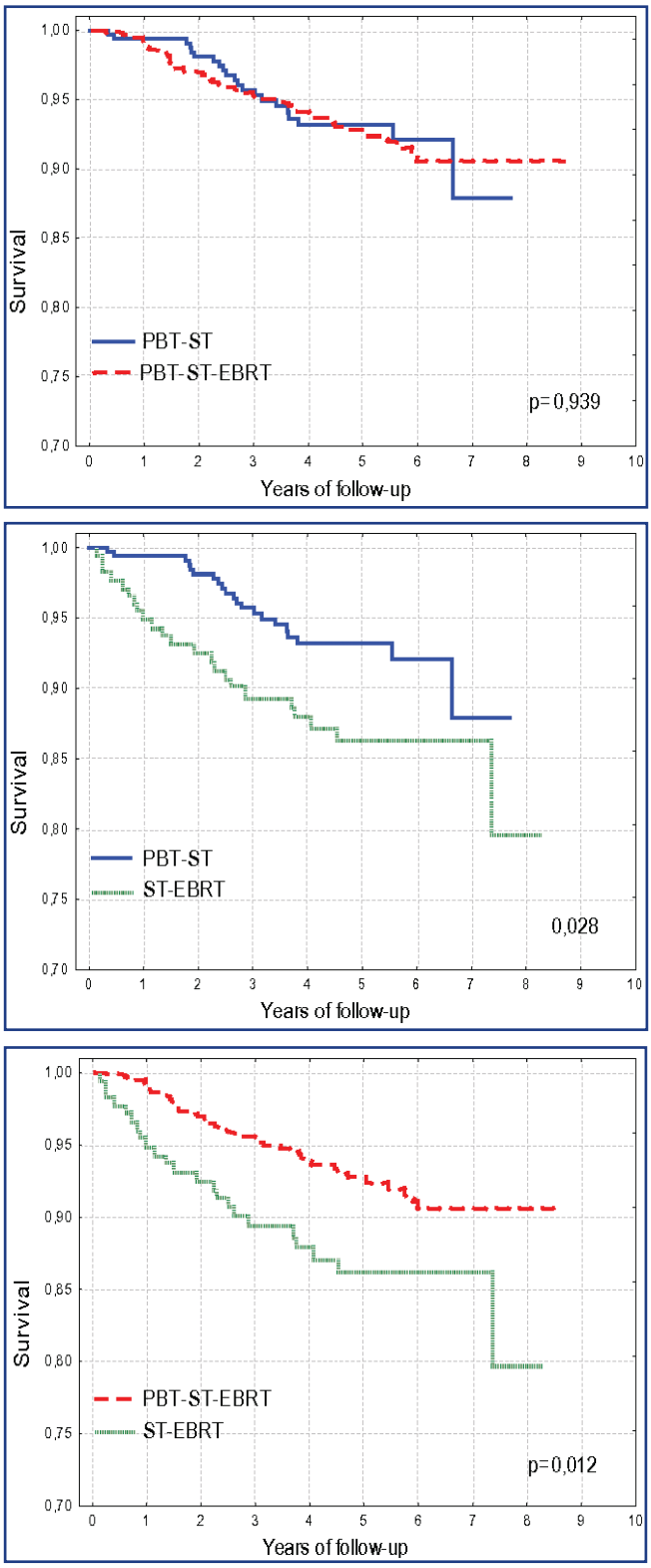

Figure 7 – Comparison of recurrence-free survival in stage IAG2 EC with invasion into the myometrium when using different methods of combined treatment

The total of 72 recurrences in the subgroup developed in 69 patients (4.8%), of them, in 40 women (3.4%) after combined treatment, in 5 (6.3%) post-surgery. After CT, local recurrences were registered in 4 female patients (0.3%), regional recurrences in pelvic lymph nodes – in 3 female patients (0.3%). Local and regional pelvic recurrences were not registered after ST (Table 4).

