DATA ON THE TREATMENT AND SURVIVAL OF PATIENTS WITH PAROTID CANCER AT THE "PROF. DR. I. CHIRICUȚĂ" INSTITUTE OF ONCOLOGY IN CLUJ-NAPOCA

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ABSTRACT: The cancer of the parotid gland, a major pair salivary gland, is considered a rare entity, dealt with in surgery and oncology centers of head an neck.
Material and Methods. The authors analyze data recorded for 135 patients suffering from primary parotid cancer, selected according to the criteria chosen for the inclusion in the present study.
The treatment consisted of surgery or surgery followed by radiotherapy and was administered between 1995 and 2008 at the "Prof. Dr. I. Chiricuță" Institute of Oncology in Cluj-Napoca. Both univariate and multivariate methods of statistic analysis have been employed.
Results. The authors conclude that the disease-free interval after 3 years was of 78.5% with a general survival rate of 88%, while after 5 years, these variables had the value of of 71.5% and 80.7% respectively.
Conclusion. The results indicate that the post-therapeutic interval at 3 years was significantly influenced by parameters pT and pN, at 5 years by age and pT, while the survival rate at 3 years was influenced, with statistic relevance, by age, pstage, pT, category pN, and the perineural invasion, while at 5 years by age and pT.
KEYWORDS: primary parotid cancer, surgery, radiotherapy, post-therapeutic survival, significance factors

1. INTRODUCTION

The present article aims at revising and postulating certain therapeutic and prognostic conclusions, by employing the database of the "Prof. Dr. I. Chiricuță" Institute of Oncology in Cluj-Napoca, a center of diagnosis and treatment of cancer (mainly) and other tumoral afflictions, focusing on salivary gland cancer, and parotid cancer in particular.

The cancer of the parotid gland is one of the cancers of the head and neck and has been estimated to represent 2.8-3% of all types of cancer [J+03]. It represents one of the locations considered rare, with an annual incidence between 0.8 and 2 per 100.000 inhabitants, with few geographic differences, including in Romania [P+10]. According to this statistic data, the general identification of the tumors of the salivary glands is of ca. 3-4% of all head and neck cancers [VHR07].
The diagnosis of tumors of the parotid glands is based on the initial observation, most often by the patient, of a swelling at the level of the anatomical region of parotid gland, later on supported by the medical clinical examination and by other investigations such as: echography, computed tomography, nuclear magnetic resonance, and positron emission tomography.
These explorations will make the difference between the tumoral or degenerative inflammatory nature of the processes that enlarge the region of the parotid gland; surgery is primarily recommended in the first case, while in case of the second category, conservative treatment is mainly recommended [BJ06].
In order to obtain better therapeutic results in the treatment of parotid cancer, during the post-surgery period one must perform detailed analyses of demographical, etiological, clinical, and therapeutic data that will aid in the selection of the best therapeutic approaches of this affliction and also compare the results reached by other therapists in other medical centers.

2. MATERIAL AND METHOD

The data on patients included in the present study was collected from the database of the "Prof. Dr. I. Chiricuță" Institute of Oncology in Cluj-Napoca, for the interval between 01 January 1995 and 31 December 2008 (13 years).
The study is analytical, of the observational, retrospective type, and includes data on 335 patients with malign tumors of the parotid gland, with the permission of the Ethics Commission no. 5.691 convened on 08 July 2009 at the "Prof. Dr. I. Chiricuță" Institute of Oncology in Cluj-Napoca (Table 1).

Table 1: Distribution of cases according to the nature of the parotid tumor

	N=335 cases (100%)
primary, malign parotid tumor	135 (40%)
secondary, malign parotid tumor	149 (44%)
pleomorphic adenoma	51 (16%)

