Egyetemi doktori értekezés

Early detection and treatment of certain malignant tumors

Ph.D. Thesis

dr. Zsolt Horváth

National Institute of Oncology
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Early detection of testicular cancer

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Recent advances in the better decision on diagnosis and treatment of inflammatory breast cancer.

Ph.D. Thesis

dr. Zsolt Horváth
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List of publications

Articles

Early detection of testicular cancer

I. Géczi L, Gomez, F, Horváth Zs, Bak M, Kisbenedek L, Bodrogi I: Three-year Results of the First Educational and Early Detection Program for Testicular Cancer in Hungary. Oncology, 2001; 60:228-234. IF: 3,009; C.I.:7

II. Géczi L, Horváth Zs, Beczássy E, Kisbenedek L, Bak M, Bodrogi I: A heredaganatok korai diagnózisa. Magyar Onkológia 2000; 44, 4:275-283.

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III. Láng I, Kahán Zs, Pintér T, Dank M, Boér K, Pajkos G, Faluhelyi Zs, Pikó B, Eckhardt S, Horváth Zs: Az emlőrák belgyógyászati onkológiai (gyógyszeres) kezelése. A 2. Emlőrák Konszenzus konferencia szakmai ajánlásai (2009. november 8–9., Kecskemét) – Magyar Onkológia, 2010; 54(3):237-254.

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Early detection of testicular cancer

I. Géczi L, Bodrogi I, Horváth Zs: „A heredaganatok korai diagnózisa" program 3 éves eredményei. MOT XXIII. Kongresszus, Budapest, 1999, p:290.

II. Géczi L, Horváth Zs, Bodrogi I: Early detection program for testicular cancer in Hungary. Three years results. Annals of Oncology 1998; 9 (S4), 266.

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IV. Géczi L, Horváth Zs, Bodrogi I: Early detection program for testicular cancer; first results in Hungary. UICC Cancer Management Meeting, Vienna, 1997 Abstract No. 202.

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VI. Géczi L, Horváth Zs, Bodrogi I: A heredaganatok ultrahang vizsgálatával végzett korai diagnosztikájának eredményei. Magyar Belorvosi Archívum 1996;S2:151.

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VIII. Horváth Zs, Ganofszky E, Hitre E, Juhos É, Nagy T, Rubovszky G, Szabó E, Láng I, Kásler M: Gyulladásos emlőrák: elméleti kérdések – válaszok saját megfigyeléseink alapján. Magyar Onkológia 53:(Suppl) (2009) Ea 0152

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Abbreviations

AFP: alfa-foetoprotein;
AJCC: American Joint Committee on Cancer;
CIS: TC in situ;
GCTC: germ cell testicular cancer;
H: histology;
IGCN: intratubular germ cell neoplasia, unclassified;
L: left, **R**: right, **D**: duplex;
LDH: lactate-dehydrogenase;
MGCT: microinvasive germ cell tum;
NCI: National Cancer Institute;
NRLA: nerve spearing RLA;
NS: non-seminoma
RLA: retroperitoneal lymphadenectomy
RPLND: retroperitoneal lymph node dissection
S: seminoma
ß-hCG: beta-human choriogonadotropic hormone;
TC: testicular cancer;
TSE: testicular self-examination;
Tu: tumor
TUS: testicular ultrasound;
US: ultrasound;
USPSTF: US Preventive Services Task Force;
WHO: World Health Organization

A+: conventional second generation antracycline containing chemotherapy;
AC: doxorubicine – cyclophosphamide protocol;
ASCO: American Society of Clinical Oncology ;
BC: breast cancer;

C.I.: confidence interval;
cCR: clinical complete remission;
CT: chemotherapy;
DLI: dermal lymphatic involvement;
EC: epirubicine – cyclophosphamide protocol;
ET: endocrine therapy;
FAC/CAF: 5-fluorouracil – doxorubicine – cyclophosphamide protocol;
FEC/CEF: 5-fluorouracil – epirubicine – cyclophosphamide protocol;
IBC: inflammatory breast cancer;
LABC: locally advanced breast cancer;
LPFS: local progression free survival;
MF: methotrexate – 5-fluorouracil protocol;
NCCN: National Comprehensive Cancer Network;
NIH: National Institute of Health;
OS: overall survival;
pCR: pathological complete remission;
PD: progressive disease;
PFS: progression free survival;
PR: partial remission;
PSCT: primary systemic chemotherapy;
RR: response rate;
RT: radiotherapy;
SD: stable disease;
SEER: Surveillance, Epidemiology and End Results
ST: surgical treatment;
T: docetaxel;
TAC: docetaxel – doxorubicine – cyclophosphamide protocol;
TE: docetaxel-epirubicine protocol;
UICC: International Union Against Cancer;

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Chapter I.

Early detection of testicular cancer

1. Introduction

Primary testicular cancers (TC) are the most common solid malignant tumors in men between the ages of 20 and 35 years. Due to its highly sensitive to chemotherapy and curability even when metastatic disease[1,2],germ cell testicular cancer (GCTC) have become an excellent testing ground for active experimental drugs (i.e., cisplatin, etoposide, and ifosfamide), all these were approved primarily on the basis of data from studies of TC. TC has been a model for multidisciplinary care, as close cooperation between professional areas do improve the cure rate.[3]

TCs are highly curable: cure rates for good-risk disease are 90-95%, and significant even in patients with metastatic disease at diagnosis[4,5]. The prognosis depends upon the histologic type of cancer (seminoma (S) versus nonseminoma (NS)), stage, and other features such as tumor marker and localization of distant metastasis. Patients with good-prognosis S (90% of all) have 86% 5-year survival; as compared with good-prognosis NS (56% of all NS) have 92-94% 5-year survival . In case of intermediate-prognosis TCs (5-year survival is 72% with S and 80-83% with NS (28% of all NS), and even the poor-prognosis NS have 48-71% 5-year survival.[6,7] The chance of cure for patients with poor prognosis - those with relapse or resistance to cisplatin based chemotherapy - is low because no standard treatment is available.

The prognosis being less favorable in eastern European countries[8], the fact that is attributable to differences in the accessibility of effective treatment or because of the lower efficacy of cisplatin-based chemotherapies due to a late determination and more advanced stages of TC. Several studies have shown that delay in presentation is common and may result in metastases and increased mortality and morbidity, especially for patients with nonseminoma.[9-12] As stage is one of the most significant determinants of survival, the earlier we can detect TC, the greater chance we could achieve longer survival. Early detection of TC theoretically can be improved by spreading medical information on the importance of self-examination and the curability of TC, and on multimodal treatment possibilities.

1.1. Screening of TC

Low age at male puberty has adverse effect on reproductive toxicity for chemicals and also has a greater incidence of behavior disorders. Altered puberty timing is also of concern for the development of reproductive tract cancers later in life.

Testicular self-examination (TSE) is an important activity that men should be taught to detect any early changes that may be signs of pathological significance. TSE can be carried out by the man himself or with the assistance of another person (e.g. carer or partner).

Poor public awareness of the disease and lack of TSE may account for late presentation. It has been shown that a delay of more than 3 months is correlated with a decreased 5-year survival[12,13]. According to statistics, the delay from initial symptoms to definitive diagnosis by radical orchiectomy has averaged 4 to 5 months.[14]

1.2. Epidemiology and etiology of TC

Over the past decade, the incidence of TC has risen approximately 1.2% per year but the absolute mortality rate has been stable or decreasing; approximately 9,000 new cases diagnosed in United States every year, and only about 350 to 400 deaths have occurred annually. [15] [16] The lifetime chance of developing testicular cancer is about 1 in 300 and the risk of dying is very low—about 1 in 5,000.

Approximately 400-420 men develop TC each year in Hungary. GCTC has its highest incidence in the European population, with an age-standardized rate ranging from 2 to 9 per 100 000 per year[17]. The incidence of GCTC is increasing in almost all developed countries[17]. The incidence of GCTC varies greatly among geographically and different ethnic groups. The highest rates occur in the Nordic countries and the lowest rates typically occur in Asia and Africa. The incidence of TC is fivefold higher in whites than in African Americans; however, African Americans tend to present with higher-grade disease and have much worse prognosis than whites[16]. The incidence in the white population of the US is similar to that of European countries.

Although the cause of TCs is unknown, the following risk factors are under consideration:

- The high occurrence rate in developed countries reflects the role of environmental **carcinogenic factors**, for example exposure to diethylstilbestrol (DES) in utero is associated with cryptorchidism[18]. Increased risk has been suggested with Agent Orange exposure and

numerous industrial occupations. - Recurrent activity such as horseback or motorcycle riding, local trauma, and increased scrotal temperature have not been associated with increased risk.

- **Cryptorchidism**: In patients with cryptorchidism, the risk of developing GCTC is 8-10%. Men with unilateral GCTC have an increased risk of GCTC in the normally descended contralateral testis, but it is not as high as in the undescended one[19]. Surgical placement of the undescended testis in the scrotum - orchiopexy - when the patient is younger than 6 years lowers the risk further. About 5-20% of patients with a history of cryptorchid testis develop tumors in the normally descended testis. Biopsies from men with maldescended testes have been reported to contain intratubular germ cell neoplasia, unclassified (IGCN) and microinvasive germ cell tumor (MGCT) in 1.8% of the examined cases (95% CI 0.5-4.6%).[20]

- Men with infertility (low sperm concentration, poor motility of spermatozoa and a high proportion of morphological abnormal spermatozoa) are nearly 3 times more likely to develop subsequent TC[21-23]. IGCN (or TC in situ, CIS) has been found in 0.4–1.1% of men undergoing testicular biopsy because of infertility. **Testicularmicrolithiasis** ($\geq$5 or more microcalcifications within a testicle) results from concentric cores of calcification of intrasubstance collagen fibers. Patients with TC (and also their families) have a higher rate of microlithiasis[24-26]. Annual ultrasonographic (US) screening of patients with microlithiasis has been suggested by some authors, but prospective studies have failed to demonstrate a positive cost-benefit ratio at this time[27,28].

- A previous **history of TC** is the strongest risk factor for GCTC. Approximately 1-2% of TC patients will develop a second primary TC contralaterally—a 500-fold higher rate than in the general population. CIS can be found in the contralateral testicle of TC patients in approximately 5 per cent of cases, which corresponds with the expected frequency of metachronous **GCTC**[29]. CIS cells are widely accepted as a precursor of GCTC[30].

- **First-degree relatives** have a higher risk of developing TC than the general population, although the incidence is low. About 2% of TC patients report having an affected relative[31] Brothers are at particularly high risk, with a relative risk of 8–10. Among sons of affected men, 2-6-fold increases in TC have been reported[32] A region of chromosome Xq27 associated with this familial risk, especially when one or more of the affected men have bilateral TC, has been described[33].

- **Malformations or abnormalities of the male genital organs**, including inguinal hernia, atrophic testes, hypospadias, hydrocele and varicocele are among the less consistent and less certain risk factors for GCTC[34].

- Patients with **gonadal dysgenesis** are at very high risk (10-50 per cent) of GCTC. Patients with **Klinefelter syndrome** (47XXY) have higher incidence of GCTC, particularly primary **mediastinal germ cel**l tumor[35]. Family members of Klinefelter syndrome patients have a six- to tenfold increased risk of germ cell tumor. Patients with **Down's syndrome** also are at increased risk for GCTC[36]. Increased risk has also been reported in patients with cutaneous ichthyosis, mullerian syndrome, androgen insensitivity syndrome (testicular feminization), and mixed gonadal dysgenesis[37].

1.3. Clinical presentation, diagnosis and local treatment of TC

The most common presenting symptom is painless enlargement or swelling, firmness, or nodule/lump of one testicle (asymmetry), that cannot be separated from the testis. In most cases the hard irregular mass filling a part or the whole testis. Patients with atrophic testes will feel enlargement. Dull ache or heavy sensation in the lower abdomen could be also presenting symptom. Patients who experience a hematoma with trauma should undergo evaluation to rule out TC. Disseminated disease have symptom of lymphatic or hematogenous spread. Man with metastasis to the paraaortic lymph nodes may present with back or loin, rarely epigastrial pain, with early satiety. Young men with a palpable supraclavicular lymph node, or gynecomastia should be examined carefully TC. In case of NS, lung metastases and mediastinal adenopathy are common that may lead to dyspnoea, cough, chest pain, and other severe pulmonary symptoms. Liver and brain metastasis are also frequent, but bone and skin metastases are very rare.

During **differential diagnosis** one should consider epididymitis, hematoma, orchitis, varico- and hydrocele, inguinal hernia, testicular torsion, spermatocele, syphilitic gumma and probably iliac or caval venous obstruction or thrombosis.

Testicular palpation and US examination of the testis usually confirms the diagnosis, and helps distinguish between masses in the body of the testis and other intrascrotal swelling[25].