Table 4 – Recurrences in stage IAG2 EC with invasion into the myometrium

Localization of recurrence	Treatment method				
	ST (%)	CT (%)	WCT (%)	RT (%)	Total (%)
Local recurrence in pelvic	-	4 (0,3)	4 (2,9)	-	8 (0,6)
Regional recurrence in lymph nodes	-	3 (0,3)	1 (0,7)	1 (1,3)	5 (0,3)
Regional recurrence in retroperitoneal lymph nodes	2 (2,5)	4 (0,3)	1 (0,7)	-	7 (0,5)
Recurrence in uterus after radiation therapy	-	-	-	2 (2,7)	2 (0,1)
Canceromatosis	-	9 (0,8)	5 (3,7)	1 (1,3)	15 (1,0)
Lungs	1 (1,3)	8 (0,7)	3 (2,2)	-	12 (0,8)
Liver	1 (1,3)	3 (0,3)	2 (1,5)	-	6 (0,4)
Bones	1 (1,3)	1 (0,1)	2 (1,5)	-	4 (0,3)
Vagina	-	3 (0,3)	3 (2,2)	-	6 (0,4)
Distant lymph nodes	-	4 (0,3)	1 (0,7)	-	5 (0,3)
Brain	-	2 (0,2)	-	-	2 (0,1)
Total number of disease recurrences	5 (6,3)	41 (3,5)	22 (16,3)	4 (5,3)	72 (5,0)
Total number of female patients	80	1161	135	75	1451

As can be seen from the table, distant metastases were more often but the survival rate in the group of patients with chemotherapy was statistically significantly lower than in the CT group which had the highest survival rates. That is, the use of chemotherapy has reduced the life expectancy.

The recurrence frequency after ST was higher (6.3%) than after CT (3.5%) despite the lack of any local recurrences.

The use of only adjuvant EBRT did not improve the long-term results in comparison with ST performed in the volume of simple HE-BSO (Figures 5-7). Therefore, adjuvant EBRT should be avoided as it did not improve survival rate. No statistical difference was revealed between the two main methods – only pre-surgical BT or pre-surgical PCT plus ERBT. The lack of difference in survival rates evidenced no effect of post-surgical EBRT at low-risk EC in any of the sub-groups.

Since EBRT is conducted within 20-23 working days and may require hospitalization because of the remoteness of the cancer care facility, the denial of EBRT would neither affect the survival of patients with low-risk EC no reduce their quality of life as they would avoid radiation reactions and complications and also save money for treatment not losing in the treatment success. The absence of statistically significant differences in these treatment regimens also confirms the correctness of the latest recommendations. When choosing a variant of RT (contact and/or external), adjuvant EBRT might be avoided as it neither improves survival and nor reduces the relapse rates compared to ST. When combined with contact RT and surgery, adjuvant EBRT does not improve the long-term outcome of CT with the use of only pre-surgical BT. Thus, the most optimal scheme of combined treatment of stage IAG2 EC with invasion into the myometrium from both the oncological and economical points of view would be PBT-ST. On the other hand, PBT is carried out before surgery, that is, before obtaining final morphological data. Therefore, in some cases diagnosis will be changed afterwards (the tumour might have more favourable characteristics than expected) and RT would be not needed in this particular case. Then, PBT will be an excessive treatment. We face a dilemma that on one hand, PBT improves survival in comparison to post-surgical EBRT, on the other hand, its prescription requires a clear assessment of the depth of invasion, the morphology and degree of differentiation of the tumour what is not always possible. The morphological characteristics of the tumour can change after surgery on the basis of the final histological examination that might give no indications for RT. But it will already be conducted. The way out might be in the change of timing of BT, namely, the use of post-surgical adjuvant BT instead of PBT. In this case, all the necessary characteristics of the tumour will be available for the prescription of adjuvant treatment. There are reasons to believe that adjuvant BT will be as effective as PBT.

This hypothesis has also been tested in the prospective randomized study that was to prove the findings of the retrospective study on the advantages of CT vs. ST and the equal efficiency of adjuvant BT was vs. PBT. It was also necessary to clarify the prognostic significance of lymphvascular space invasion.