From the total of 335 patients who underwent surgery for parotid cancer, 135 were selected and their data was included in the study and analyzed following the histopathologic examination that confirmed the primary malign parotid tumor entity.
The descriptive and analytical statistic analysis is performed with the aid of frequency indicators, tests, and specific methods.
In order to estimate the probability of disease-free survival and the generate rate of survival, we have employed the Kaplan-Meier method (univariate analysis). We have also analyzed the average and median survival time (disease-free interval).
The interpretation of results is also performed by comparison to data published in specialized literature.
We have compared the rate of "disease-free intervals" between groups with the aid of the log rank test and considering statistically significant values ≤0.05.
The Cocs regression analysis was employed for the hazard rate in the multivariate analysis. A degree of probability of ≤0.05 was considered statistically significant.
The survival / disease-free interval at 3 and 5 years are described through survival and hazard curves. Statistic processing (descriptive and analytical) was performed with the SPSS 13 software.
135 patients with malign primary parotid tumors were admitted at the "Prof. Dr. Ion Chiricuță" Institute of Oncology in Cluj-Napoca between 1995 and 2008 for diagnosis and/or treatment. They benefited from surgical interventions on the level of the parotid gland (partial parotidectomy, total parotidectomy with/without facial nerve resection, and neck dissection), as well as from another therapeutic sequence associated or not to surgery inside the institute, mainly postsurgical radiotherapy.
The TNM AJCC classification of March 2002 [***02a] was employed for the stadialization of cancers of the parotid gland.
The following classifications were employed in the histopathological grouping of the primary malign parotid tumors subjected to surgical interventions: the Histopathological Classification of the World Health Organization created in 1992 and the one in 2002 [SS92, Bat79] (Table 2).
For these 135 patients diagnosed with cancer of the parotid gland, we have analyzed their development over periods of 3 and 5 years.

Table 2: Postsurgical histopathologic survey of the 135 patients with malign parotid tumors
{[***02b] UICC 6th ed. 2002 (pstage=tumoral stage, according to the international cancer stadialization) (pT=characteristics of the malign tumor, according to the international cancer stadialization) (pN=lymph nodes characteristics, according to the international cancer stadialization)}

Degree and type of malignity [SS92, Bat79]	**N=135 cases (100%)**
low	**32 (23.70%)**
cc acinar cells	12 (8.90%)
cc mucoepidermoid	20 (14.80%)
high	**103 (76.30%)**
cc mucoepidermoid	0 (0%)
adenocarcinoma	26 (19.3%)
cc cystic adenoid	22 (16.30%)
cc ex pleomorphic adenoma	6 (4.40%)
cc squamous	32 (23.7%)
cc undifferentiated	17 (12.60%)
lateralization	
right	66 (48.90%)
left	69 (51.10%)
p TNM stage*	
I	11 (8.1%)
II	16 (11.9%)
III	40 (29.6%)
IV	68 (50.4%)
pT*	
1	14 (10.4%)
2	26 (19.3%)
3	49 (36.3%)
4	46 (34.1%)
pN*	
0	39 (28.9%)
1	33 (24.4%)
2	57 (42.2%)
3	6 (4.4%)
perineural invasion	
no	81 (60%)
yes	54 (40%)
lymphatic vascular emboli	
no	67 (49.6%)
yes	68 (50.4%)
venous vascular emboli	
no	104 (77%)
yes	31 (23%)

The clinical examination, diagnostic biopsy / surgical intervention, and stadialization of these cases were performed at the "Prof. Dr. I. Chiricuță" Institute of Oncology in Cluj-Napoca.
The following criteria were used in the selection of patients for the present study:

- age between 14 and 90, at the moment the diagnosis was established;
- both genders;
- paraclinical imagistic investigations (ultrasonography, thorax radiography, computed tomography) and laboratory investigations**;**
- identical presurgical survey;
- fine-needle aspiration punction;
- surgical intervention - partial or total parotidectomy, with or without the preservation of the facial nerve with modified radical laterocervical lymphanedectomy;
- with or without postsurgical radiotherapy;
- histopathologic result of surgical items, with the confirmation of the malignity and pTNM rendering;
- histopathologic diagnosis of primary malign tumor of the parotid gland;
- stadialization according to the UICC/AJCC;
- absence of distant metastasis at the time of the surgical sequence;
- absence of other, previous specialized treatments;
- data on patient control land status recorded at intervals of 3, 6, 12, 36, and 60 months.

