

CERVICAL CANCER EVOLUTION BY THERAPEUTIC CONDUCT

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Abstract. The purpose of this study has been to determine the effectiveness of the therapeutic conduct options for the patients with cervical lesions that can develop into cancer. The county of Galati was discovered to have the highest incidence in Romania, 45.80 o/oooo of the feminine population. If there were a screening of the general population, the results would be a real gain for the prevention of cervical cancer.. The study was performed in the period of time between 2003 and 2012, in the County Hospital of Galati, on a number of 1885 cases of women with a suspicion of neoplastic lesion, aged between 16 and 92, who were treated surgically and/or oncologically by using conservative methods. The conservative conduct highlights a better accuracy after establishing the cytological diagnosis of high degree lesion (64.9%) and after performing the biopsy (40.7%). If prior to the treatment the patient had been diagnosed after biopsy and histological examination, the surgical treatment was more effective, having an accuracy of about 25%. The efficiency of the oncologic treatment shows a better accuracy after establishing the cytological diagnostic of high degree lesion (62.8%) and also in the case of biopsy (40.4%). We consider that the patients with cervical cancer must not be abandoned, no matter what their stage is when they come to the doctor, because, it is not rare when they have a satisfactory evolution after a well conducted complex treatment.

INTRODUCTION

Cervical cancer represents an important public health issue, being the second in Romania, after breast cancer, with respect to the incidence and also mortality by malignant tumours in women (MS Romania, 2010). Its incidence is continuously growing, and the therapeutic results are not satisfactory, despite the progress made lately in knowing the natural evolution of the disease, despite the improvement of the diagnostic methods and the improvement of the quality of the treatment (Chan et al, 2009, Neacsu et al, 2011).

The continuously ascending mortality of cervical cancer in Romania truly justifies the fact that now all the efforts are focused on the primary and secondary prophylaxis/prevention of the disease and also underlines the necessity of urgent intervention nationwide.

A number of authors proved that women with an infection with *Human Papilloma Virus* (HPV) belong to the group of patients with risk of getting cervical cancer, as in their case there are cumulated risk factors: early beginning of sexual activity, getting pregnant and giving birth at a very young age, 14-20 years old, a big number of sexual partners, increased frequency of occasional sexual relationships, precarious local hygiene, a very low socio-economical level, smoking etc (ACOG, 2004, 2009, 2010, Barr et al, 2008, Benagiano et al , 2006, Choudhury and Gingh, 2006, Naucler et al, 2007, Wang et al, 2009, WHO, 2007, Wright et al, 2009).

It is a chronic disease with a severe evolution, especially when it is discovered in its more advanced stages (Arbyn et al, 2010, Chansaenroj et al, 2010).

The stadial classification of cervical cancer reflects the degree of tumour extension. There have been some attempts lately, that are statistically founded, that can represent elements of prognostic appreciation, depending on the dimensions of the lesion- when it is strictly limited to the cervix – or to the direction and limitrophe extension degree - in the cases where the tumour is extended over the limits of the cervix (De Francesco et al, 2010, Ungureanu et al, 2010, Woodman et al, 2003).

Though, the Bethesda system restates the fact that the cellular aspects are not always clear and cannot always be interpreted without a doubt and there are also some ambiguous changes that they try to limit as much as possible. The Bethesda version 2001 identifies the benign changes more clearly, placing them in the category of the negative results for a malignant or an intraepithelial lesion, even if the smear shows the aspects of an inflammation that is the ground for the respective changes (Bethesda, 2001).

The certainty of the diagnostic is given by the hystopathological examination of the material obtained through biopsy (Massad et al, 2001). In simple words, the lesions with a low degree represent transitory infections with HPV, that can cause certain cellular changes, but that disappear spontaneously in most cases (Aksu et al, 2006, Balan et al, 2010, Spencer et al, 2009). If the presence of a lesion could not be proved, it is recommended that all cytologic, colposcopic or even histo-pathologic evaluations should be reviewed, as long as this is possible (Chan et al, 2009, Neacsu et al, 2011).

If the diagnostic of the invasive forms can be easily established, the diagnostic of *in situ* carcinoma or of moderate/severe dysplasia sometimes requires the biopsy to be repeated.

If the biopsy confirms the presence of a CIN (Cervical Intraepithelial Neoplasia), the therapeutic procedure that is to be adopted will be established depending on the severity of the intraepithelial lesion (Massad et al, 2001). If the pluri-disciplinary re-evaluation of the case leads to different interpretations, the conduct must change according to these results (Gree et al, 2010).