According to the prospective study, 5-year OS, CSS and RFS were 90.7% (95% CI 86.1943%) 93.4% (95% CI 89.4-96.4%), and 92.2% (95% CI 87.7-95.4%), respectively. In the prospective study, the statistically significant differences were established in RFS, and no statistically significant differences were received for OS and CSS after combining the two groups receiving RT in one CT group and the comparison of survival rates with ST in the volume of simple HE-BSO (Fig. 8).

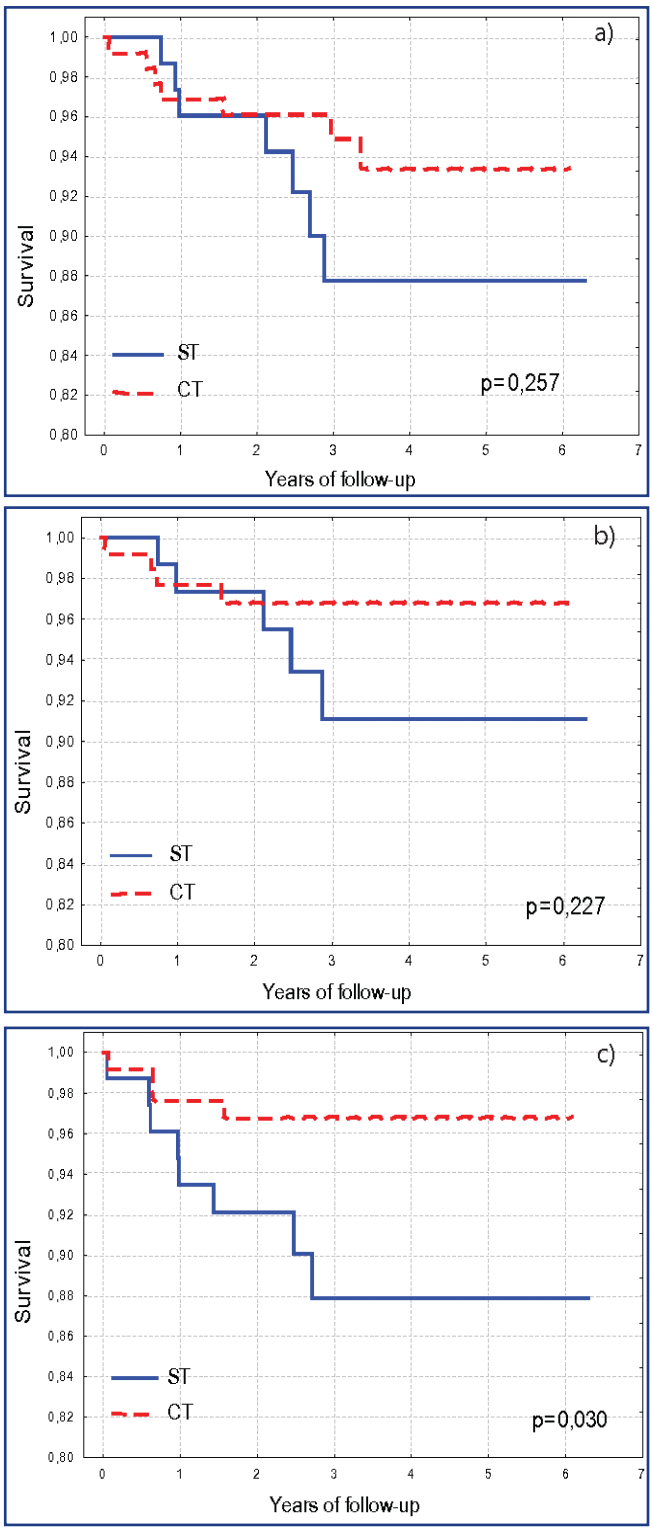

Figure 8 – Overall (a), specified (b) and recurrence-free (c) survival in stage IAG2 EC with invasion into the myometrium, depending on the method of treatment

That data fully coincided with the results of studies which established that RT improved RFS and did not affect CSS, but the difference in 5-year OS and CSS was 5% and 6%, respectively. However, those results mainly concerned adjuvant EBRT. The presence of significant differences in RFS and the fact that CT group was comprised of two groups with different treatment methods made it possible to compare the results of all three study groups from the point of OS, CSS and RFS rates (Figures 9-11).