3. RESULTS AND DISCUSION

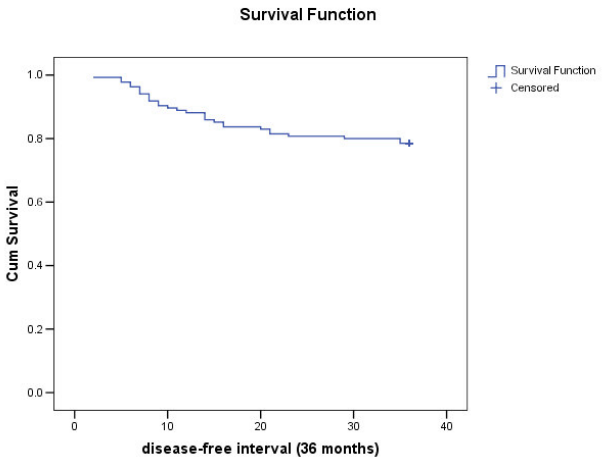
One of the most complete cassification, with a wide validity, verified through years and in the present, on the cancer of major salivary glands, both clinically and especially histopathologically, belongs to the World Health Organization and was designed by authors Seifert G and Sobin LH [SS92]; it was also employed in the classification of patients included in the present study.
Tumors of the salivary glands, including those of the parotid gland, are entities eminently treatable through surgery according to the clinical stage at presentation, are naturally classified starting from their histopathologic character, which is in fact the main prognosis characteristic.
From this perspective, tumors of the salivary glands are grouped, according to some authors, in tumors with low and tumors with an elevated degree of malignity [SS92, Bat79] (Table 2).
The analyzed parameters are prognosis factors in cancers of the parotid gland: age (2 groups, namely <50 years and ≥ 50 years respectively), patient gender, degree of malignity (low, high), sub-degree of malignity, stage (grouped into incipient and advanced stages), lateralization, type of surgical intervention, perineural invasion, lymphatic vascular emboli, venous vascular emboli, fine-needle aspiration punction and therapeutic sequence (surgery±radiotherapy). The average age of the 135 patients was of 53.92 years±15.6 (95%IC: 51.26-56.57) with interval 14-86 years (Table 3).

Table 3: Average demographic values at the time when the diagnosis was established and clinical-therapeutic characteristics of the 135 patients with malign parotid tumors

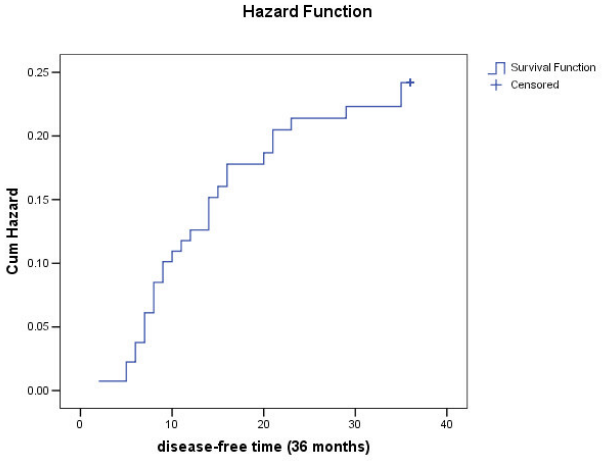
	N=135 cases (100%)
average age (years)	**53.92±15.60**
gender	
female	65 (48.10%)
male	70 (51.90%)
lateralization	
right	66 (48.90%)
left	69 (51.10%)
fine-needle aspiration punction	
no	20 (14.8%)
inconclusive	26 (19.3%)
negative	5 (3.7%)
positive	84 (62.2%)
type of surgery	
conservative total parotidectomy	74 (54.8%)
total parotidectomy with facial nerve resection	51 (37.8%)
partial parotidectomy	10 (7.4%)
therapeutic sequence	
surgery	38 (28.10%)
surgery+radiotherapy	97 (71.9%)

The average duration of the disease-free interval at 3 years, calculated from the date of the surgical intervention, was in months 31.18±10.06 (95%IC: 29.46-32.89) during an interval of between 2 and 36 months.
The average duration for survival at 3 years, calculated from the date of the surgical intervention, was in months 33.63±6.99 (95%IC: 32.44-34.82) during an interval of between 6 and 36 months.
The median of disease-free time and of survival, in the case of half of the patients in the lot, was between 36 months and 3 years.
Table 4 presents the results at 3 years for the rate of disease-free time and for the survival rate. In case of the disease-free interval at 3 years, the rate is of 78.5% and for the total survival the rate obtained was of 88.1% (Graph. 1, Graph. 2, Graph. 3, Graph. 4).
Higher rates were obtained in both analyses for the following groups of patients: male patients, patients aged <50 years, incipient stages, pT 1-2, absence of ganglia (pN"0"), absence of perineural invasion, absence of lymphatic emboli, absence of venous emboli, high degree of malignity and surgical sequence.