1.3.1. US examination of the testis

During the US examination a high frequency linear transducer (7.0 MHz) was used by which we could perform both power and spectral Doppler exam. The scrotum was scanned from at least two directions, along the longitudinal and - from the right - transverse axis. The first scan is performed in a long axis showing a longitudinal cut through the testis with the epididymis. Both testicles were visualized side by side from a coronal scan in order to identify differences in size and echotexture and vascularity.

Abnormal collection of fluid in the space between the visceral and parietal layers of the tunica vaginalis called **hydrocele**. Complex hydrocele may contain internal from cholesterol crystal formation[38,39].

Compressed and dilated veins within the pampiniform plexus of the spermatic cord due to incompetent valves of the testicular vein called **varicocele**. Adult males can present this finding is relatively frequent (15%) that almost always located on the left side. Power Doppler can confirm blood flow in the anechoic serpiginous tubular structures of varicocele mainly in the epididimic region[40].

Acute **epididymitis** is characterized by an enlarged epididymis with decreased echogenicity, frequently accompanied with a reactive hydrocele and increased blood flow. Orchitis is depicted by testicular enlargement, tenderness and inflammation with heterogeneous echotexture , however this appearance is nonspecific and can be seen in such conditions as tumors, metastasis, torsion and infarct.

1.3.2. US appearance of TCs

Seminomas are more homogenously hypoechoic relative to the surrounding parenchyma and well defined in the tunica albuginea than nonseminomatous, embryonal cell lesions, which are often more cystic, with interspersed areas of calcification[41,42]. Teratomas and choriocarcinomas have often heterogeneous structure with multiple internal calcifications present as well. Stromal cell tumors (eg, Leydig and Sertoli cell tumors) are generally well defined and hypoechoic, but calcifications are frequently found. Lymphoma and leukemia of the testicle generally present as an ill-defined and hypoechoic. The tumor tissue type cannot be reliably differentiated solely by its ultrasonographic appearance.

Although the specificity and sensitivity have not been reported, general consensus exists that a palpable mass with an US finding of a solid or mixed cystic and solid hypoechoic intratesticular mass is an indication for surgical exploration and radical inguinal orchiectomy.

1.3.3. Local and systemic treatment of TC

Radical inguinal orchiectomy is the definitive procedure to provide local tumor control and to permit histological evaluation of the primary tumor. Retroperitoneal lymph node dissection (RPLND) is the standard and reliable method to identify nodal micrometastases and provide accurate pathologic staging of the retroperitoneal spread. Both the number and size of involved retroperitoneal lymph nodes are of prognostic importance.

The availability of reliable tumor markers assays has greatly facilitated the management of GCTC. The major markers are AFP which is elevated in 50-60% NS but not in S and ß-hCG which is elevated in 30-35% of NS (mainly in presence of choriocarcinoma component) and 10-25% of S. LDH has independent prognostic significance, as it's increased level reflects high tumor burden, and elevated growth rate.

An extended diagnostic work-up require to rule out metastatic disease. The standard staging examinations are radiological imaging (CT scan, MRI, in case of suspicion bone scan, and PET/CT).

1.4. Histological classification of TCs

GCTCs are divided into two major subgroups - S and NS - each accounting for approximately for half of TC cases. The widely used WHO classification (See Appendix 1.) aims to describe in detail the cell types present in a particular tumor[43], but other well-known classifications should be considered also (e.g. according to Rosai et al[44]) Less than 50% of malignant GCTCs are of a single cell type; roughly 50% of these are Ss. S frequently appears in the fourth decade of life, but some rare variants are seen mostly in men over 60

NS is the collective noun of different histological subtypes, such as embryonal carcinoma, choriocarcinoma, yolk sac tumor and teratoma, which are diagnosed most frequently in the third decade of life. Most NS are mixed, consisting at least of two components of the tumor. Even when S is a component of the tumor, the presence of any non-seminomatous elements classifies the tumor as NS. Teratomas are terminally differentiated tumors, slowly progressing tumors and chemotherapy insensitive tumors that bear all three germ layers with varying degrees of differentiation. Generally these tumors are technically not malignant, but death may occur due to

unresectable local disease. Embryonal carcinomas are the most frequent component of mixed as opposed to choriocarcinomas that are the least common type of NS but these are the most aggressive ones with widespread hematological metastasis can occur very early in the disease course. Yolk cell elements are also common type in of mixed germ cell tumors, associated with elevated AFP but without ß-hCG.

1.5. Clinical staging of TC (WHO, TNM) and clinical prognostic factors - the International Germ Cell Consensus Group Classification (IGCCCG)

Various staging systems have been used to classify and subsequently manage patients with TC[31]. In Appendix 2. and 3. we summarized TNM and AJCC staging system, that were integrated with risk classification as well by the IGCCCG classification system (Appendix 4).[45] The following prognostic factors are considered: the site of primary tumor (testicular or extragenital), histological type of tumor (S or NS), localization of metastases (visceral or nonvisceral) and the levels of serum tumor markers[45]. Towards to correct decision on treatment a meticulous pathological report must acquire.[46]

1.6. Treatment of TC

The prognosis of men with TC has improved markedly following the introduction of cisplatin-based chemotherapy. It has also been demonstrated that treatment in specialized centers results in a better clinical outcome[47]. Collaborative and multicenter clinical trials have led to significant improvements in the management of TC, these improvements have been incorporated into treatment guidelines[5].

The main goal of the rationalized the risk-adapted treatment policy[48] is to select and treat patients according to their individual clinical risk, decrease side effects and treatment costs, and increase the patient's quality of life[49]. Initial therapy is selected according to AJCC stage group; risk stratification (good, intermediate, or poor risk), as per the guidelines of IGCCCG and histology (S versus NS). While our Thesis do not concern to therapeutic issues, we only summarized the risk-adapted therapy in Appendix 5.

2. Aim of the Thesis

For the above-mentioned statements we started an educational and screening program in order to determine:

1. **the efficacy of this early detection program on the figures of TC found;**

2. **the changes in delay in the diagnosis of TC;**
3. **changes in mortality in TC.**

3. Patients and methods

3.1. Educational and early detection program for TC

A media and teach-in campaign organized by National Cancer League on the early signs and the risk factors of TC, the correct method of testicular self examination (TSE) and the importance of early detection were conducted. Volunteers who demanded testicular screening were invited to an appointment for medical examination. Recruitment was not limited to any age groups or complaint categories, as we intended to analyze the demographic characteristics and the presence or absence of complaints of the volunteers. The medical examination consisted of

a. physical and
b. US examination of the testicles and
c. in any case of suspicious malignancy tumor markers (AFP, ß-hCG) were also checked.

An Acuson 128 PX US device, with a 7 MHz linear transducer was used for the testicular ultrasound examination (TUS). A single type of non-malignant pathological finding was considered as *one* pathological event regardless of bilateral or multiple appearances: for example testicular cysts, hydroceles, etc. Between April 1995 and April 1998 5056 volunteers participated in the program.

3.2. Grouping volunteers according to complaints

Findings were analyzed according to the volunteers classification, who were divided into two main groups based on

a. the presence or
b. absence of complaints.

3.3. Grouping volunteers with complaints according to the nature of complaints

Volunteers with complaints were subdivided according to the nature of the complaint observed through TSE:

a. pain,
b. sensitivity to palpation of the testicle,
c. palpable lump,

d. swelling of the testicle, or

e. a complaint unrelated to the testicle, such as dysuria, impotence etc.

If multiple complaints were present, we *classified them according to their most important one*.

3.4. In case of TC was detected…

When TC was detected clinical details are also presented. Clinical staging, histological classification of the tumors, course of treatment, way of response evaluation and follow-up of patients was in line with the institutional policy at that time.

3.5. Delay in the diagnosis

Delay in the diagnosis of patients treated by chemotherapy in our Department in 1994 and in 1998 was also retrospectively analyzed and compared to measure the educational impact of the program.

3.6. Mortality rate of TC patients

Mortality rate of TC patients in Hungary between 1994 and 1998, and subsequent years was also analyzed in order to detect the probable impact of our early detection program on survival.

3.7. Statistical work-up

The proportions of the findings between the complaints free and the with-complaints population were compared using the Chi-square test. The diagnostic and medical delays between 1994 and 1998 were analyzed by the Student-t test. A difference was regarded as significant if the P value was < 0.05.

4. Results

The median age of the 5056 volunteers was 42 years (range 16-76 years), and 32 tumors were diagnosed in 30 patients (0.6%).

4.1. Distribution of patient according to their complaints and findings

Among the 5056 volunteers, 2714 were complaint-free and 2342 patients presented different complaints.

In the **complaint-free population** 1323 men had no physical or radiology findings (49%), but in the remaining 1391 men 1599 different findings were detected by physical examination and/or TUS. **No tumors were found in the complaint-free population** (Table 1). [1]

Of the 2342 men with different **complaints**, 532 (23%) had no detectable findings, but in the remaining 1810 men 2194 findings were discovered. The incidence of patients with tumors in this subgroup (i. e. both complaints and findings) was 1.66% (30/1810) representing 1.37% (30/2194) of the findings detected. The incidence of men having tumor in the group of 2342 volunteers with complaints was 1.28% (30/2342). Although, the frequency of findings in the complaint-fee and the with-complaints population were nearly equal (1.15 and 1.21 findings/man, respectively), ***a highly significant relationship can be detected between complaints and findings***: χ^2=366,7 (p<<0,0001).

Table1.: Distribution of findings in the complaint-free population and in the population with complaints

Findings	Complaint-free population		Population with complaints		P	Complaint-free population	Population with complaints
	2714 volunteers		2342 volunteers			1599 findings	2194 findings
	N	%	N	%		%	%
Epididymal and testicular cyst	526	19.4	676	28.9	<0.001	32.9	30.8
Testicular atrophy	124	4.6	136	5.8	0.06	7.8	6.2
Hydrocele	480	17.7	585	25.0	<0.001	30.0	26.7
Epididymitis	39	1.4	232	9.9	<0.001	2.4	10.6
Varicocele	399	14.7	497	21.2	0.10	25.0	22.7
Tumor	0	0.0	30*	1.3	<0.001	0.0	1.5
Microcalcification	11	0.4	11	0.5	0.73	0.7	0.5
Others	20	0.7	25	1.1	0.22	1.3	1.1

*30 patients with 32 tumors

The abnormal findings in the group of volunteers with complaints were significantly more often than in the complaint-free population (77% vs. 51%,respectively; p<0.001). Cysts (p<0.001), hydroceles (p<0.001) and epididymitis (p<0.001) occurred more frequently in the group with complaints. Patients with clinically detected significant nonmalignant abnormalities were referred to an urologist (3.9% in the with-complaint vs. 0.9% and complaint-free group). The remaining were informed about their findings and were directed to a general practitioner, with suggestions for treatment.

[1] For an easier understanding, we should keep in mind that numbers can be different according to volunteers, complaints and findings, i.e. a volunteer may have more complaints and/or findings.

A history of cryptorchidism was noted in 1.9% of the men with complaints and in 0.8% of the complaint-free population ($p<0.001$). Testicular hypoplasia and microcalcification did not differ significantly between the two groups.

4.2. Connection between main symptoms and TC

The v**olunteers with complaints were subdivided according to their main symptoms as follows**: 457 (20,8%) had testicular pain, 782 (35,6%) had sensitivity to palpation of the testicle, 477 patients (21,7%) had palpable lump, 249 (11,3%) had swollen testicle, and 229 patients (10,4%) had symptoms unrelated to the testicles We did not find any tumor in the group with pain, sensitivity, or complaints unrelated to the testicle; these abnormalities were mainly of cysts, hydroceles and varicoceles.

Table 2. Findings according to the volunteers' main complaint

Findings	**Pain**		**Sensitivity**		**Palpable lump**		**Swollen testicle**		**Unrelated complaints**	
all N of findings	457		782		477		249		229	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Epididymal and testicular cyst	125	27,4	246	31,5	207	43,4	46	18,5	52	22,7
Testicular atrophy	20	4,4	63	8,1	11	2,3	10	4,0	32	14,0
Hydrocele	103	22,5	209	26,7	75	15,7	139	55,9	59	25,8
Epididymitis	62	13,6	88	11,2	50	10,5	19	7,6	13	5,7
Varicocele	141	30,9	169	21,6	98	20,6	21	8,4	68	29,7
Tumor	0	0	0	0	**22**	**4,6**	**10**	**4,0**	0	0
Microcalcification	2	0,4	4	0,5	2	0,4	0	0,0	3	1,3
Other	4	0,8	3	0,4	12	2,5	4	1,6	2	0,8
All men	373		636		464		228		186	

Of the 464 men who palpated a **lump**, 64 (14%) had no detectable abnormalities. Together 477 lumps were discovered, among them 22 tumors. The incidence of tumors in the group of men with palpated lump was 4.74% (22/464), and these represented 4,61% (22/477) of all lumps. However, in case of palpable lump cysts and varicoceles and hydroceles were the most frequent findings.

Among the 228 men whose main complaint was **swollen testicle**, no abnormalities were detected in 13 (5.4%), but in the remaining 215 men had 249 findings, with 10 tumors in between. The incidence of patients with tumor was 4.38% (10/228) in this group, representing 4.01% (10/249) of all detected swollenness. Hydrocele was the most frequent finding in men (56%) with a swollen testicle.