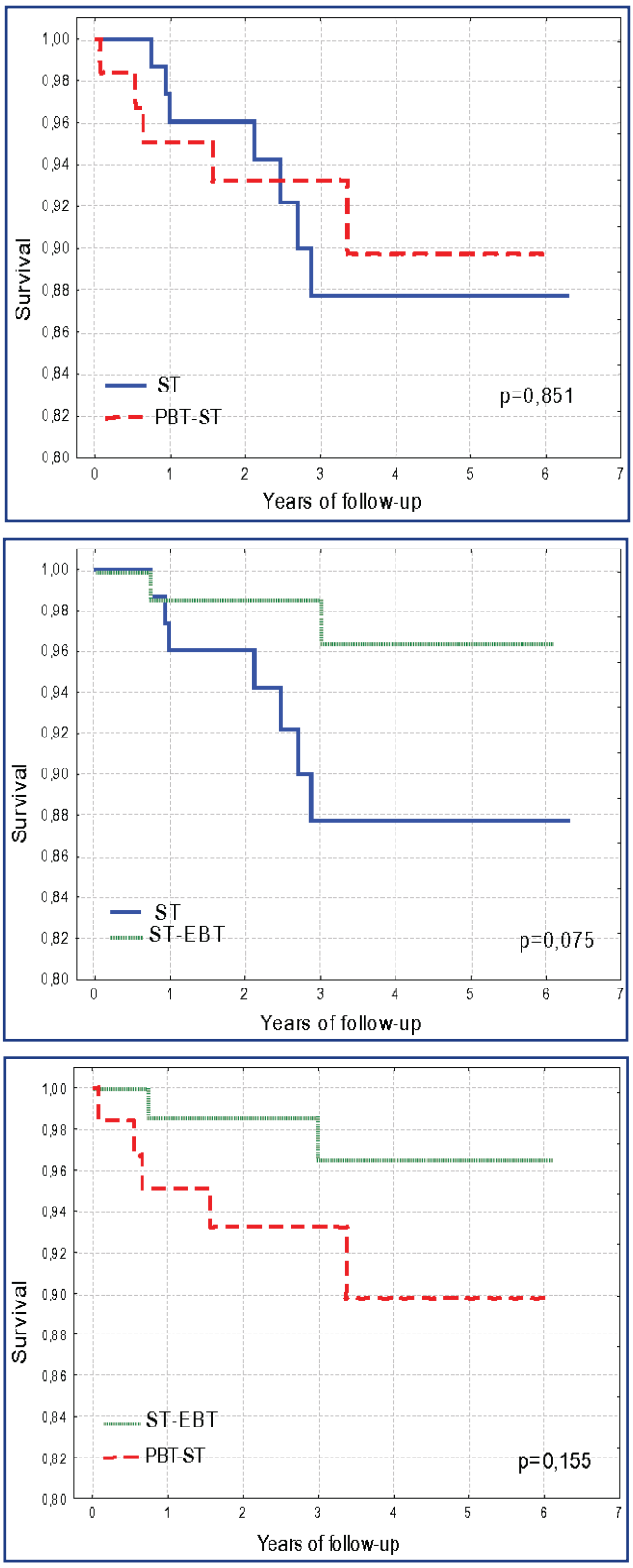

Figure 9 – Overall survival in stage IAG2 EC with invasion into the myometrium at studied treatment methods