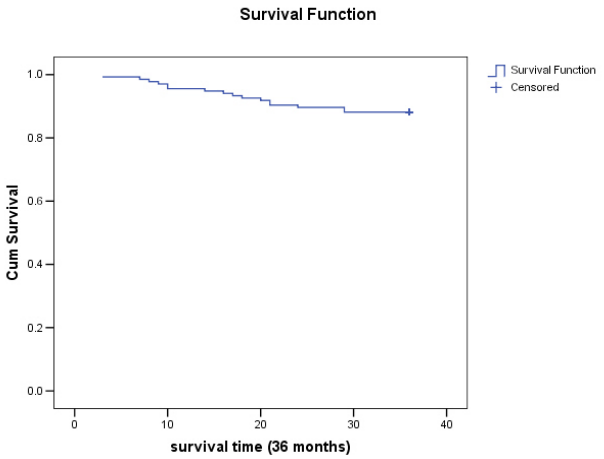
At 3 years, the disease-free interval was significantly influenced by: pT (p=0.034) and pN (p=0.047), while the survival rate was significantly influenced by: age (p=0.033), pstage (p=0.050), pT (p=0.007), pN (p=0.039) and perineural invasion (p=0.047).



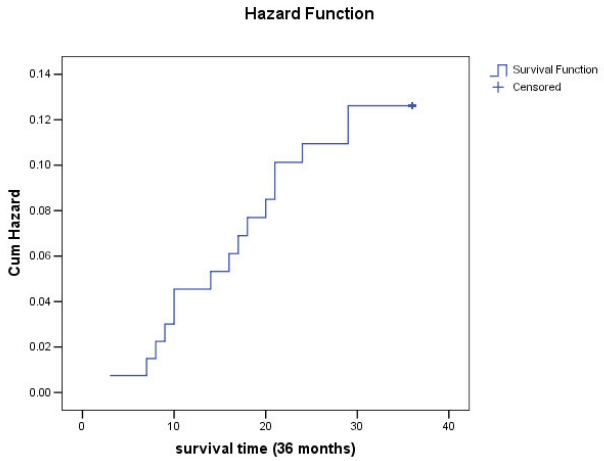
Graph. 1: Disease-free interval at 3 years for the 135 patients with parotid gland cancer



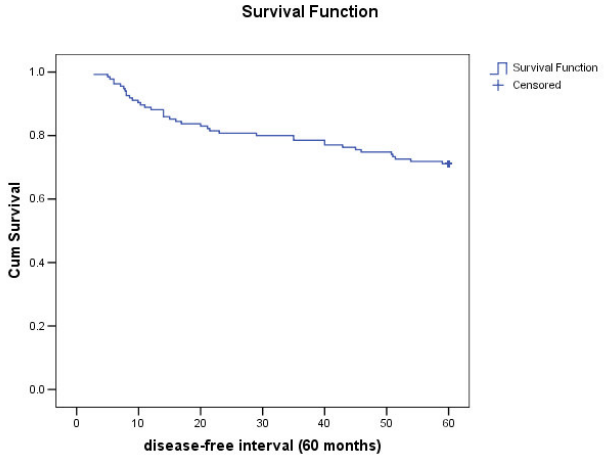
Graph. 2: Hazard for the disease-free interval at 3 years for the 135 patients with parotid gland cancer



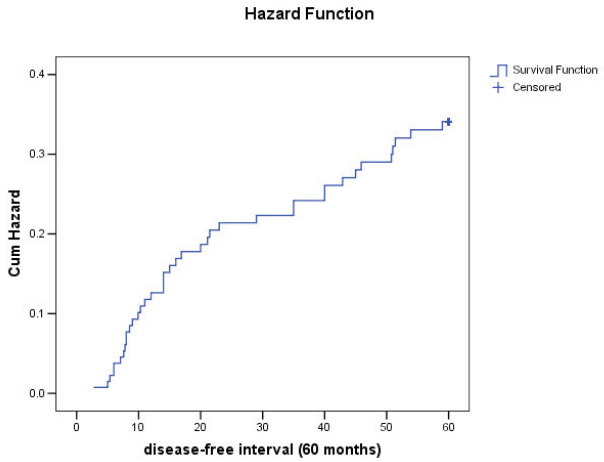
Graph. 3: General survival at 3 years for the 135 patients with parotid gland cancer