4.3. Description of TCs detected during the early detection program

During the 3-year period, 4 benign testicular tumors were discovered among 5056 volunteers (0.08%). The histological findings were: cavernous hemangioma, dermoid cyst, Leydig-cell tumor and adenomatoid tumor. Testicular exploration helped to identify benign lesions, and allowed testicular preservation in two cases.

Table 3: TGCTs found in 5056 volunteers between April 1995 and April 1998

No	Age (yr)	Side	Symptom Duration (weeks)	Size of Tu. by US (cm)	Palpation of the testicle	Tu TNM 1997	Stage	H	Treatment: orchidectomy +	AFP	βhCG	LDH
1.	39	L	24	3.0x3.5x2.2	lump	T/2	II/A	NS	nRLA +4VPB	77	□ 4	371
2.	48	R	8	3.6x4.8x3.0	swelling	T/2	I/B	S	2 VPB	< 5	□ 4	452
3.	36	D	16	2.4x1.1x1.2 0.8x0.9x10	lump lump	T/1 T/1	I/A	S	wait and see	<5	□ 4	620
4.	34	R	1	2.6x2.5x1.4	hard surface	T/2	I/B	S	2 VPB	< 5	26	376
5.	20	R	12	4.2x4.5x4.4	swelling	T/1	II/B	NS	RLA+4VPB	< 5	27	401
6.	26	L	3	4.5x3.6x2.5	swelling	T/1	I/A	S	irradiation	< 5	< 4	534
7.	48	R	24	5.5x3.5x4.5	swelling	T/1	I/A	S	irradiation	< 5	< 4	481
8.	39	R	12	6.5x4.5x5.0	swelling	T/1	I/S	S	2 VPB	< 5	< 4	2746
9.	28	L	24	2.4x1.9x1.5	lump	T/1	I/A	S	wait and see	< 5	< 4	412
10.	33	R	16	1.0x0.8x1.5	lump	T/1	II/A	NS	nRLA+4VPB	< 5	< 4	312
11.	35	D	16	1.1x1.9x1.7 0.8x1.6x1.5	lump non-palpable	T/1 T/1	I/A	S	irradiation	< 5	< 4	397
12.	24	R	48	3.2x3.3x2.7	lump	T/1	I/A	NS	nRLA+2VPB	< 5	< 4	433
13.	45	R	2	3.2x2.3x2.8	lump	T/2	III/B	NS	RLA+6BEP	< 5	< 4	509
14.	23	R	2	3x2x2	lump	T/2	I/B	NS	2 VPB	686	689	359
15.	26	R	2	2x1.5x1	lump	T/2	I/B	NS	2 VPB	< 5	< 4	424
16.	45	R	4	5.1x4x4.5	swelling	T/2	I/B	S	2 VPB	< 5	< 4	590
17.	20	R	8	1.7x1.5x1.2	swelling	T/2	I/B	NS	2 VPB	< 5	< 4	307
18.	33	L	24	2x2.1x1.9	lump	T/2	I/B	S	2 VPB	5	< 4	386
19.	36	L	4	2x1.1x0.9	lump	T/1	I/A	S	irradiation	< 5	< 4	452
20.	29	R	20	3.5x2.8x2.9	lump	T/2	I/B	S	2 VPB	< 5	< 4	526
21.	34		1	2.5x2x2.2	lump	T/1	I/A	S	irradiation	< 5	< 4	570
22.	26	R	1	3.8x4x3.3	swelling	T/2	I/B	NS	2 VPB	302	163	243
23.	27	R	1	2.5x2x1.8	lump	T/2	III/B	NS	nRLA+6 BEP	< 5	25	491
24.	47	L	24	2.7x2.5x2.2	lump	T/1	II/A	NS	nRLA+4VPB	6	336	401
25.	23	R	4	0.9x0.8x0.9	lump	T/1	I/A	NS	wait and see	< 5	< 4	283
26.	41	R	4	3.5x4x3.6	swelling	T/1	I/S	NS	refused	1272	375	508

Abbreviations: NRLA: nerve spearing RLA, L: left, R: right, D: duplex, S: Seminoma, NS: non-seminoma, H: histology, Tu: tumor

Out of the 26 men with TC, two patients with bilateral synchronous Ss were detected. The frequency of detection of bilateral GCTC during the screening program (7%) is probably a statistical artifact, since the incidence of bilateral synchronous TC is about only 0.5%[50-53]. Among the 26 men with GCTC, 19 stage I. tumors were detected (Table 4). The median age was 33 years (range of 20-48 years) and the overall median duration of complaints was less than 12 weeks (range 1-48 weeks). Fifteen S (2 of them bilateral), and 13 NS tumors were

diagnosed. The clinical stages were: 9 I/A, 9 I/B, 1 I/S, 3 II/A, 1 II/B, and 2 III/B. One patient refused any further treatment and was lost of follow-up.

Because of the early stages and the high percentage of S, the tumor markers aided in cancer diagnosis in only 8 cases: 7 with increased β-hCG and 4 with increased AFP were detected. Both β-hCG and AFP were elevated in 3 cases. Elevated tumor markers in all except on were NSs.

The occurrence of TC was most frequent (1.6%) in the 15 to 40 age group. Only 3 TC were detected in men over the age of 45 (0.3 %), two of these revealed S.

According to the IGCCCG classification, all patients belonged to the good prognostic group, except for the patient who was lost to follow-up after orchidectomy. The median follow up time of patients in December 1999 was 36 months (16-49 months). At this time (2011.03.) all patients were cured.

Table 4. Diagnostic and medical delay of GCTC patients treated by chemotherapy in 1994 and 1998* in our Department (weeks)

	Diagnostic delay [(a)] (weeks)					Medical delay [(b)] (weeks)		
Stage	**N**	**1994**	**No**	**1998**	**P**	**1994**	**1998**	**P**
I.	87	14 (1-48)	86	13 (1-96)	0.66	3 (0-32)	3 (0-64)	0.78
II.	95	18 (2-96)	76	16 (1-72)	0.33	4 (0-40)	5 (0-48)	0.77
III.	48	26 (2-72)	52	27 (1-112)	0.78	11 (0-48)	7 (0-44)	0.07
Total	230	18 (1-96)	214	17 (1-112)	0.58	6 (0-48)	4 (0-54)	0.33

(a) average time to first appearance of any symptoms to the date of diagnosis
(b) average time to first medical consultation related to the symptoms to the time of diagnosis (excludes men diagnosed in the current program)

4.4. Observations on changing of diagnostic and medical delays

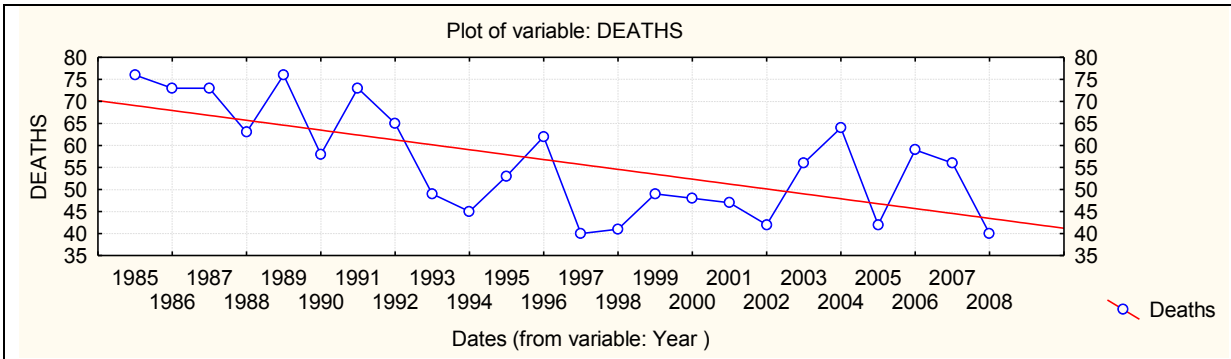
Concerning the educational aspect of the program, ***we did not observe a significant decrease in the diagnostic and medical delay*** in the patient population treated by chemotherapy in our department between 1994 and 1998 (p=0.58). There is a non-significant tendency for a decrease in the duration of medical delay in favor of 1998 especially in stage III patients (Table 4), suggesting a greater awareness of the need for treatment, especially among stage III patients.

4.5. Changes in trend of TC mortality rate between 1985 and 2008

The changes in the mortality rate of TC in Hungary between 1985 and 2008 is demonstrated in Figure 1. The data show that after a clear decrease in the first 10 years of this time period, there were no significant changes in the figures of death rates in this following years. However there were a

period between 1997 and 2002, where the number of deaths were clearly and continuously under the regression curve, that is followed by a discrete elevation in the recent years.

Figure 1. TC mortality rate in Hungary between 1985 and 2008 (Number of death by year and regression)



5. Discussion

The results of the early detection program confirmed that the screening of asymptomatic patients does not necessarily lead to the detection of tumors[54-58], and the incidence of detected tumors is low even in volunteers with complaints. The results show that the probability of detecting existing pathology is much higher in the population with complaints than in volunteers without complaints. However, diagnosed pathology which required further urological health care still remained low[59].

No tumors were found in the group with pain, sensitivity, or complaints unrelated to the testicle. From our results we can conclude that physical examination alone appears to be sufficient for the first medical consultation in an early detection program in cases of men with pain, with sensitivity to palpation, and with symptoms unrelated to the testicle. Despite the specificity of both swelling and lump for TC, the predictive value of these complaints to tumor positivity is very low. In the case of a palpable lump and/or a swollen testicle, TUS is obligatory to aid the physical examination at the time of the first consultation, especially in young men.

Of the 26 GCTC patients, 13 had S and all had stage I tumors. Among the 13 NSGCT patients, 4 had clinically detected regional metastases, and 2 had hematogenous dissemination. This data suggests that S is detected more frequently and earlier in an early detection program than NSGCT. The low incidence of detection in the age range of 15-40 years (1,6%) and the detected rate of S in our patient population does not justify an early

detection program even in this age group, in spite of the increasing incidence of TC [60]. In most cases the diagnosis was based on the physical and US examination, confirmed by histology. Because of the early stages and the high percentage of S tumor markers, had a limited role in an early detection program.

During the 3-year period, only 3-4% of the estimated TCs in Hungary were discovered by the program. The incidence was 0,51% in the entire screened population, and 1,66% in the population of patients with complaints *and* findings. This is the same magnitude that was found by Carmignani and coworkers[61] when they compared testis-sparing surgery of TCs with standard orchiectomy. In their study on 1320 patients with scrotal or testicular symptoms, 27 (2,0%) had TC, and 17 (1,3%) of these tumors were palpable. In an other study Chen et al. analyzed the connection between testicular microlythiasis and cancer, and found 8/513 (1,6%) TC in symptomatic Taiwanese males[26]. These latter figures underlines the value of our results. Although early detection might help in the identification of some TCs, the efficiency of the program is limited. The effect of the program on outcome is uncertain since the contribution of early detection to the probable 100% cure rate cannot be estimated. The majority of diagnosed TCs were stage I tumors, and all of the treated patients belonged to the good prognostic group: this fact made it possible to apply less aggressive treatment and improve the patients' quality of life.

In 2004, the US Preventive Services Task Force (USPSTF) concluded that screening asymptomatic men for TC was "unlikely to produce any additional benefits over clinical detection because of its relative rarity, the lack of evidence showing the accuracy of clinical or self-examination, and highly favorable outcomes from treatment". Researchers from the Agency for Healthcare Research and Quality in 2010 report that there is "no new evidence to support changing the existing guidelines" and the USPSTF encouraged clinicians to "consider TC in their differential diagnosis for patients with testicular symptoms"[62]. The National Cancer Institute (NCI) notes[63] that, on the basis of current evidence, "screening for TC would not result in an appreciable decrease in mortality, in part because therapy at each stage is so effective." [However] Patients presenting with a painless testicular mass, scrotal heaviness, a dull ache, or acute pain should receive a thorough examination.[64]

In this context, increasing health care education with better public and self awareness could improve the figures of early TC. The impact of this educational and early detection program for TC mortality difficult to be justified. However there were a period between 1997

and 2002, where the number of deaths were clearly and continuously under the regression curve. In contrary to the NCI statement, our educational and screening program that was finished in 1998 may have some positive immediate and carry-over effect in the next few years on the figures of mortality. This improvement diminishes, ceases in recent years probably due to the lack of such programs.

In a comparative study demonstrates an increase in public awareness and modest concomitant increase in TSE since 1986[65]. There was no difference in knowledge across age groups in this study. Furthermore, men who demonstrate a superior degree of knowledge were more likely to perform TSE. Students who have never heard of TSE were more likely to report intention to delay health care seeking with symptoms of TC[66]. In their study, Khadra et al demonstrated that TSE was associated with age >35 years, white ethnicity, knowing someone with TC, having attended a Men's Health Clinic and having heard of the 'Everyman' TC awareness campaign. As the opposite, students who have never heard of TSE were more likely to report intention to delay health care seeking with symptoms of TC.[66] Data supports, that learning difficulties[67] and depressive attitude[68] may have clinical impact on cancer awareness and TSE activity.