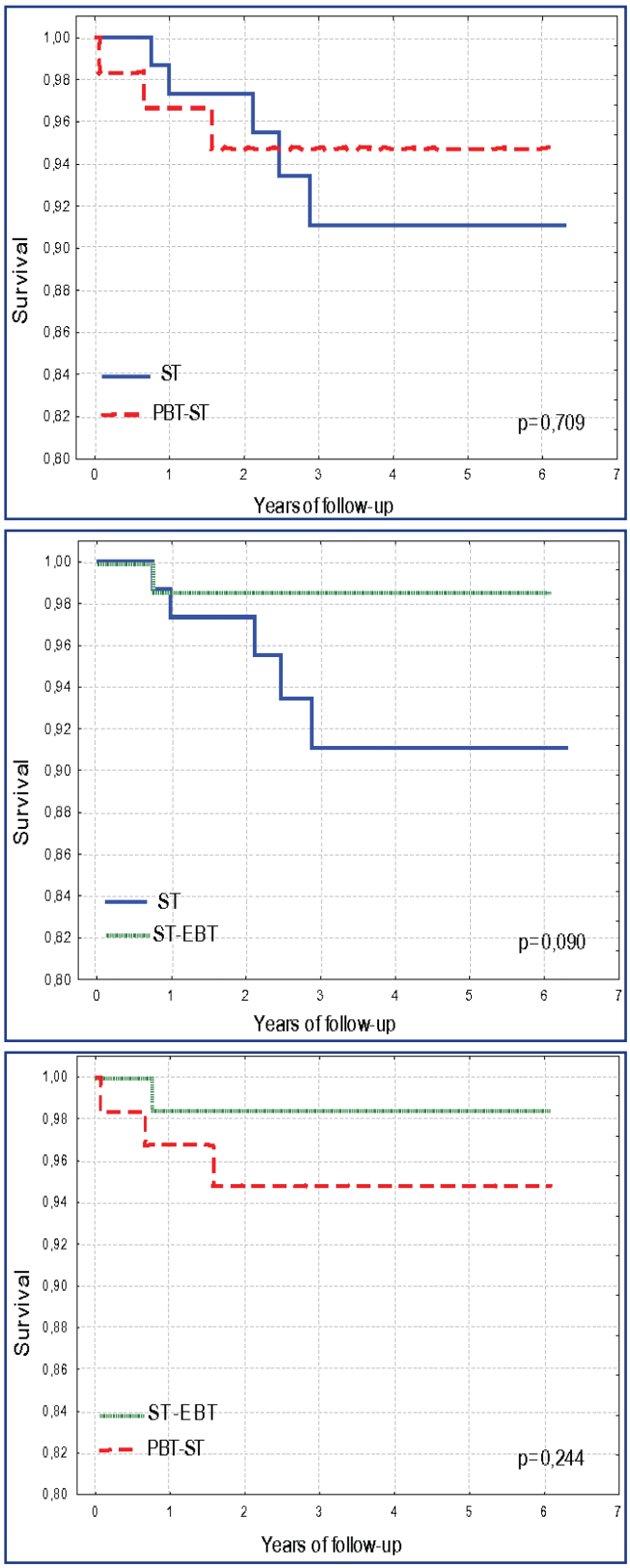

Figure 10 – Cancer-specific survival in stage IAG2 EC with invasion into the myometrium at different treatment methods