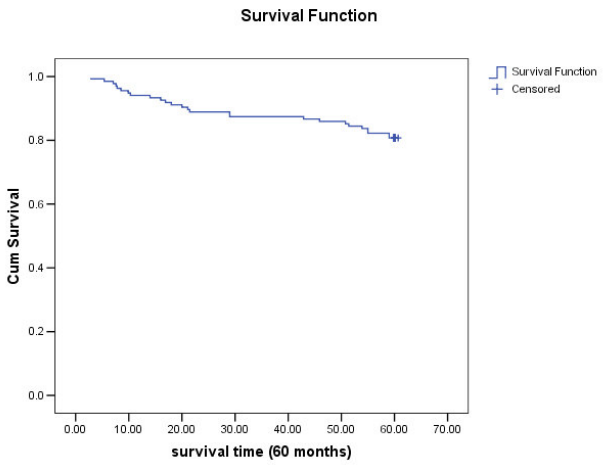
Graph. 4: Hazard for the survival at 3 years for the 135 patients with parotid gland cancer



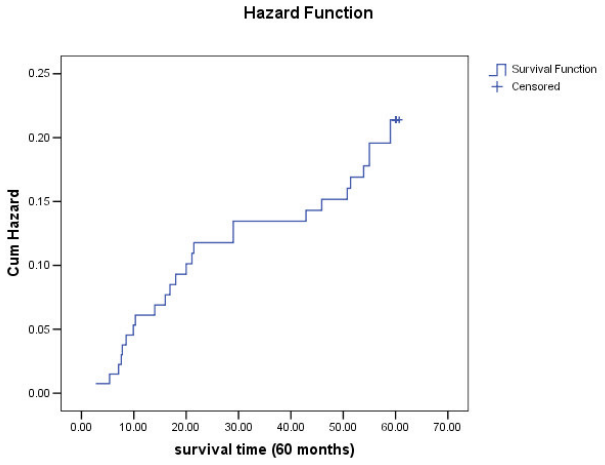
Graph. 5: Disease-free interval at 5 years for the 135 patients with parotid gland cancer



Graph. 6: Hazard for the disease-free interval at 5 years for the 135 patients with parotid gland cancer



Graph. 7: General survival at 5 years for the 135 patients with parotid gland cancer



Graph. 8: Hazard for the survival at 5 years for the 135 patients with parotid gland cancer

Between March 1995 and January 2006, at the Samsung Medical Center and the Sungkyunkwan University School of Medicine in Seoul, Southern Korea, by analyzing a lot of 94 patients with primary cancers of the parotid gland treated with surgery and radiotherapy, specialists have reached the following results: at 5 years a rate of the disease-free interval of 74.4%, and for the general survival of 96%, while for the group of patiently only treated with surgery, the value was of 100% [N+10].

According to a study performed in 2003, Wander Poorter and his collaborators have reported a general survival rate at 5 years of 62% [P+03], and in 2009 on another study lot, he reported a general survival rate for the same category of 69% [P+09].

Another report, based on the same interest in the analysis of treatments for primary parotid cancers, belongs to a group of Chinese authors who, in March 2012, analyzing statistically the data of 135 patients, have calculated a rate of survival at 5 years of 74%, with the following most significant prognosis factors: age, pT, degree of malignity, and postsurgical radiotherapy [S+12].

The 2009 issue of Acta Oncologica includes a study performed by a group of Swedish authors from the University Hospital in Uppsala, who mention, on a lot of 144 patients with primary parotid cancer, a general survival rate at 5 years of 53% with age, pN, and the advanced stage pT as significant prognosis factors [C+09].

In the case of our study, the average duration of the disease-free interval at 5 years, calculated from the moment of the surgical intervention, was in months 49.18±19.32 (95%IC: 45.89-52.47) during an interval between 3 to 60 months. Half of the patients experienced a disease-free interval of 60 months.

The average duration for survival at 5 years, calculated from the moment of the surgical interventions, was in months 53.76±15.41 (95%IC: 51.14-56.38) during an interval between 2 to 60 months.

The median disease-free time and survival, for half of the patients in the lot, was of 60 months at 5 years. Table 5 presents the results reached at 5 years for the rate of the disease-free interval and for the survival rate.