If the interpretation of the cytological smear shows an H-SIL (High Grade Squamous Intraepithelial Lesion) type again, or when the re-evaluation of the smear is not possible, it is preferable to use an excisional procedure of diagnostic for the patients who are not pregnant. It is acceptable to skip the harvesting of the evaluation samples from the endo-cervix when the doctor intends to use an excisional procedure of diagnostic immediately (Chan et al, 2009).

An H-SIL type cytological result indicates a significant risk for that patient to develop a pre-invasive cervical lesion or invasive cancer. According to some studies made when elaborating the Bethesda 2001 recommendations regarding the conduct when facing an H-SIL type cytology, the chance for a patient with H-SIL type cytology to have a CIN II/III confirmation biopsy is about 70-75%, and its chance of having invasive cancer is 1-2% (Solomon et al, 2002, Wied et al, 1992). That is why, the traditional conduct recommended as optimum in case of an H-SIL type cytology consists of a colposcopy associated with the evaluation of the endo-cervix.

The aim of this study has been to determine the effectiveness of the therapeutic conduct options for the patients with cervical lesions that can develop into cancer.

MATERIAL AND METHODS

In the 10 years of the study (2003-2012), there were 5047 gynaecological consults performed, for suspicion of cervical neoplasia, in the County Hospital of Galati, out of which there were 3206 specific examinations (63.5%), but only 1885 cases consented to enter the screening programme (37.3% of the total consults; 58.8% of the cases investigated for suspicion of cervical neoplasia).

The screening was performed while following the epidemiologic risk indicators, that identify the target group of women whose testing is a priority, especially those women who have never had a cytological smear harvested, so the age limit went down to 18-20.

The statistical analysis of the epidemiologic characteristics helped us sketch a profile for the patient at risk of cervical neoplasia, as follows (Table 1):

Table 1. The profile of the patient with cervical neoplasia

Epidemiological characteristic	Profile	%
Average age	45.26 ± 13.38 years old	-
Area of origin	urban	77.3
Marital status	married	73.0
Studies	high school	66.3
Occupation	worker	37.7
Life conditions	tobacco	30.7
	coffee consumption	22.9
Debut of sex life	17-19 years old	68.4
Number of partners	1-2	88.8
Number of sexual intercourses/ week	2	71.3

After performing the cytological screening for the women with an increased oncogenic risk, the next step was the clinical examination, even if it does not offer the possibility of an early diagnostic, but it opens the door for the other means of investigation.

The cytological smear studies the changes that have a hormonal nature, or those having an atypical, neoplastic nature, that appear in the cells that have been desquamate from the exo-cervix or from the cervical canal.

The describing of the elementary colposcopic lesions and the fact that we established their correspondence with the histopathological sub-layer offered the possibility to determine some degrees of gravity for the colposcopic images that are pretty precise, thus succeeding to eliminate the lesions that are not suspicious, from the numerous clinical and pathological aspects of the cervix, this way reducing considerably the number of biopsies that are necessary for the diagnosing. In brief, the value of colposcopy consists in revealing where and how a biopsy needs to be made.

The histological examination is the only one to establish the diagnostic of certainty. This examination will specify:

- *The type of the lesion*: inflammation, dysplasia (mild, moderate, severe), benign or malignant tumour; the diagnostic of carcinoma *in situ* remains provisory based on the simple biopsy; its elaboration requires highlighting the basal membrane (silver impregnation or PAS reaction), and its integrity is compulsory for the non-invasive forms of carcinoma;
- *the grading of proliferation*;
- *the prognostic factor* (intravascular - V or intra-lymphatic - L invasion).

RESULTS AND DISCUSSION

The cervix can be easily examined clinically, colposcopically and cytologically. The use of these methods of investigation should lead to the detection of the disease in its early stages, which are 100% curable. Unfortunately, the lack of a coherent mass detection programme allows most cases to be diagnosed in their late stages.

The cytological examination represents a simple, fast and cheap method, being considered the most efficient technique of prevention and detection of the precancerous stages of the cervix which, if treated correctly, can offer primary prevention for cervical cancer.

The introduction of the modern means of investigation - colposcopy, cytological examination, biopsy – allowed the early diagnostic to move back to the most incipient stages of the disease that are infra-clinical or subclinical, such as intraepithelial cancer, micro-invasive cancer and micro-cancer.

The immediate colposcopy, followed by biopsy if needed, represents the aggressive manner of conduct.