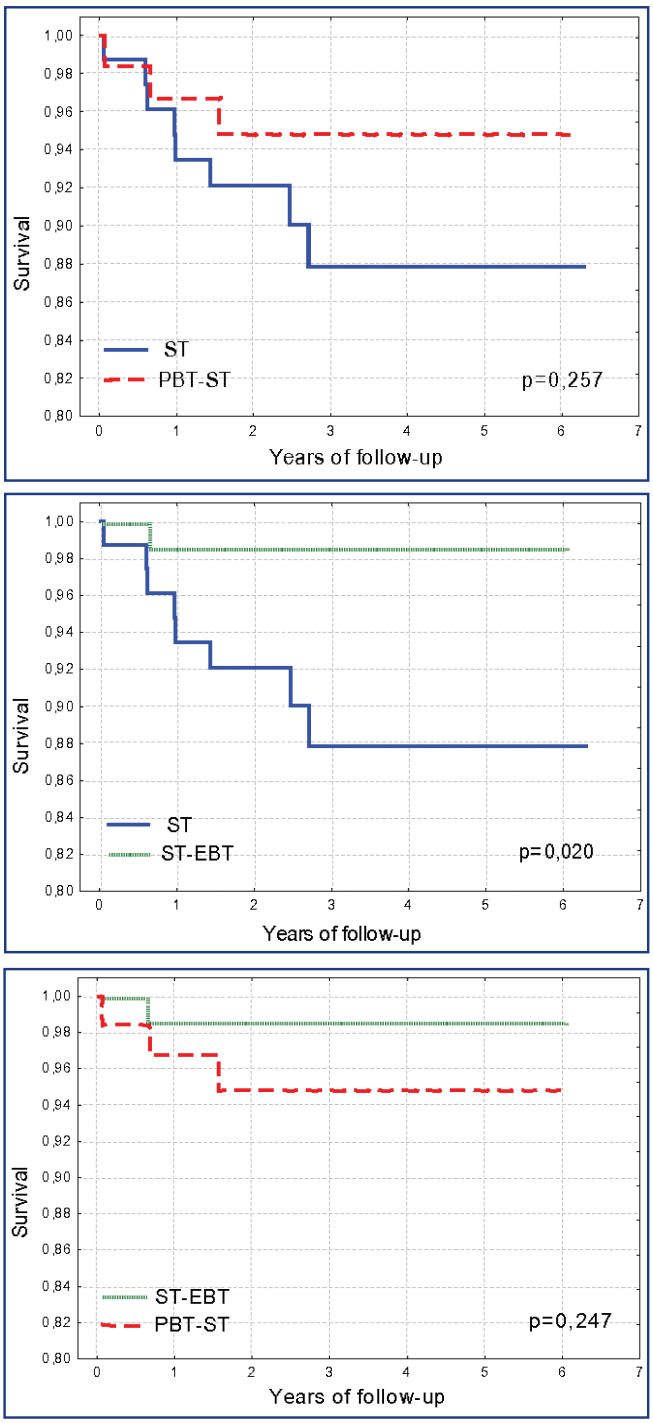

Figure 11 – Recurrence-free survival in stage IAG2 EC with invasion into the myometrium at different treatment methods

No statistically significant differences in survival rates were obtained between ST and PBT-ST groups, as well as between PBT-ST and ST-EBT groups. The statistically significant differences in RFS were obtained and the trend of differences in OS and CSS were noted between ST and ST-EBT groups. The presence of differences and their trend indicated that in stage IAG2 EC with invasion, CT should be method of choice. The absence of statistically significant differences between PBT-ST group and other groups showed its intermediate position between ST and ST-EBT groups but it was not efficient enough to improve survival. The most efficient method was ST-EBT.

The survival rates in stage IAG2 EC with invasion into the myometrium bring us to the conclusion that only operative treatment is not enough in this group as all patients routinely have been prescribed adjuvant BT post-surgery.

The need for adjuvant RT for all patients without exception with that stage was evidenced by the fact that the LVSI did not show its prognostic significance in that group (Figure 12). As can be seen in the figure, starting from the third year of follow-up, the curves of CSS and RFS in the presence or absence of LVSI were practically congruent.