For the disease-free interval at 5 years, the rate is of 71.1% while for the global survival, the obtained rate was of 80.7% (Graph. 5, Graph. 6, Graph. 7, Graph. 8).

Higher rates were obtained in both analyses for the following groups of patients: male patients, patients aged <50 years, incipient stages, pT 1-2, absence of ganglia (pN"0"), absence of perineural invasion, absence of lymphatic emboli, absence of venous emboli, the elevated degree of malignity, and the surgical therapeutic sequence.

At 5 years, the disease-free interval was significantly influenced by: age (p=0.004), pT (p=0.026), and the survival rate was significantly influenced by the same parameters, i.e. age (p=0.038) and pT (p=0.020).

Table 5 presents the results at 5 years for the rate of disease-free interval and the survival rate. The first was of 71.1% while the rate of global survival was of 80.7%.

Table 4: Prognosis factors for the disease-free interval and general survival at 3 years, of the 135 patients with malign parotid tumors

variable	*disease-free interval*		*general survival*	
	3 years rate (%)	*value "p"*	*3 years rate (%)*	*value "p"*
	78.5		88.1	
age				
< 50 years	84	0.223	96	0.033*
≥ 50 years	75.3		83.5	
gender				
male	74.3	0.239	90	0.496
female	83.1		86.2	
therapeutic sequence				
surgery	76.3	0.708	89.5	0.735
surgery+radiotherapy	79.4		87.6	
p stage				
I-II (**early**)	92.3	0.065	100	0.050*
III-IV (advanced)	75.2		86.2	
pT				
1-2	90	0.034*	100	0.007*
3-4	73.7		83.2	
p N				
„N0"	89.7	0.047*	97.4	0.039*
„N+" (1-2-3)	74		84.4	
perineural invasion				
no	84	0.064	92.6	0.047*
yes	70.4		81.5	
lymphatic vascular emboli				
no	83.6	0.161	92.5	0.124
yes	73.5		83.8	
venous vascular emboli				
no	79.8	0,436	89,4	0.366
yes	74.2		83,9	
degree of malignity				
low	87.5	0.152	90.6	0.632
high	75.7		87.4	

Table 5: Prognosis factors for the disease-free interval and general survival at 5 years, of the 135 patients with malign parotid tumors

variable	*disease-free interval*		*general survival*	
	5 years rate (%)	*value „p"*	*5 years rate (%)*	*value „p"*
	71.1		80.7	
age				
< 50 years	82	0.038*	94	0.004*
≥ 50 years	64.7		72.9	
gender				
male	67.1	0.305	78.6	0.556
female	75.4		83.1	
therapeutic sequence				
surgery	68.4	0.661	81.6	0.789
surgery+radiotherapy	77.2		80.4	
p stage				
I-II (**early**)	84.6	0.089	88.5	0.264
III-IV (advanced)	67.9		78.9	
pT				
1-2	85	0.020*	92.5	0.026*
3-4	65.3		75.8	
p N				
„N0"	82.1	0.071	87.2	0.224
„N+" (1-2-3)	66.7		78.1	
perineural invasion				
no	76.5	0.083	85.2	0.098
yes	63		74.1	
lymphatic vascular emboli				
no	76.1	0.191	83.6	0.396
yes	66.2		77.9	
venous vascular emboli				
no	74	0.149	82.7	0.257
yes	61.3		74.2	
degree of malignity				
low	84.4	0.061	87.5	0.277
high	67		78.6	

4. CONCLUSIONS

The results of the study focusing on the lot of 135 patients with primary parotid gland cancers have indicated that the postsurgical period of 3 years was significantly influenced by parameters pT and pN, while the survival rate was influenced, with statistical significance, by age, pstage, pT, category pN, and the perineural invasion.

At 5 years, the disease-free interval and the general survival rate have age and pT as prognosis factors with statistical significance.

Cancers of the parotid gland are treated with good results, both at 3 and 5 years, both through surgery and by combining surgery and postsurgical radiotherapy.

As for the results obtained through the analysis of the therapeutic sequence, at 3 years, we have noted a higher rate of the disease-free interval in the case of patients who have been treated through a combination of surgery and postsurgical radiotherapy (79.4%, p=0.708). Referring to the results obtained in case of the therapeutic sequence at 3 years, we have noted a higher rate of survival for patients who were only treated through surgery (89.5%, p=0.735).

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