Population that need to be screened are those men who had cryptorchidism, infertility and malformations or abnormalities of the male genital organs in their medical history, who had first degree relatives with GCTC. In case of gonadal dysgenesia or Klinefelter-syndrome and Down's-syndrome, patients have to screen routinely due to the high incidence of TC.

Concerning the educational aspect of the program we did not observe a significant decrease in the diagnostic and medical delay in the patient population treated by chemotherapy in our department between 1994 and 1998. A tendency for the medical delay to decrease may be promising, suggesting greater awareness of the need for treatment, especially among stage III patients.

Early diagnosis should be based on an educational program for the population at risk, the appropriate training of doctors and staff engaged in the health care of the young, and the use of early US examination for men with palpable lumps and swollen testicles, especially in young men. To detect the disease at an early stage, it is important that young men know about the prevalence of TC, can identify the most common early symptoms, and are familiar with the performance of TSE[69-71] It has been pointed out that school nurses are in an ideal position to promote awareness of TC and TSE to adolescent men.[72]

6. New statements

1. By means of our early detection and screening program, the incidence of mortality could be decreased during the time of the program and in the next following years. Meanwhile, early diagnosis of TC should be based rather on widespread and continuous health education adapting to the curriculum mostly for the young population at higher risk, than by means of a screening program.
2. The screening of asymptomatic, complaint-free volunteers is not necessary. This observation has got into international statements since then. In this group regular TSE is recommended.
3. Further assignation to detailed urological examination by general practitioners should be based on evaluating of complaints and clinical findings. The TUS examination at short notice for patients who have revealed with swollenness and lump, can be recommended.
4. For certain high-risk groups regular TSE and in case of complaints and/or physical findings TUS can be recommended

7. References

(see at the end of Chapter II.)

Chapter II.

Recent advances in the better decisions on diagnosis and treatment of inflammatory breast cancer.

1. Introduction

1.1. Introduction to breast cancer, to its locally advanced form and primary systemic chemotherapy.

Invasive breast cancer (BC) is the most commonly diagnosed malignancy in women after skin cancers. 7000-7500 new cases are diagnosed yearly in Hungary, and one-fifth to one-fourth of them are expected to die from invasive cancer making it the second most frequent cause of cancer deaths in women. Although the incidence of invasive BC has risen steadily during the past several decades, BC–related mortality has begun to decline in recent years. This is due to both upgrading screening rates and improvements in systemic adjuvant therapy, that - when applied against microscopic disease - can lead to a significant reduction in risk of local and distant recurrence and death. Principles of diagnosis, treatment and follow-up of primary BC are based on well-accepted guidelines (Hungarian[73], ESMO[74], NCI[75], NCCN[76], St. Gallen Consensus[77]).

Locally advanced breast cancer (LABC) is defined as stage III disease and is represented by stage IIIA (T0N2M0; T1/2N2M0; T3N1/2M0), stage IIIB (T4N0-2,M0), and stage IIIC (TanyN3M0). Stage IIIA (T3N1M0) patients are considered to have resectable LABC, whereas all other LABC is considered irresectable. According to a SEER analysis 4.6% of BC cases were identified as LABC. Inflammatory breast cancer (IBC) as the third group of LABC defined as irresectable T4d disease (UICC TNM 6.0).

Primary systemic chemotherapy (PSCT) –or neoadjuvant CT - is performed prior to BC surgery. It offers several advantages over standard postoperative CT. Patients who undergo PSCT are more likely to have breast-conserving surgery. Moreover, the use of PSCT permits in vivo monitoring of tumor response. Since there are many active agents available for the treatment of breast cancer, it is important to know early in the course of treatment whether the drug chosen will be effective. However, PSCT with classical drug of choice does not offer any survival benefit over postoperative CT to date.

1.2. Inflammatory breast cancer – general overview

IBC is the most aggressive form of BCs comprising 1-6% (most often 2-3%) of all invasive BC cases[78,79]. The incidence (0,7-1.6 /100.000) of IBC is growing more rapidly comparing to the non-inflammatory form of BC and women diagnosed with IBC had statistically significantly poorer 5-year disease-free survival than women with either LABC (50% vs. 35%; p=0.02)[80,81] or non-T4 breast cancer[,82, 83,84]. The mean age at diagnosis was 60.6 years, significantly older than the age at diagnosis—58.4 years—for patients with IBC (P < 0.0001).[85] Concrete epidemiological evidence on the incidence and prevalence of IBC is hindered by a lack of consensus regarding the case definition for the disease.

Consistently with Haagensen's original description of IBC[86], the American Joint Committee on Cancer (AJCC) provides the current definition for this form of BC, describing it as both a clinical *and* a pathologic entity that is characterized by diffuse erythema affecting at least one-third of the underlying skin and often without an underlying palpable mass. Edema (peau d'orange) affecting at least two-third of the breast, induration (often without border), touchiness and warmth can also be detected. The nipple usually gets flattened or inverted. The development of clinical signs and symptoms of IBC is always fulminant: usually it takes less then 3 months. Palpable axillary lymph node enlargement can be found in most of the patients and distant metastases can be detected in one-third of the cases at the time of diagnosis. Although skin changes associated with IBC resemble an acute inflammatory process, it is hardly to confirm true inflammation.

Skin changes can be attributed to dermal lymphatic invasion (DLI). In course of this invasive tumor emboli leading to obstruction of lymphatic drainage. Numerous studies dealt with the importance of DLI and it is performed routinely in daily practice, but proof of DLI is not considered to be prerequisite for the diagnosis of IBC[87], since it can be detected only in 75% of the patients. The diagnosis of IBC is based on clinical symptoms rather than the pathological confirmation of DLI[88], although it is very useful.

IBC is usually associated with high-grade and Ki67, aneuploid, high S-phase fraction, invasive ductal carcinoma with peritumoral lymphatic invasion, hormone receptor negativity and HER2 positivity[89,90,91], and with extensive angiogenic signs including overexpression of angiogenic and lymphangiogenic factors[92]. Several molecular biological changes have been described as well [93,94,95]

1.3. Prognosis of IBC

From a clinical point of view, the first step in treatment of IBC is the conversion of the primary irresectable cancer to a resectable one; otherwise this the patient is incurable. Getting resectability we must achieve clinical CR (cCR) or partial remission (PR); minimal change or stable disease (SD) means abiding in the state of irresecability. Beyond other prognostic and predictive factors, *response to PSCT*, particularly achieving pathological complete remission (pCR) dominantly determines survival[83,96,97].

1.4. The multidisciplinary management of IBC

The multidisciplinary management of IBC includes PSCT and radiotherapy (RT). In case of achieving resecability surgery (ST) must be performed, and in case of hormone receptor positivity postoperative endocrine therapy (ET). According to the NCCN guideline, an anthracycline-based (A+) regimen in combination with concomitant or sequential taxane is the standard PSCT recommended for the treatment of LABC. The addition of neoadjuvant and adjuvant trastuzumab or other anti-HER-2 treatment to neoadjuvant chemotherapy should be considered for women with HER2-positive LABC or IBC to improve event-free survival, overall survival (OS), and clinical and pathological tumor responses. [98,99]

Although the length and components of PSCT in the neoadjuvant setting are by and large predefined, there are only few data available *specifically* for the PSCT of IBC. Adding a taxane to an anthracycline-containing regimen further improved the DFS in most of the neoadjuvant and adjuvant trials. However there is a large degree of heterogenity in evidences regarding the effectiveness of taxane-containing regimens compared to non-taxane-containing protocols in terms of interventions, comparators and populations[100]. It is not quite clear, that in case of achieving resecability with PSCT is it worth to give all cycles *before* ST or is it better to perform a short-term operation and *after* completing CT with other adjuvant modalities. Moreover, if we detect only a minimal change or SD on PSCT, then which drugs and in how many cycles should we apply instead and over of our PSCT?

2. Aims of the thesis:

In our thesis we look for the answers of the following questions:

1. Can we further improve the efficacy (response) of conventional non-taxane based, A+ protocols with adding a taxene (docetaxel) to an anthracycline (epirubicine) in IBC patients?

2. Can we demonstrate relationship between response to PSCT and survival parameters?

3. Can we demonstrate relationship between number of treatment cycles – either given them pre-or pre- and postoperatively - and survival parameters?

3. Patients and methods

3.1. Patients and diagnostic work-up

Clinical records of 82 IBC patients referred to the Multidisciplinary Breast Cancer Consulting Committee of the National Institute of Oncology between 1.1.1997 and 31.12.2004 were analyzed retrospectively. ***The diagnosis of IBC had been set up according to Haagensen's criteria***. In order to evaluate the primary tumors and presurgical clinical responses - beyond physical examination - mammography and ultrasonography, were performed. State of malignancy was set by aspiration cytologies and/or core biopsies as well. Routine staging examinations revaled distant metastasis in 8 patients so they were disclosed from further analysis. Four IBC patients received docetaxel-carboplatin, and CMF treatments, they were also excluded from the further PSCT analysis due to the small number of these cases that could not enter any of the homogenous treatment groups[2]. At least, we could analyse the data of 70 patients from the point of PSCT.

3.2. Treatment and follow-up

In case of the evaluable 70 patients the following PSCT protocols were used: 6-8 cycles of FAC/FEC (500 mg/m2 5-fluorouracil (5-FU), 50 mg/m2 doxorubicine or 70-75 mg/m2 epirubicine and 500 mg/m2 cyclophosphamide, d1 q3w) or AC (60 mg/m2 doxorubicine and 600 mg/m2 cyclophosphamide, d1 q3w), 6 cycles of CEF (500 mg/m2 5-FU, 70-75 mg/m2 epirubicine and 500 mg/m2 cyclophosphamide, d1,8 q4w); these protocols further designated as **A+**. **TE** protocol consisted 6 cycles of 75 mg/m2 docetaxel and 75 mg/m2 epirubicine, d1 q3w. Postoperative adjuvant chemotherapies were the above-mentioned: A+ and TE protocols, as well as the TC (75 mg/m2 docetaxel and carboplatin AUC 5 or 300 mg/m2 for 4-6 cycles) and CMF (cyclophosphamide 600 mg/m2, metothrexate 40 mg/m2 and 5-FU 600 mg/m2 on days 1 and 8 every 4 weeks for 6 cycles) protocols.

[2] The data of these 4 patients were only considered in PSCT + adjuvant CT in the analysis.

For the improvement of local control, preoperative radiotherapy could be applied after PSCT by the physician's individual pretreatment or peri-treatment decision. In the preoperative setting loco-regional radiotherapy (RT) consisted of whole breast irradiation using paralell opposed tangential 6-9 MV photon beams matched with an AP supraclavicular-axillary 6-9 MV photon beam up to a total dose of 50-50 Gy with conventional fractionation (2 Gy/day, 5 fractions/week). A boost dose of 10 to 20 Gy was given to the tumour bed using 6-18 MeV direct electron beams. The same technique and doses were applied in the postoperative setting for patients treated with breast-conserving surgery (n=2) after neoadjuvant chemotherapy. After mastectomy the chest-wall was irradiated via tangential 6-9 MV photon or direct 6-12 MeV electron fields matched with an AP supraclavicular-axillary 6-9 MV photon field up to a total dose of 50-50 Gy using conventional fractionation. No boost dose was given to the chest-wall. For patients with clinically or pathologically positive axillary nodes and central or inner quadrant lesions or with radiographic evidence of positive internal mammary nodes, treatment of the internal mammary nodes were administered either with deep tangents or mixed photons and electrons. A CT-based treatment planning was used for all patients.

If resecability was achieved, surgery and – depending on the histological findings - adjuvant chemo-, radio- and endocrine therapies were also applied. In case of hormone receptor positivity (defined by ER and/or PR immunhistochemical positivity $\geq$ 10%) the appropriate endocrine treatments (ET) were used postoperatively (N=42) for 5 years. In case of HER2 positivity (confirmed by IHC or FISH), adjuvant trastuzumab was given for 1 year (n=6). In Table 1. we summarized the main patient, disease and treatment characteristics.

Table 1.: Summary of main patient and disease characteristics

Patients:	
Age at time of diagnosis (average ± S.D. [range])	**57.38 ± 11.4 [27.5 – 77.0] year**
Menopausal status:	
premenopausal	25.71%
perimenopausal	2.86%
postmenopausal	71.43%
Median time to first perception of breast mass to diagnosis	6.0 months
Median time from diagnosis to start PSCT	22.3 days
Measurable tumor sizes (average ± S.D.)	
mammography	40.2 ± 33.6 mm
ultrasound	30.8 ± 24.7 mm
physical examination	56.53 ± 32.1 mm

3.3. Evaluation and statistical methods

To determine the efficacy of PSCT, we analyzed the clinical therapeutic responses, histological result of surgery, and different survival parameters. The evaluation of clinical response was based on the consultant physician's and the surgeon's description given before surgery considering the physical findings and preoperative imaging results. Clinical response evaluation with imaging methods was usually performed after the 4th - 6th cycles of PSCT.