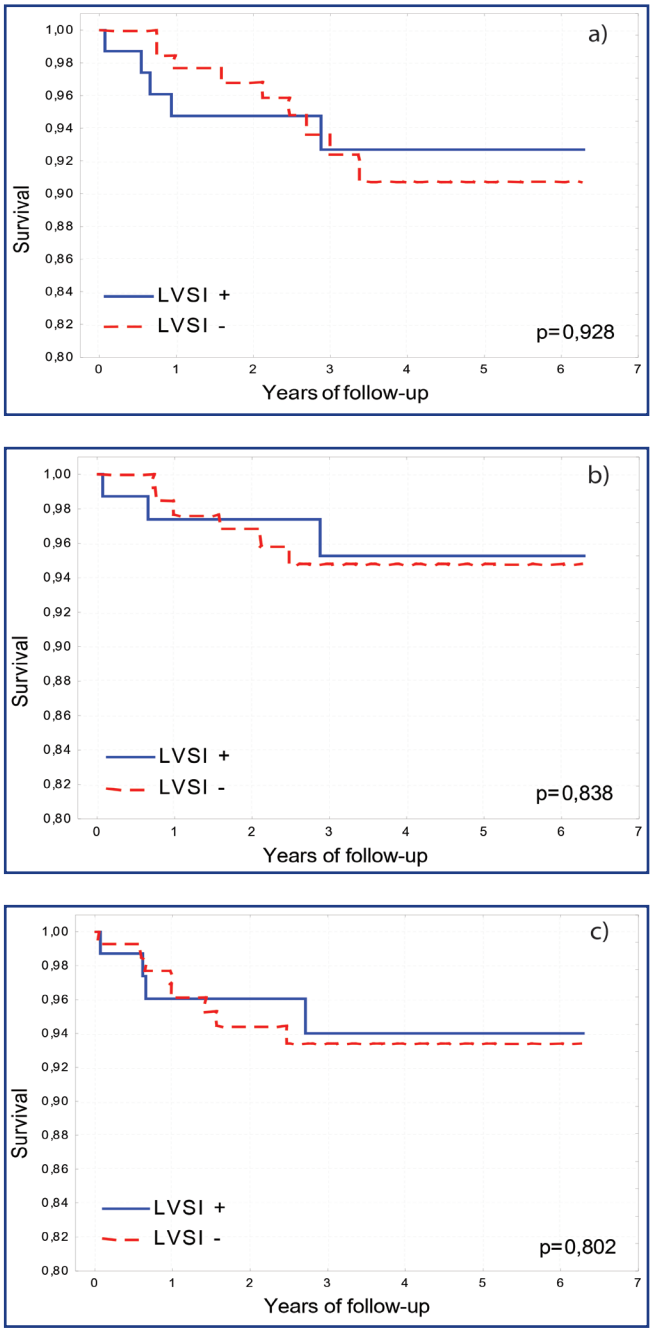

Figure 12 – Overall (a), cancer-specific (b) and recurrence-free (c) survival in stage IAG2 EC with invasion into the myometrium, depending on LVSI

Probably, in stage IAG2 EC with invasion into the myometrium, the aggressive properties of G2 endometrioid carcinoma with invasion of the myometrium were such that lymphvascular space invasion proved to be a non-primary factor, that is, its presence or absence had no significant effect on survival.

This is quite a new conclusion on LVSI, and if it is confirmed by other studies, it may be necessary to review the latest recommendations for adjuvant treatment of EC stage I, and low risk in particular.

Only age had a statistically significant effect on the relative risk of unfavourable outcome for OS and RFS rates and also demonstrated a trend in CSS. Thus, judging by OS parameter, the relative risk was equal to 1.072 (95% CI 1.002-1.148) (p = 0.044), judging by RFS, it was equal to 1.101 (95% CI 1.020-1.181) (p = 0.013), and judging by CSS, it was equal to 1.081 95% CI 0.994-1.175) (p = 0.068). The prognostic significance of other predictors was not established. Taking into account the obtained results, multifactor analysis was not performed.

The whole group had 14 unfavourable outcomes (6.5%), of them, 9 patients died from EC (4.2%), and 5 (2.3%) – from other diseases. In ST group, there were 7 (8.5%) unfavourable outcomes out of 82 female patients, of them, 5 (6.1%) – from EC, and 2 (2.4%) – from other diseases. In PBT-ST group, 5 (7.8%) unfavourable outcomes were registered out of 64 female patients, of them, 3 (4.7%) unfavourable outcomes were from the EC, and 2 (3.1%) – from other diseases. In ST-EBT group, there were 2 (2.9%) unfavourable outcomes out of 70 female patients; one of them – from EC and another (1.4%) – from other diseases.