In the conservative conduct the patients were performed colposcopy and biopsy only if the repeated cytology suggested more severe changes.

The conservative conduct consists in the treatment of chronic cervicitis, dysplasias, traumatic lesions, periodical consults, cytology, colposcopy, local and sexual hygiene (the conisation must be reduced to zero).

In our study the conservative conduct is represented by the fact that the cytology is repeated when the patients are admitted in the study lot (the initial cytology was performed before this moment). This lot was made of 1249 patients (66.3% of the whole study lot).

The distribution of the patients where the conservative conduct was applied showed the following aspects (Table 2):

- 54.5% of the patients are over 45 years old ($p=0.012$);
- 73.7% of the patients come from the urban area ($p=0.001$);
- 68.6% of the patients are married ($p=0.001$);
- only 7.1% of the patients ($p=0.956$) were detected as being HPV positive;
- for 67.9% of the patients treated in a conservative manner the cyto-diagnostic was of high degree ($p=0.191$);
- 21.8% of the patients treated in a conservative manner were performed colposcopy ($p=0.001$);
- prior to the conservative treatment, biopsy was performed for 56.4% of the patients ($p=0.001$);
- we checked anatomo-pathologically samples harvested from 56.6% of the patients treated in a conservative manner ($p=0.001$).

Table 2. Comparative analysis of accuracy according to conservative conduct

Diagnostic	VPP (%)	VPN (%)	Sensitivity (%)	Specificity (%)	Accuracy	p
HPV (+)	7.1	7.1	13.1	3.7	8.4	0.956
H-SIL	67.9	64.8	79.1	50.7	64.9	0.191

Diagnostic	VPP (%)	VPN (%)	Sensitivity (%)	Specificity (%)	Accuracy	p
Colposcopy	21.8	13.7	33.1	8.2	20.6	0.001
Biopsy	56.4	24.2	59.4	22.0	40.7	0.001
Histopathology	56.6	21.7	58.7	20.3	39.5	0.001

HPV - Human Papilloma Virus

H-SIL - High Grade Squamous Intraepithelial Lesion

For the patients who were diagnosed through cytology, colposcopy, biopsy and histo-pathology, with or without HPV viral infection, the efficiency of the conservative conduct shows a better accuracy of the conduct after establishing the high degree diagnostic (64.9%) and also in the case of biopsy (40.7%). The presence of the HPV viral infection in patients treated in a conservative manner did not lead to significant conclusions, which will allow the results to be extrapolated (Fig. 1).

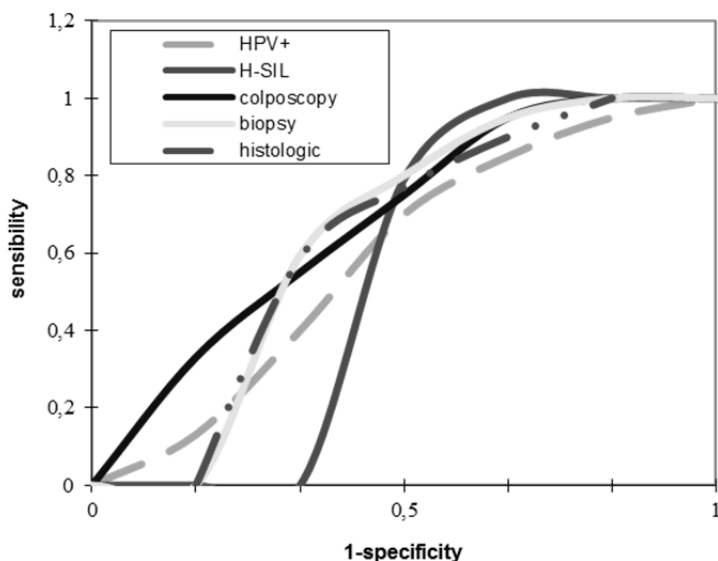


Fig. 1. The efficiency of the conservative therapy

The classic surgical treatment consists of Wertheim-Meigs total enlarged hysterectomy (extensive), beginning with conisations to the total hysterectomy with or without anexectomy. The ratio of the patients who were treated surgically was 54.6%. The study group showed the following characteristics (Table 3):

- 66% of the patients are over 45 years old (p=0.001);
- 72.8% come from the urban area (p=0.001);
- 80% of the patients are married (p=0.001);
- only 16% of the patients were detected being HPV positive (p=0.053);
- for 66.7% of the patients treated surgically the cyto-diagnostic was of high degree (p=0.923);
- for 34% of the patients treated surgically, the initial diagnostic was established by colposcopy (p=0.001);

- having a positive predictive value of de 83.3%, biopsy preceded the surgical treatment (p=0.001);
- for 82% the diagnostic of certainty was established through histopathology (p=0.001).