Complete clinical remission (cCR) was recorded if any signs or symptoms of IBC have disappeared by both physical examination *and* imaging. Progressive disease (PD) was considered if the disease progressed according to the description of signs and symptoms or imaging studies or when the preexisting tumor diameter became 25% larger. Clinical partial response (cPR) was defined by the clear, greater than 50% remission in diameter of the primary tumor with the concomitant achievement of resecability. Cases falling between cPR and PD were considered as stable disease (SD) irrespectively from achieving resecability or not. In cases showing irresolvable discrepancies between results of physical evaluation and the imaging results, we accepted the *worse* clinical result category. Complete pathological response (pCR) was stated if both the invasive and non-invasive parts of the tumor have been completely disappeared from the breast and the lymph nodes. This corresponds to regression grade 5 according to the modified regression grading system described by Sinn et al [101].

Overall survival (OS) was defined as time from starting PSCT until death from any cause. Censoring time for living patients was 01.09.2008. or the last contact closest to this date. Progression-free survival (PFS) was defined as time from starting PSCT to first loco-regional or distant progression of breast cancer, second primary breast cancer or death from any cause. Local-regional recurrence was defined as ipsilateral disease recurring at the chest wall close to surgical scar, axilla and/or supraclavicular-parasternal region. Time to locoregional progression, named LPFS, was defined as time from starting chemotherapy to first local recurrence of breast cancer in the mentioned areas.

Histological work-ups were routinely performed from both the available core biopsies and postoperative specimens determining usual histopathologic features (nuclear grade, mitotic activity, histological grade[102] and hormone- (ER and PR) and c-erbB2 (CB11) receptor status.

Statistical analyses were conducted with using *Statistica® 7.1* software (StatSoft® Inc., Tulsa, OK, USA). Descriptive stastistics to characterize variables and matched pair tests were performed. Univariate analysis was used for describing the difference between two proportions for qualitative data (Pearson's χ^2-test). (In case of small sample size we used the results of Fischer's exact test or the Yates-corrected χ^2-test.) For quantitative data we used Wilcoxon's rank sum test. Continuously measured parameters were compared using the Kruskal-Wallis test. Non-parametric comparisons between two groups were made with Mann-Whitney U-test. Three-year PFS, LPFS, and OS were calculated from the first day of the primary chemotherapy and were estimated by using the Kaplan-Meier method. Between-group comparisons were performed by log-rank test. For multivariate analysis we use general discriminant analysis. *p* of 0,05 or lower was considered statistically significant.

4. Results

In Table 2. we provide relevant initial staging, histopathological findings and treatments of our patients. Palpable supraclavicular lymph nodes (cT3c) have been found in 4 patients (5.7%). Core biopsy was performed in 32 cases (45.7%). Due to the fragmentation of the specimen it was not possible to determine the histological grade in 4 cases and the HER2/neu status in 3 cases. Significantly more hormone receptor negative patients were detected between TE treated patients.

4.1. Results of imaging studies.

The median time from first perception of palpable breast mass to diagnosis was 6 months; the median time from diagnosis to start PCT was 22.3 days. Diagnoses of IBC were based solely on clinical/radiological examinations in 57.1% (n=40) or pathological examination in 42.9% (n=30), as well. Visible tumor diameters measured by mammography (40.2±33.6 mm) and US (30.8±24.7 mm) were significantly correlated (r=0.64; p>0.001). Tumor diameters defined by physical examinations (56.5±32.1 mm) were also correlated significantly with mammography (r=0.59; p>0.003) or US (r=0.47; p=0.02) results.

Discussion:

Definition of pCR is considered to be a well-known problem in comparing different studies. In our study we use the strictest definition of pCR [103,104] which explains a shift of the proportions of patients from CR to PR within ORR, and to SD from ORR can be seen.

Table 2.: Distribution of the preoperative stage, main histopathologic features, receptor status and treatments between the two chemotherapy protocol arms

		A+ (N=48)	TE (N=22)	
		N / all %	N / all %	p
Nodal status (cN)*	**cN0**	9 / 12.9%	5 / 7.1%	0.75
	cN1	23 / 32.9%	9 / 12.9%	0.39
	cN2	16 / 22.9%	8 / 11.4%	0.5
Clinical stage	**III/B (T4, N0-2)**	44 / 62.9%	21 / 30.0%	0.5
	III/C(any T, N3)	4 / 5.7%	1 / 1.4%	
Histology from core biopsy	**Invasive ductal**	14 / 45.2%	11 / 35.,5%	0.1
	Invasive lobular	0 / 0.0%	3 / 9.7%	0.12
	Invasive apocrin	1 / 3.2%	1 / 3.2%	0.74
	No tumor (fibrosis)	0 / 0.0%	1 / 3.2%	0.52
Histological grade	**I**	0 / 0.0%	1 / 3.6%	0.5
	II	3 / 10.7%	6 / 21.4%	0.21
	III	11 / 39.3%	7 / 25.0%	0.12
Hormone receptor status†	**negative**	2 / 6.3%	8 / 25.0%	**0.027**
	positive	14 / 43.8%	8 / 25.0%	
HER2	**negative**	9 / 31.0%	11 / 37.9%	0.45
	positive	5 / 17.2%	4 / 13.8%	
Treatments:	**preoperative RT**	13 / 18.6	9 / 12.9	0.19
	adjuvant CT	22 / 31.4	15 / 21.4	0.07
	adjuvant RT	21 / 30.0%	9 / 12.9%	0.52
	adjuvant ET therapy	30 / 62.5%	12 / 54.5%	0.35
	adjuvant trastuzumab treatment	4 / 5,7%	0 / 0%	0.21

* palpable supraclavicular lymph node (cT3c) 4 (5,71%) ; † three of them from cytology

However, it is still problematic to define PR and SD, when results of physical examination and imaging are different. In our study, significant difference (approximately 2 cm) could be detected between physical examination and imaging studies; i.e. it is great enough for changing the actual stage definition of the remaining tumor! After taking into account the pathological measures in evaluating the therapeutic response 21,4% (15/70) of the results had to be changed! The same difference can be noticed in the GeparTrio trial, where 10-15% difference was reported between the overall responses measured by US and physical examination at non-responding patient[101], and the difference was approximately doubled at the responding patients. Further refining the evaluation rules, introducing new imaging techniques (PET-CT, dynamic contrast-enhanced MRI) with tempering the subjective considerations could make a step forward in this sensitive field, which can determine the validity of all clinical studies in the field of LABC / IBC.

4.2. Effect of the two types of PSCTs on therapeutic response

The objective RR was 56.8% with the clinical benefit (at least SD) of 92.9%. Clinical complete remission (cCR) was shown in 17 patients (24.3%). Results of histological

evaluations of cCR and pCR patients are provided on Table 3. Detailed results comparing the two types of PSCT can be seen on Table. 4.

Table 3.: Results in patients achieved cCR (N=17)

Not operated	3	
Pathological CR	**4 [+1]* (7,14%)**	
Partial response	9	
Stable disease	1	
Histology unavailable (but presence of tumor confirmed)		2
Histology available:	DCIS	2
	Invasive ductal carcinoma	3#
	Invasive mucinosus carcinoma	1
	Inflammatory breast cancer	1
	pCR, but lymph node metastasis	1

* one patient with clinically SD became pCR; # one only microscopic in size

Table 4.: Clinical and pathological responses according to the PSCTs

	Clinical Response				**Pathological Response**			
	A+ /%	**TE/%**	**$\chi 2$**	**p**	**A+/%**	**TE/%**	**$\chi 2$**	**p**
cCR / pCR	13 /27.1	1 /4,5	4.79	**0.03**	5 /10.4	0 /0	2.47	0.12
Major response (CR+PR)	26 /54.2	12 /54,5	1.16	0.28	23 /47.9	9 /40.9	0.15	0.70
Clinical benefit (CR+PR+SD)	44 /91.7	21 /95,5	0.33	0.57	44 /91.7	21 /95.9	0.33	0.59
All	**48 /100**	**22 /100**			**48 /100**	**22 /100**		

Clinical CR rate of patients receiving A+ was significantly better, however the objective RR and the clinical benefit were not different. Although, we cannot demonstrate any significant difference between the two treatment groups in major response and pathological results, it is notably, that 5 pCRs were seen on the non-taxane arm vs. nil on the TE arm. Response rates in all cases were inferior according to time to first perception of tumor to diagnosis (R=0.35; p=0.003), to histological grade (HG II vs. III: Z=2.29; p=0.01), to progesterone receptor status (negative vs. positive: Z=2.15; p=0.05), to both hormone receptor staining frequency: ER% (R=0.55; p=0.0001) and PR% (R=0.37; p=0.03) and marginally to HER2 status (negative vs. positive: Z=1.98; p=0.07). However, between group comparisons revealed that only progesterone receptor status was significantly more positive (F=14.0, p=0.002) in the TE group.

The toxicity profile of these regimens are well known, and basically not really important in the decision making process. However, we did not observe more frequent or more severe side effects, then they have already been described.

Discussion:

In this set of patients, we could not detect significant difference between the A+ and TE protocols, in terms of clinical response parameters, however an unexpected elevation was

seen in pCR rate after A+ probably due to statistical terms.[105] Introduction of doxorubicin-based chemotherapy significantly improved results in IBC[106]. Three cycles of CAF or CEF followed by surgery, adjuvant chemotherapy and adjuvant irradiation also found to be equivalent in ORR, 5 and 10 year DFS and OS[107].More intense chemotherapeutical protocols showed a significant improvement in both local relapse-free survival and breast cancer specific survival compared to AC/MF or FAC [83].

In a large series of MD Anderson's retrospective analysis taxane-containing regimens produced higher pCR rates compared to 3-4 cycles of A+. Here, the prognostic value of pCR was independent from type of the used chemotherapy and from the ER status [108]. Integrating sequential paclitaxel to an A+ resulted significantly higher pCR, median PFS and median OS [82,109]. The sequential A+ followed by adjuvant T improved RR and pCR rate compared to A alone[110], but, in contrast, concomitant T and A in the neoadjuvant setting failed to improve efficacy[111]. In the NSABP B-27 trial[112] adding sequential T to AC did not significantly affect OS, slightly improved DFS and decreased the incidence of local recurrences on stage II-III patients. Moreover, the improvement of pCR rate using second generation taxane-containing protocols did not turned to clinically meaningful improvements in long-term outcomes on operable patients.[113] Changing 5FU to T (i.e. TEC vs. FEC) in the third generation concomitant protocol, however, showed further significant improvement in the neoadjuvant therapy of operable breast cancer.[114]

4.3. Effect the two types of PSCT in terms of survivals.

Survival parameters were inferior in greater tumors, lymph node positivity, higher grade, hormone receptor negativity, HER2 positivity, absence of necrosis in tumor, progesterone receptor negativity. In case of pCR, the fact of ST and RT, survival parameters were better in univariate analysis. No meaningful multivariate analysis can be performed due to the small number of cases.

After an average of 2.6±2.4 [0.16-10.0] years of follow-up 50% (n=35) of the patients was alive, and 32.9% (n=23) of the entire population was free of disease. Distribution of disease and survival status was presented in Table 5. For the entire population the median PFS was 1.9 year, the median LPFS was 5.4 years, and the median OS was 4.0 years.

Table 5.: Disease and survival status at censoring time

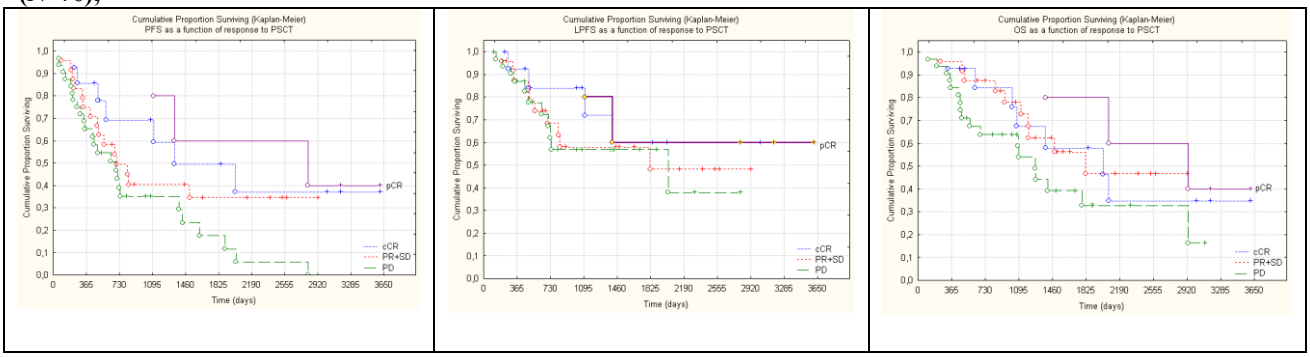
Status: N=70	Cause	N / %	Cumulative N / %	Alive at censoring N/ %
Survival, no progression	-		23 / 32.9	23 / 32.9
Survival, progression	Locoregional Distant Locoregion.+Distant	19 / 27.1 22 / 31.4 6 / 8.6	47 / 67.1	12 / 17.1
Death	BC Cerebral hemorrhage*	21 / 31.4 1 / 1.4	35 / 50.0	-

* without BC

Patients achieved cCR had a tendency for longer survival parameters comparing to PR-SD patients, with a median PFS of 3.7 vs. 1.9 years (p=0,41); with a not reached median LPFS vs. 5.0 years (p=0.44) and with an OS of 5.5 vs. 5.0 years (p=0,79).