Disease recurrence happened in 8 (3.7%) women: 6 (7.3%) from ST group, 1 (1.6%) – from PBT-ST group, and 1 (1.4%) – from ST-EBT group. In ST group, one female patient had a local recurrence in vaginal cuff, two patients had regional recurrences in pelvic lymph nodes, one patient had it in retroperitoneal lymph nodes, two patients had it in peritoneal sarcomatosis, and one had lung metastases. Peritoneal carcinomatosis was established in both cases in female patients in PBT-ST and ST-EBT groups.

Conclusion. Based on the retrospective study we can state that in endometrial cancer stage IAG2 with invasion into the myometrium combined treatment including surgery in the volume of simple hysterectomy with bilateral salpingo-oophorectomy and pre-surgical brachytherapy has demonstrated a statistically significantly better efficacy vs. surgical treatment or combined treatment with adjuvant external-beam radiotherapy. Therefore, adjuvant external-beam radiotherapy may be discarded in favour of contact radiotherapy.

In the prospective study, the best long-term results were obtained using combined treatment that included surgery in the volume of simple hysterectomy with bilateral salpingo-oophorectomy and adjuvant pre-surgical brachytherapy. The statistically significant differences in overall survival and a trend of differences in cancer-specific and recurrent-free survival were obtained between the group treated by the mentioned method and the

group receiving only surgery. That data confirmed the findings of the retrospective study that evidenced the use of combined treatment in stage IAG2 EC with invasion into the myometrium. No statistically significant differences were found between PBT-ST and ST-EBT groups, despite the difference in the 5-year survival rates from 2% to 8% in favour of ST-EBT group.

However, the use of ST-EBT scheme is logical and more justified, since the decision to conduct adjuvant radiotherapy is taken on the basis of the final morphology of the tumour what allows avoiding the excessive use of radiotherapy in the cases when it is not needed.

For lymphvascular space invasion, widely studied as a forecast factor specifically in stage IAG2 EC with invasion into the myometrium, no prognostic significance has been established, the curves of cancer-specific and recurrence-free-survival in groups with lymphvascular space invasion and without it were similar.

Thus, simple hysterectomy with bilateral salpingo-oophorectomy and adjuvant brachytherapy can be considered as optimal treatment tactics for all patients with EC stage IAG2 with invasion into the myometrium regardless of lymphvascular space invasion.

References:

1. Okeanov A.E., Moiseev P.I., Levin L.F., Evmenenko A.A. Statistika onkologicheskikh zabolevaniy v Respublike Belarus' (2007-2016) [Statistics of cancer diseases in the Repulic of Belarus (2007-2016)] / ed. O.G. Sukonko. – Minsk,2017. – 288 c.

2. Malkasian G.D. Carcinoma of the endometrium: effect of stage and grade on survival // Cancer. – 1978. – Vol. 41, N 3. – P. 996–1001.

3. Wui-Jin K., Greer B.E., Abu-Rustum N.R., Apte S.M., Campos S.M., Cho K.R., Chu C., Cohn D., Crispens M.A. NCCN Guidelines Version 1.2018. Uterine Neoplasms // National Comprehensive Cancer Net- work, Version 1.2018 – 2017. – P.105.

4. Burke W.M., Orr J., Leitao M., Salom E., Gehrig P., Olawaiye A.B., Brewer M., Boruta D., Villella J., Herzog T., Abu Sha. Endometrial can- cer: A review and current management strategies: Part II / SGO Clinical Practice Endometrial Cancer Working Group; for the Society of Gyne- cologic Oncology Clinical Practice Committee // Gynecologic Oncolo- gy. – 2014 – Vol. 134(2). – P. 393-402.

5. Colombo N., Creutzberg C., Amant F., Bosse T., Antonio Gonza- lez-Martin A., Ledermann J., Marth C., Nout R., Querleu D., Raza Mirza M., Sessa C. ESMO-ESGO-ESTRO Consensus Conference on Endometri- al Cancer: diagnosis, treatment and follow-up // International Journal of Gynecological Cancer. – 2016. – Vol. 26. – P. 2–30.