Table 3. Comparative analysis of accuracy according to surgical treatment

Diagnostic	VPP (%)	VPN (%)	Sensitivity (%)	Specificity (%)	Accuracy	p
HPV (+)	6.0	8.4	7.3	6.9	7.1	0.053
H-SIL	66.7	67.0	70.9	62.6	66.7	0.923
Colposcopy	34.0	1.1	29.9	1.3	15.6	0.001
Biopsy	83.3	0	50.1	0	25.1	0.001
Histopathology	82.0	0	49.7	0	24.9	0.001

HPV - Human Papilloma Virus
 H-SIL - High Grade Squamous Intraepithelial Lesion

The efficiency of the surgical treatment is shown by drawing the ROC curve, depending on the prior diagnostic that was established through cytology, colposcopy, biopsy and histopathology, with or without HPV viral infection. This highlighted the accuracy of biopsy and of the histological examination which both precede the surgical treatment. The presence of HPV viral infection for the patients who were surgically treated did not lead to significant conclusions which will allow the results to be extrapolated (Fig.2).

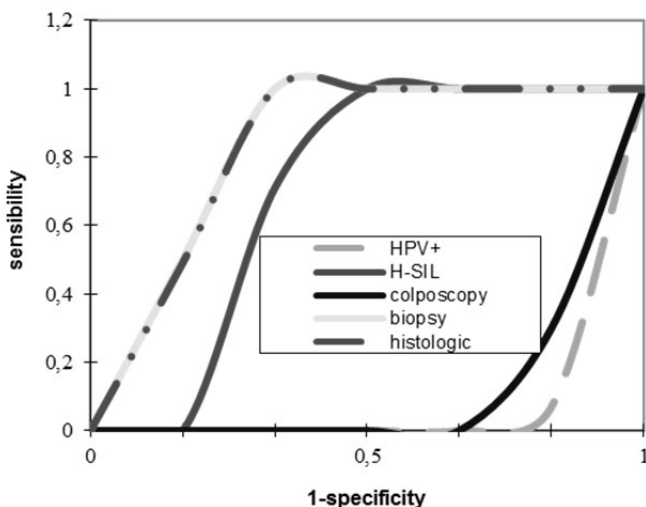


Fig. 2. The efficiency of the surgical treatment

The specific oncologic treatment consists of radiotherapy (external and/or internal, pre and/or post operatory), chemotherapy, immune therapy and hormone therapy.

The distribution of the patients sent to the oncologic department for specific treatment was about 31.3%.

The characteristics of the group of patients treated in the oncologic department show the following aspects (Table 4):

- 51.5% of the patients are below 45 years old (p=0.024);

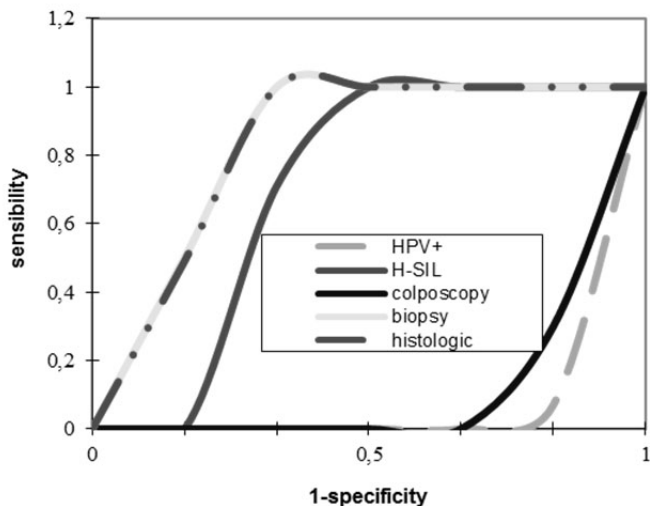
- 84.6% of the patients come from the urban area (p=0.001);
- 81.4% of the patients are married (p=0.001);
- for 64.4% of the patients treated oncologically, the cyto-diagnostic was of high degree (p=0.143);
- 14.2% of the patients had colposcopy performed before (p=0.001);
- biopsy was performed in 23.4% of the patients sent for oncologic treatment (p=0.001);
- after the histo-pathologic diagnostic was established, 20.7% of the patients were sent to oncology clinics for specialized treatment (p=0.001).