In terms of PFS and OS but not in LPFS, a clear survival advantage was demonstrated for patients who achieved pCR. Survival curves are shown on Figure 1.

Figure 1.: Kaplan-Meier survival curves: According to clinical response after PSCT- A: PFS; B: LPFS; C: OS (N=70);



Note: Comparing cCR vs. PR+SD: PFS Z=1.11 (p=0.27); LPFS Z=0.83 (p=0.41); OS Z=-0.09 (p=0.93); Note: Solid line indicates pCR

We could not demonstrate any difference between the two types of PSCT in terms of survivals. Although the 3-year PFS/LPFS rates were somewhat higher with the conventional A+ protocols, this was not significant and the reverse effect was detected on the OS.

At the censoring time, proportion of patients *dead or alive* (A:17/31 vs. TE: 5/17; χ^2=1,13; p=0,29), and *without BC or relapsed* (A:15/33 vs. TE: 8/14; χ^2=0,18; p=0,67) was not different. There was no type of comparisons which demonstrated any significant difference between the two types of PSCT. Similarly, median overall survival and 3 year survival rates (see Table 6. and Figure 2.) were identical in both arms.

Discussion:

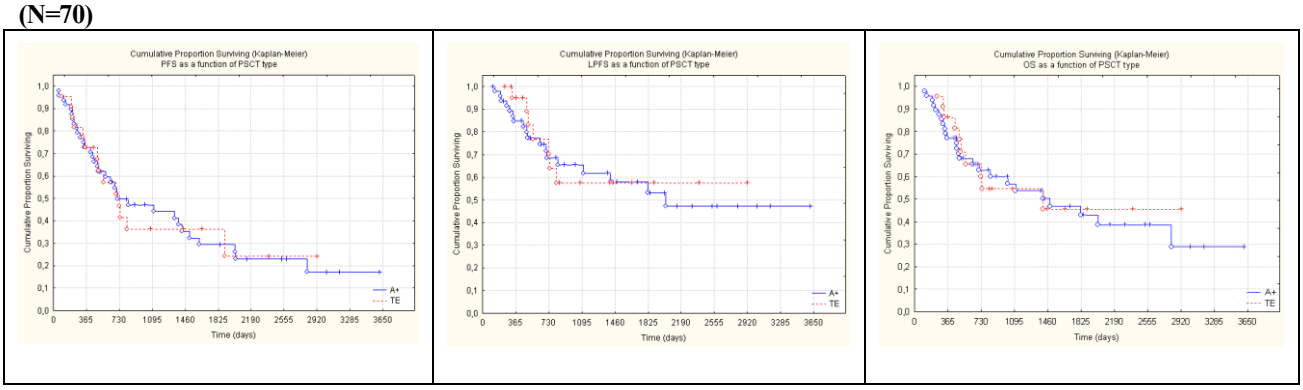
The problem of the mentioned clinical response evaluation is reflected in the observed difference in cCR and pCR. We found, that cCR was approximately three-fold higher, than

Table 6.: Survivals as a function of type of PSCT

		Median survival			3 y survival			
Type of chemotherapy	**N**	**PFS y**	**LPFS y**	**OS y**		**PFS%**	**LPFS %**	**OS%**
Anthracycline-(non-taxane) combination	48	2,28	5,53	4,07		47,1	65,5	60.9
Docetaxel+epirubicine	22	1,99	not yet achieved	3,86		36,4	57,5	74,8
Log-rank p		0,13 0,90	-0,53 0,60	-0.39 0,7	**HR** (C.I.± 95%)	1,30 (0,18-2,42)	1,06 (0,08-2,04)	0,76 (0,34-1,19)

pCR in our patient population, that may reflect the definition of pCR.[105] Other studies demonstrated less (approximately 1,5-2-fold)[82,115,116] or the same[117] differences. The median survival of patients achieved pCR is one year longer than patients reaching only cCR. Achieving pCR with PSCT is a direct and quick measure of sensitivity to chemotherapy.

Figure 2.: Type of PSCT and survival parameters. Kaplan-Meier survival curves. A: PFS; B: LPFS; C: OS (N=70)



Note: Comparing A+ vs. TE: PFS Z=-0.01 (p=0.99); LPFS Z=-0.53 (p=0.60); OS Z = -0.35 (p=0.73)

A positive correlation could be seen between response to PSCT in combination with multimodal approach and survival, CR patients would have significantly better long-term survival than others.[83,96,97,108,118,119,120,121,122]. One group described 87% 5 year DFS-t and 89% 5 year OS in CR patients having histologically negative breast and axilla after PSCT[118]. However, it seems to be quite provoking, that longer DFS and OS after achieving pCR may reflect a disease with better prognosis and an indolent course, but not necessarily a better sensitivity to chemotherapy[107].

Comparing the taxane non-containing protocols to concomitant TE protocol in our study response rates and survival data were equivalent and analogous with results of these and other [123] [124] groups. We could also confirm that achieving pCR renders a greater probability of longer PFS and LPFS, but not significant tendency in OS data. There is no clear explanation for the significant difference observed between the two treatment groups in cCR/pCR. One

meaningful difference detected between the two treatment groups was the higher PR content in TE group. The anti-apoptotic effect of PR is documented. In their study, Schmidt et al revealed that PR-rich tumors have decreased chemosensitivity to paclitaxel[125]. PR-A-rich tumors have heightened aggressiveness, and that abnormal PR-A excess is found in the healthy breasts of women with *BRCA1/2* mutations.[126] If so, these results along with others could be hypothesis-generating that needs to be confirmed in larger studies.

4.4. Effectivity of PSCT and adjuvant CT in terms of survival parameters[3]

Fourty-one patients received postoperative adjuvant CT and 33 did not. Three patients were excluded from the analysis: 2 received TC pre- and postoperatively, and 1 received CMF as PSCT, but nil postoperatively. The distribution of the patients was presented in Table 7.

Table 7.: Distribution of patients recieved A+ or A+ and taxane (docetaxel) pre- and/or postoperatively (N=74)

PSCT	Adjuvant CT	N	group
A+	nil	26	**A**
A+	A+	17	**A**
A+	TE	1	**B**
A+	TC	4	**B**
TE	nil	7	**B**
TE	TE	8	**B**
TE	A+	3	**B**
TE	CMF	4	**B**
TC	TC	2	**Excluded again**
TC	TE	1	**B**
CMF	nil	1	**Excluded again**

Two groups were formed: in the first group patients received only A+ protocols (N=43; 60,56%); in the second they received both anthracycline and taxane (docetaxel) (N=28; 39,44%). However, in the further statistics, we did not take into account whether these protocols were given as PSCT and/or adjuvant CT, because we assumed that the fact – namely, taxane (docetaxel) was given or not – is more important than the question: *when* it was given. Number of cycles given were identical: A+: 5.9; A+ and docetaxel: 5.1; t=1.73 p=0.09).

At the censoring time, proportion of patients *dead or alive* (A+:27/16 vs. TE: 22/6; χ^2=1,77; p=0,16), and *without BC or relapsed* (A+:13/30 vs. TE: 10/18; χ^2=0,23; p=0,63) was

[3] In this analysis we could enter those 4 patients, who were excluded from the PSCT analysis.

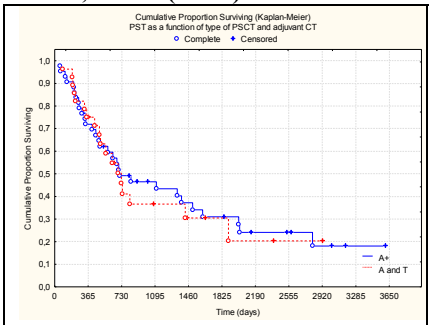
not different. There were no comparisons which demonstrated any significant difference between the two types of PSCT. Similarly, median overall survival and 3 year survival rates (see Table 8. and Figure 3.) were identical in both arms.

From the point of survival parameters, we could not demonstrate any meaningful difference between A+ and docetaxel-containing protocols irrespectively given them as PSCTor split them pre- and postoperatively. So, the next logical step was to examine those patients who did not respond well enough to PSCT. Could we further improve the survival with the change of CT protocol in those patients who did not respond well to PSCT?

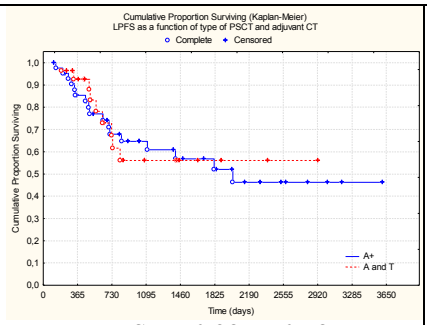
Table 8.: Survivals as a function of type of PSCT and adjuvant CT:

		Median survival				3 y survival		
Type of chemotherapy	**N**	**PFS y**	**LPFS y**	**OS y**		**PFS%**	**LPFS %**	**OS%**
Anthracycline-(non-taxane) combination	**43**	1.94	5.52	4.07		46.5	61	59.8
Anthracycline and taxane (docetaxel) combination	**28**	1.99	Not reached yet	4.87		36.6	56	75.3
Log-rank p		-0.13 0.90	0.38 0.70	0.45 0.65	**HR (C.I.± 95%)**	1.22 0.43-1.77	1.28 -0.14 -1.84	0.59 0.35-0.75

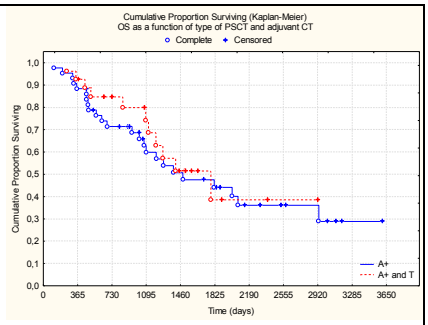
Figure 3.: Type of PSCT+adjuvant CT and survival parameters. Kaplan-Meier survival curves. A: PFS; B: LPFS; C: OS (N=71)



PFS Z=0.07, p=0.94



LPFS Z=-0.28, p=0,78;



OS Z=-0.73, p=0,46;

Due to the small number of patients that fell into {cCR; PR+SD; PD} groups we could not perform statistics, so we regrouped the patients as “major response” {cCR+PR}, and “minor-no response” {SD+PD}(for approximate appraisal. In Table 9. we summarized the distribution of patients.

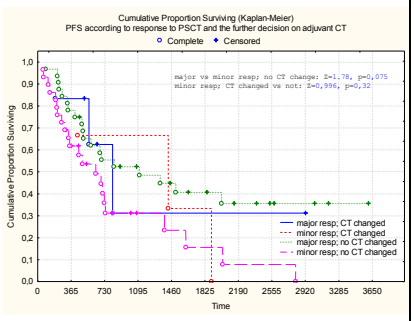
Here, we observe a curious thing that in case of “minor – no response” only 12.9% of the patients had changing in their protocol, but 41.4% had not! Due to the small number of patients falling into the “CT changed” group do not let us make firm conclusions, despite the difference between median PFS (“major response”: 1625 days vs. “minor response” 635

days). However, we could detect the same result, as mentioned above: the better response to PSCT leads the better survival parameters in the group of patients with unchanged protocol.

Table 9.: Distribution of patients according to response to PSCT and the following therapeutic practice

	N	%
Major response; CT changed	6	8.6
Minor response; CT changed	3	4.3
Major response; CT did not changed	32	45.7
Minor response; CT did not changed	29	41.4

Figure 4.: Survivals according to the clinical practice (changed or unchanged CT regimen) after registering response to PSCT (major or minor-no response) A: PFS; B: LPFS; C: OS (N=70)

	At least one sample has no uncensored cases; cannot perform analysis.	At least one sample has no uncensored cases; cannot perform analysis.

Discussion:

In one study for improving clinical results and resecability paclitaxel were used after initial PSCT for SD and PD patients and finally they were able to perform mastectomy on 7 of 16 patients[109]. *The practice in which therapeutic decisions – i.e. continue or change the initial protocol - based on the early response,* were evaluated in different trials. On the basis of developed nomograms pCR and metastasis-free survival is predictable; low and intermediate-high chemotherapy sensitive patients can be identified, helping to determine who will benefit the most from an optimized schedule of paclitaxel after four course of antracycline[120]. Authors of this study suggest to those who have low probability to achieve pCR after anthracycline treatment should be steered toward clinical trials incorporating novel agents that may revert that kind of chemotherapy resistance. Aberdeen trial[110] patients with clinical responses were randomly assigned to continue the previous doxorubicin-containing regimen, or T and others with no responses were continued on T. That practice increased the rate of clinical responses and pCRs in the responding group, but just marginally improved the outcome in the non-responders. With opposing results, GeparTrio investigators[104] randomized patients not responding to initial TAC protocol to a non-cross-resistant (vinorelbine-capecitabine; NX) protocol or to continue TAC, and showed that the efficacy of NX was not

inferior to TAC. In residual disease after PSCT, usage a non-cross resistant adjuvant protocol different from preoperatively used regimens has not demonstrated significant DFS advantage, but there was a trend favoring the use of non-cross resistant protocol[127]. However, we cannot draw firm conclusions from these trials, since they were little or not at all concerned of IBC patients. Dividing the CT into pre- and postoperative parts also seems to be equally effective in our group of patients. This setup has slightly improved the relapse-free survival on non IBC population[112], but it was not demonstrated in IBC series so far. In line with this in GeparTrio trial, splitting of protocol to a presurgical and adjuvant part seems significantly better than if it would be given as complete PSCT.

4.5. Effect of PSCT or PSCT and adjuvant treatment on survival parameters

Most patients were treated with 6 cycles of PSCT (n=48, 68.6 %,), 10.0% (n=7) got 3 cycles, 17.1% (n=12) received 4-5 cycles, and 4.3% (n=3) had more than 6 cycles. In terms of all pre- and postoperative cycles proportion of patients received less, than 6 cycles was 7.1% (n=5), 6 cycles: 47.1% (n=33); 7-8 cycles: 30.0% (n=21); more than 8 cycles: 15.7% (n=15.7). Survival parameters (PFS, LPFS, OS) were not significantly different between groups.

Those, who were treated with less than 6 pre- *and* postoperative cycles seem to have practically the same survival parameters, than those who had 6 cycles or more: PFS: χ^2= 5.28, p=0.15; LPFS: χ^2=1,15, p=0.77; OS: χ^2=4.01, p=0.26.

Discussion

Results of the studies that are in line with this question are non-equivocal. More cycles of CT was an independent predictor of pCR in ABCSG-14 trial or elsewhere[114, 128]. Opposing these results in GeparTrio trial - in terms of pCR - eight cycles of TAC was not significantly better than six cycles, but the majority of these patients have not IBC[101]. – Most of our patients got 6 or more cycles of CT, but survival did not improved with ascending cycle numbers. Six months length CT (i.e. 6-8 cycles) seems acceptable given either PSCT or splitting as pre-and postoperative treatment.[105]

5. New statements

1. Anthracycline-containing, but docetaxel non-containing protocols were equally effective with the docetaxel-epirubicine protocol in terms of response.
2. Patients achieved cCR had a tendency for longer survival parameters comparing to PR-SD patients, however we could not demonstrate any difference between the two types of PSCT in terms of survivals.
3. From the point of survival parameters, we could not demonstrate any meaningful difference between A+ and taxane-containing protocols irrespectively given them as PSCT or split them pre- and postoperatively.
4. Survival parameters (PFS, LPFS, OS) are not significantly different according to the cumulative number of cycles administered pre- and postoperatively.

Összefoglalás - I. fejezet – A heredaganatok korai felismerése

Célunk annak a kérdésnek a megválaszolása volt, hogy a here önvizsgálatával kapcsolatos egészségnevelési célzatú ismeretek terjesztése, illetve szűrőprogram szervezése az erre önkéntesen jelentkezők számára hozzájárul-e a heredaganatok korábbi felismeréséhez. A Magyar Rákliga közreműködésével szervezett médiakampányban részletesen bemutattuk a hererákok tüneteit, a here önvizsgálatának helyes módját és a korai felismerés jelentőségét. 1995. április és 1998. április között összesen 5056 férfi jelentkezett a szűrőprogramra, melynek során a releváns anamnesztikus adatok mellett a herék fizikális vizsgálatát és here UH vizsgálatot végeztünk el. Tumor gyanu esetén a megfelelő tumormarket is ellenőriztük.

A talált eredmények közül kiemeljük, hogy nem találtunk daganatot azon betegeink között, akik panaszmentesek voltak, illetve azok között, akinek panasza herefájdalom, nyomásérzékenység, vagy a heréktől független panasza volt. A heredaganatok korai felismerését célzó program adatainak elemzése tehát azt igazolta, hogy tünetmentes betegek szűrése nem vezet új daganatok felismeréséhez; sőt, a felfedezett daganatok incidenciája még a panasszal jelentkező önkéntesek esetén is alacsony, így ezekben a csoportokban a fizikális vizsgálat elégséges az első orvosi vizit során. Heredaganatot csak azoknál a betegeknél találtunk, akiknek a panasza csomó, vagy a here megduzzadása volt. A teljes vizsgált populációban 1.28% heredaganatot találtunk, melyből 4 jóindulatú volt, 2 esetben pedig bilaterális rákot fedeztünk fel. Mivel ez a szám az adott időszakra eső összes daganatnak

csupán 3-4%-a, a szűrőprogram hatékonysága alacsonynak mondható. A felismert daganatok 15 esetben seminomának, 13 esetben nem-seminomának bizonyultak. Egy kivételével mind a jó prognosztikai csoportba sorolhatóak és - az egy magasabb rizikójú, a követésből még a szűrés idején kiesett beteget leszámítva -, mindegyik beteg gyógyultnak tekinthető a szakmai protokollnak megfelelő kezelések befejezése óta.

A program egészségnevelési részét tekintve, nem észleltünk sem a diagnosztikus, sem a terápiás késés szempontjából szignifikáns javulást. A mortalitási adatokban azonban korábbi elemzésünkhöz képest változást észleltünk: a program idejét megelőző 2 évben, a program ideje alatt és az azt követő 4 évben (1993-2002) - egy év kivételével – a legalacsonyabb mortalitási adatok láthatók. Ezt követően lassú emelkedés észlelhető. A kedvező adatok egyrészt magyarázhatók az ekkorra már teljesen befogadott – azidőtájt – legkorszerűbb cisplatin-alapú kemoterápiák hatásával, és egészségnevelési program járulékos hatásával, mely a program befejezését követően még néhány évig eltartott.. Erre való tekintettel az egészségnevelési program folyamatos fenntartása, a here önvizsgálatának a tanrendbe történő beépítése javasolt. A heredaganatok szűrővizsgálatával kapcsolatos legfrissebb, 2010-es nemzetközi irányelvek korábbi megállapításainkat újólag megerősítették.

<u>Új megállapításaink</u>:

1. Az egészségnevelési és szűrőprogram révén a hererák mortalitása csökkenthető volt már a program ideje alatt is és az azt követő években. Mindazonáltal, a heredaganatok korai diagnózisát leginkább a széleskörűen és folyamatosan, a leginkább érintett fiatal férfi populáció iskolai tanrendjének keretében végzett egészségnevelési program révén kell elérni, semmint szűrőprogramok révén.
2. A tünet- és panaszmentes férfiak szűrővizsgálata nem szükséges. Ezt a megállapításunkat a vizsgálat befejezése után kiadott nemzetközi állásfoglalások is megerősítették.
3. A családorvos csak a tünetek és panaszok kiértékelését követően utalja be a beteget részletes urológiai kivizsgálásra. Sürgős here UH vizsgálat kérésére csak hereduzzadás és csomó esetén kerüljön sor.
4. Egyes, magas rizikójú csoportok esetén a rendszeres here-önvizsgálat javasolt, panasz és/vagy tapintható elváltozás esetén here UH vizsgálat elvégzése szükséges.

Összefoglalás – II. fejezet –

A gyulladásos emlőrák diagnózisának és kezelésének újabb lehetőségei

A gyulladásos emlőrák kicsi, de – sajnos – igen rossz prognózisú entitást képvisel az emlőrákok között. Diagnosztikájának és kezelésének alapja a lokálisan előrehaladott irrezekábilis emlőrákok esetében alkalmazott elvekkel megegyező, azonban mind a diagnosztikával, mind a terápiával kapcsolatban számos nyitott kérdés sorolható fel. A dolgozatban megvizsgáltuk, hogy a hagyományos antraciklin-alapú protokollok antraciklin-taxán - esetünkben docetaxel - dublet kombinációjával való felváltása javítja-e a klinikai és patológiai választ, valamint a betegségmentes és teljes túlélést. Bizonyítékot kerestünk arra, hogy a komplett klinikai (és patológiai) remisszió valóban a túlélés javulásával jár együtt. Megvizsgáltuk, hogy a kemoterápiás kezelés felosztása a műtét előtti és a műtét utáni szakaszokra, valamint a kezelési ciklusok számának emelése tovább javítja-e a kezelések eredményességét.

Retrospektív analízisünkben, melyben az 1997. január és 2004. december között felfedezett gyulladásos emlőrákos betegeinket vontuk be, összesen 70 beteg adatait és klinikai kórlefolyását vizsgáltuk a primer szisztémás kezelés megkezdésétől az első progresszióig. A hagyományos antraciklin-alapú neoadjuváns kezelést 48 beteg, míg a TE protokollt 22 beteg kapta. Megállapításaink a következők:

A klinikai remisszió pontos megállapítása döntő a kezelés további menetének megtervezésében. Ezért egyfelől a patológiai CR definíciójának azonosan történő értelmezése szükséges a klinikai vizsgálatok összehasonlíthatósága érdekében. Másfelől, a képalkotó módszerek további javítása szükséges. Eredményeinkből kiemeljük, hogy a klinikai CR gyakorisága a patológiai CR-hez képest háromszoros volt. A patológiai CR-be került betegeink esetében igazolni tudtuk a hosszabb túléléssel kapcsolatos összefüggéseket. Ugyanakkor a két protokoll összehasonlítása során semmiféle érdemi különbséget nem sikerült kimutatnunk, sem a válaszadási arány, sem a túlélési paraméterek szempontjából, akár az egész kemoterápiát preoperative, akár megosztva (preoperative és adjuváns formában) kapták azt a betegek. Eredményeink szerint 6 ciklus kezelés elegendő a klinikai CR-be került betegek számára, de azokban az esetekben, ahol nem észlelünk érdemi klinikai javulást az eredeti protokoll nem-keresztrezisztens gyógyszerekkel való cseréje javasolt.

Összegezve: mivel a hagyományos antraciklin-alapú protokollokat azonos hatékonyságúnak találtuk az epirubicin-docetaxel kombinációval, a továbbiakban ez utóbbiaknál fokozottabb hatékonyságú, un. harmadik generációs, szekvenciális vagy konkomittáló, három vagy négy gyógyszert tartalmazó protokollokat kell alkalmazni a gyulladásos emlőrák kezelésére, illetve az új, molekulárisan célzott terápiákat kell beemelni a protokollokba a hatékonyság, a patológiai CR arány növelése érdekében.

Új megállapításaink:

1. Az antraciklin-tartalmú, docetaxelt nem tartalmazó protokollok a docetaxel-epirubicin protokollal azonos klinikai választ eredményeznek.
2. A patológiai CR-be került betegek túlélési paraméterei tendenciaszerűen hosszabbak, mint a PR-SD-be került betegek, ugyanakkor a két kezelési protokoll között a túlélés szempontjából nem találtunk különbséget.
3. Nincs érdemi túlélési különbség a csak antraciklin-tartalmú és a TE protokoll között akkor, ha csak primer szisztémás kemoterápiaként vagy megosztva, PSCT és adjuváns kezelésként adjuk azokat.
4. A túlélési paraméterek (PFS, LPFS, OS) nem különböznek az alkalmazott kemoterápiás ciklusszám tekintetében, függetlenül attól, hogy a kemoterápiát pre- vagy megosztva, pre- és posztoperatívan adtuk-e.

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Appendix

Early detection of testicular cancer

Appendix 1. : The WHO uses following histologic classification of malignant GCTC.

1. Intratubular germ cell neoplasia, unclassified.
2. Malignant pure germ cell tumor (showing a single cell type):
A. Seminoma
B. Embryonal carcinoma
C. Teratoma
D. Choriocarcinoma
E. Yolk sac tumor
3. Malignant mixed germ cell tumor (showing more than one histologic pattern):
A. Embryonal carcinoma and teratoma with or without seminoma.
B. Embryonal carcinoma and yolk sac tumor with or without seminoma.
C. Embryonal carcinoma and seminoma.
D. Yolk sac tumor and teratoma with or without seminoma.
E. Choriocarcinoma and any other element.
4. Polyembryoma

Appendix 2. : Staging for testicular cancer follows the TNM (tumor, node, metastasis) system:

Primary tumor (pT) – The extent of primary tumor is classified after radical orchiectomy

pTX – Primary tumor cannot be assessed (if radical orchiectomy has not been performed, Tx is used)

pT0 – No evidence of primary tumor (eg, histologic scar in testis)

pTis – Intratubular germ cell neoplasia (carcinoma in situ)

pT1 – Tumor limited to the testis and epididymis without vascular/lymphatic invasion, or tumor invasion into the tunica albuginea but not the tunical vaginalis

pT2 – Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis

pT3 – Tumor invades the spermatic cord with or without vascular/lymphatic invasion

pT4 – Tumor invades the scrotum with or without vascular/lymphatic invasion

Regional lymph nodes – Clinical (N) or pathologic (pN) staging

NX or **pNX** – Regional lymph nodes cannot be assessed

N0 or **pN0** – No regional lymph node metastasis

N1 or **pN1** – Metastases with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension

N2 or **pN2** – Metastases with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension.