The efficiency of the specialized treatment in the oncology clinics, depending on the diagnostic that was established before through cytology, colposcopy, biopsy and histopatology, with or without HPV viral infection, showed a better accuracy of the oncologic treatment, after the cytologic diagnostic of high degree has been established (62.8 and also in the case of biopsy (40.4%). The presence of HPV viral infections in the case of the patients treated oncologically did not lead to significant conclusions, which will allow the results to be extrapolated (Fig. 3).

Table 4. Comparative analysis of accuracy according to cancer treatment

Diagnostic	VPP (%)	VPN (%)	Sensitivity (%)	Specificity (%)	Accuracy	p
HPV (+)	6.9	7.2	3.3	14.5	8.9	0.932
H-SIL	64.4	68.0	44.8	80.7	62.8	0.143
Colposcopy	14.2	21.2	7.6	35.2	21.4	0.001
Biopsy	23.4	55.6	19.4	61.4	40.4	0.001
Histopathology	20.7	55.8	17.6	60.7	39.2	0.001

HPV - *Human Papilloma Virus*
 H-SIL - High Grade Squamous Intraepithelial Lesion



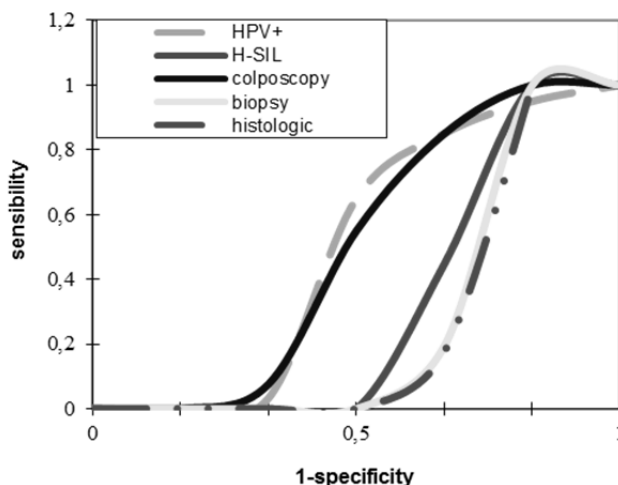


Fig. 3. The efficiency of the oncologic treatment

The evolution of the cases treated for cervical neoplasia

After the treatment had been applied, the probability for the patients below 60 to survive cervical cancer dropped to 60% in the first year after diagnosing, and below 40% in the first two years after being diagnosed, regardless of the age of the patient.

The probability for the patients to survive cervical neoplasia was below 40% in the first two years after the diagnosing, especially for the patients coming from the rural area.

You will notice the following aspects, depending on the stage of the neoplasia (Fig. 4):

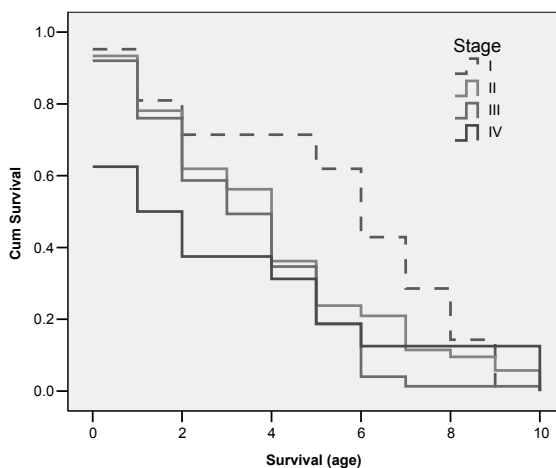


Fig. 4. Survival of the patients with cervical neoplasia by stage

- for the patients diagnosed with stage II, the probability to survive drops to 78% in the first year after being diagnosed, after two years it drops to 65% and after 7 years from being diagnosed it drops to 10%;

- for the patients diagnosed with stage III, the probability to survive drops to 60% in the first two years and after 4 years it drops to 40%, being theoretically zero after 6 years from the diagnostic;
- for the patients diagnosed with stage IV, the probability to survive drops below 50% ever since the first year.

The patients who responded to the pre-operative treatment are more likely to survive when compared to the patients who did not have a favourable response to the conservative treatment; the latter have a surviving probability of most 20% after 5 years from the moment when they were diagnosed with cervical neoplasia (Fig. 5).

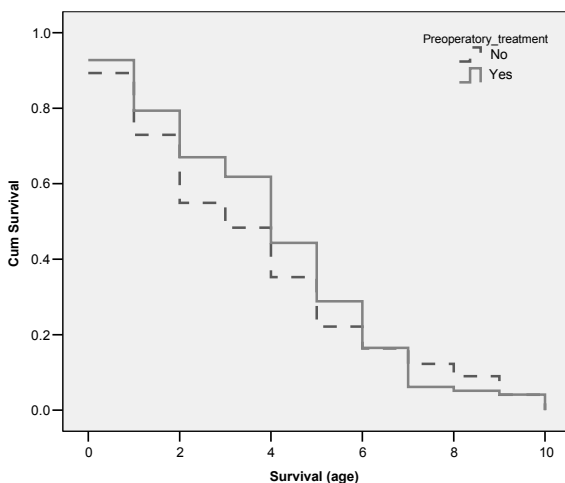


Fig. 5. Survival of the patients with cervical neoplasia depending on the preoperative conservative treatment

The surviving probability drops to about 70% in the first year after diagnostic for the patients who had post-operative complications (Fig. 6).

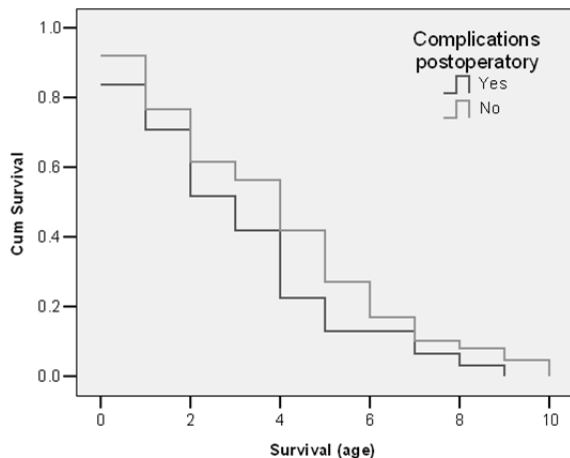


Fig. 6. Survival of the patients with cervical neoplasia depending on the postoperative complications

The patients sent to the departments of oncology, were generally lost for screening, but the ones who came back for a medical check-up are more likely to survive in the first 5 years, in comparison with the patients diagnosed with cervical neoplasia, but which did not undergo oncologic treatment (Fig. 7).

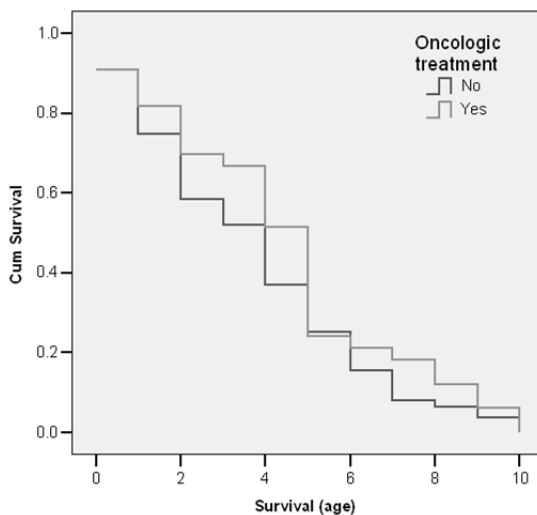


Fig. 7. Survival of the patients with cervical neoplasia depending on the oncologic treatment

CONCLUSIONS

The comparison of the three methods allowed us to determine: how effective is each of the conduct options in the early detection of the serious changes, which can progress towards cancer; how acceptable is each of the conduct options for the patients; what is the ratio cost/effectiveness corresponding to each option.

The diagnostic certainty was obtained after performing the histopathological examination of the material obtained through biopsy in comparison with colposcopy, with an accuracy of the method of 50.1%.

The patients who responded to the pre-operative treatment are more likely to survive in comparison with the patients who did not respond favourably to conservator treatment. The survival probability drops to about 45% in the first year after diagnostic for the patients who had post-operative complications.

The conservative conduct is represented by the fact that the cytology is performed again when the patients are admitted in the study lot (the initial cytology was made before this moment). The patients underwent colposcopy and biopsy only if the cytology being repeated suggested more severe changes.

The immediate colposcopy, followed by biopsy if needed, represents the aggressive manner of conduct.

If the cytology showed more severe changes or if it showed the presence of high oncogenic risk, the patients were sent for colposcopy.

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