N3 or **pN3** – Metastases with a lymph node mass more than 5 cm in greatest dimension

Distant metastasis (M)

MX – Distant metastasis cannot be assessed

M0 – No distant metastasis

M1 – Distant metastasis

M1a – Nonregional nodal or pulmonary metastasis

M1b – Distant metastasis other than to nonregional lymph nodes and lungs.

Appendix 3.:American Joint Committee on Cancer (AJCC) Stage Groupings

The AJCC stage groupings use both TNM staging and serum tumor marker levels. The designation SX indicates that markers were unavailable or not performed; S0 indicates normal levels. The table below defines other S categories.

Stage grouping of serum tumor markers TC

Stage	LDH	HCG (mIU/mL)	AFP (ng/mL)
S1	<1.5 times normal	<5,000	<1,000
S2	1.5-10 times normal	5,000-50,000	1,000-10,000
S3	>10 times normal	>50,000	>10,000

AJCC stage groupings are as follows :

Stage	T	N	M	S
Stage 0	**is**	**0**	**0**	**0**
Stage I	**1-4**	**0**	**0**	**X**
Stage IA	1	0	0	0
Stage IB	2-4	0	0	0
Stage IS	any	0	0	1-3
Stage II	**any**	**1-3**	**0**	**X**
Stage IIA	any	1	0	0-1
Stage IIB	any	2	0	0-1
Stage IIC	any	3	0	0-1
Stage III	**any**	**any**	**1**	**X**
Stage IIIA	any	any	1a	0-1
Stage IIIB	any	1-3	0	2
	any	any	1a	2
Stage IIIC	any	1-3	0	3
	any	any	1a	3
	any	any	1b	any

Appendix 4: .IGCCCG Risk classification

Good- risk NS

Testicular or retroperitoneal primary tumor, **and**
No nonpulmonary visceral metastases, **and**
Good markers; all of:

- Alpha-fetoprotein (AFP) < 1,000 ng/mL, **and**
- ß-hCG < 5,000 IU/mL (1,000 ng/mL), **and**
- Lactate dehydrogenase (LDH) < 1.5 times the upper limit of normal

Intermediate- risk NS

Testicular or retroperitoneal primary tumor, **and**
No nonpulmonary visceral metastases, **and**
Intermediate markers; any of:

- AFP 1,000 to 10,000 ng/mL, **or**
- ß-hCG 5,000 IU/L to 50,000 IU/L, or
- LDH 1.5 to 10 times the upper limit of normal

Poor-risk NS

Mediastinal primary, **or**
Nonpulmonary visceral metastases, **or**
Poor markers; any of:

- AFP > 10,000 ng/mL, or
- ß-hCG > 50,000 IU/mL (10,000 ng/mL), **or**
- LDH > 10 times the upper limit of normal

Good-risk S

Any primary site, **and**
No nonpulmonary visceral metastases, **and**
Normal AFP, any ß-hCG, any LDH

Intermediate-risk S

Any primary site, **and**
Nonpulmonary visceral metastases, **and**
Normal AFP, any ß-hCG, any LDH

Poor-risk S

No patients are classified as poor prognosis.

Appendix 5.: Summary of risk-adapted therapy in GCTC

Treatment group	Active surveillance	Adjuvant radiation therapy	Adjuvant chemotherapy	Comment
Seminoma stage IA, IB	Yes[1]	- 20-30 Gy: PAO/PIL - ± ipsilateral ileoinguinal nodes	- single dose of carboplatin;	CT is alternative to RT
Seminoma stage IS		- 20-30 Gy: PAO/PIL - ± ipsilateral ileoinguinal nodes		
Seminoma stage IIA, IIB	No	- 35-40 Gy: PAO/PIL	- EP^2 4×	
Seminoma stage IIC, III **- good risk** **- intermediate risk**	No	 - -	 - EP^2 4× or BEP 3× - BEP 4×	
Seminoma Stage IIB, IIC, III	After primary Rx	-	- primary CT	
Nonseminoma[3] stage **- IA** **- IB** **- IS**	 Yes / No[4] Yes[5]	 - - -	 - BEP 2× - EP^2 4× or BEP 3×	
Nonseminoma[3] stage **- IIA** with normal tumor markers (TM) **- IIA** with persistent elevation of TM **- IIB** with normal TM + LN metastasis **- IIB** with normal TM + multifocal symptomatic LN metastases - **IIB with persistent elevation of TM**	No	 - - - - - -	 - EP^2 4× or BEP 3× - EP^2 4× or BEP 3× - EP^2 4× or BEP 3× - EP^2 4× or BEP 3× - EP^2 4× or BEP 3×	 **-within lymphatic drainage site by CT** **-with aberrant lymphatic drainage by CT**

Nonseminoma[3] stage **- IIC, IIIA good risk** **- IIIB intermediate risk** **- IIIB poor risk** **- brain metastases** **- IIC, IIIA, IIIB, IIIC post-CT**	No Yes/ No[6]	 - - - - WBRT -	 - EP[2] 4× or BEP 3× - BEP 4× - BEP/VIP[2] 4× /trial - primary CT - EP/TIP[2]/VIP/VeIP[2] 2×	**post-chemotherapy management See[6]**
Recurrent disease and salvage treatment **- with** a favorable prognosis[7] **- with an unfavorable prognosis[8]**	No	palliation	- VeIP/TIP → incomplete: HDCT+ASCT or trial; - trial; HDCT+ASCT; VeIP /TIP; - BSC → third-line: +CPA/IFO; GEMOX[2]	Patients who do not have a CR to first-line therapy, or whose disease recurs after CR.

[1] Recommended for patients with horseshoe or pelvic kidney or inflammatory bowel disease and for those who have received prior radiotherapy; optional in selected T1-2 patients.

[2] EP: etoposide and cisplatin; BEP: bleomycin, etoposide, and cisplatin; VIP: etoposide, ifosfamide, mesna, cisplatin; VeIP: vinblastine, ifosfamide, mesna, cisplatin; TIP: paclitaxel, ifosfamide and cisplatin; CPA/IFO: cyclophosphamide, ifosfamide, mesna; GEMOX: Gemcitabine, oxaliplatin;

[3] Retroperitoneal lymph node dissection (RPLND) is used to guide CT; the number of positive nodes present in the sample determines the number of CT cycles given.

[4] Active surveillance in compliant patients. In case of non-compliance patient should be offered RPLND within 4 weeks of the CT scan. If RPLND results are negative, no adjuvant CT is recommended. If RPLND results are positive, adjuvant CT is recommended.

[5] Active surveillance for compliant patients who have T2 disease without any vascular invasion.

[6] In case of CR, options are surveillance or open nerve-sparing RPLND. If residual disease is present but TM levels are normal, all the residual disease should be resected. If the resection specimen shows only necrotic tissue or teratoma, no further therapy is recommended and active surveillance should be done. If residual embryonal, yolk sac, choriocarcinoma, or seminoma elements are present, the patient should receive 2 cycles of CT with EP, TIP, VIP, or VeIP. Patients who do not have a CR to CT and/or whose disease cannot be resected should receive salvage CT.

[7] Favorable prognosis: Patients with low TM levels, low-volume disease, complete response to first-line CT, and testis primary.

[8] Unfavorable prognosis: Patients with an incomplete response to first-line CT, high TM levels, high-volume disease, extratesticular primary, and late relapse

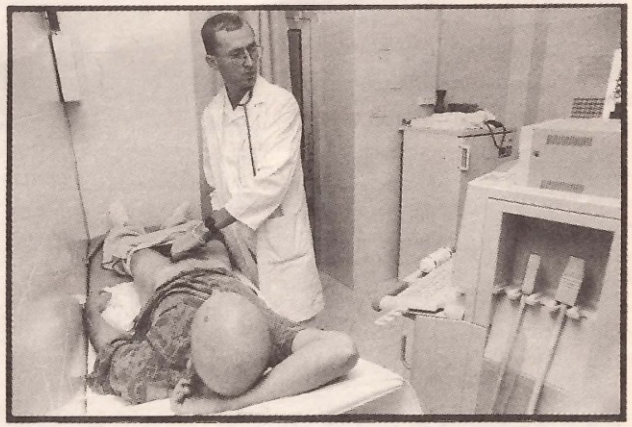
A rosszindulat ellen

Simon ma huszonkét éves lenne, ha mert volna beszélni arról, hogy egyik heréje kétszeresére duzzadt meg. De nem mert. A hozzá legközelebb állók előtt is eltitkolta e rendellenességet, úgy érezte, férfiassága számára mérhetetlen csapás lenne, ha kiderülne titka. Egy év alatt elvitte a rák.

A történet annak az angol oktatófilmnek a bevezetőjében hangzik el, ami a kevéssé ismert, ám jellegét és lefolyási idejét tekintve annál veszélyesebb betegségről szól. Egy yorkshire-i felmérés szerint az Egyesült Királyságban leggyakrabban a 15 és 40 év közötti fiatalok körében jelentkezik a kór; évente 900 férfi esetében jelennek meg tünetei: a here kismértékű megnagyobbodása vagy a benne kitapintható csomó jelentkezése. Tíz beteg közül csak egy érez fájdalmat a herében, sokszor csak annak húzódását, megnagyobbodását észleli. A következő stádiumban az alhasban görcsös tünetek jelentkeznek, s leggyakrabban ez vezeti el a megriadt férfit az első rendelőig. A felmérés kimutatta, hogy a minimális késlekedés is emberéletet követel.

A film az „önvizsgálati módszer" bemutatására vállalkozott, a szakértő szerint havonta egyszeri, egy percig sem tartó tapintásos ellenőrzéssel idejében észlelhető a baj, s azonnali orvosi beavatkozással könnyen lokalizálható a betegség. (A fürdés utáni önvizsgálatot ajánlják, mivel ekkor nemi szervünk lágyabbá válik ezen a tájékon.)

A magyarországi tapasztalatok az egészségkultúra jelenlegi viszonyai közepette sejthetők. A film például 1987-ben videókazettán eljutott a szakma vezető intézeteihez és az Állami Nemzeti Tisztiorvosi Szolgálat – akkoriban még Köjál volt a neve – összes megyei hivatalához, hogy azok továbbküldhessék az iskoláknak, szakorvosoknak. Utóbbi lehetőség máig adott. Az 1986-os madridi orvoskonferencián szerezte meg a filmet ingyen – kizárólag oktatási, s nem üzleti céllal – dr. Bodrogi István, az Országos Onkológiai Intézet Kemoterápia C osztályának vezető főorvosa, aki szerint számos nyugati ország iskoláiban tananyagként vetítik le. A téma hazai mérsékelt publicitásában közrejátszhatott, hogy a monopolhelyzetben lévő elektronikus médium vágatlan formában nem akarta bemutatni az anyagot, melyben meztelen férfi modellálja az önvizsgálati módszert.



Fotó: Lukács Dávid

Az onkológiai intézet most újabb kampányt indít, mivel az Országos Egészségbiztosítási Pénztártól pályázat útján ultrahangkészüléket kapott, mellyel a daganat tapinthatóvá válása előtt is ki lehet szűrni a betegséget. A főorvos arra számít, hogy a fájdalommentes és ingyenes vizsgálatnak – melynek költségeit az intézet állja, a magánszektorban ára 5-6000 forint – a fiatalok nagy számban vetik alá magukat. Megerősítette, hogy a hererák a daganatos megbetegedések közül az egyik legkönnyebben gyógyítható. Ha a tünetek jelentkezése előtt felismerik, a gyógyulás teljesen biztos, előrehaladott stádiumban azonban csak az esetek egyharmadánál tudnak maximális eredményt elérni, de csak egymásfél éves intenzív gyógyszeres és/vagy sugárkezeléssel, aminek komoly mellékhatásai vannak. Hazánkban a megbetegedett férfiak száma tízévenként megduplázódik, átlagéletkoruk 27-28 év között van, de nem ritka a 16 év körüli diagnózis sem. A 15 és 35 év közötti korosztály esetében az összes daganatos betegség előfordulási mutatóit tekintve a hererák a harmadik leggyakoribb rosszindulatú daganatos betegség.

„A beteg a beavatkozással másodlagos nemi jellegét tekintve nem szenved maradandó károsodást, minden lehetőség adott, hogy utána teljes életet éljen; egy here is elegendő spermiumot termel a fogamzáshoz" – mondja dr. Bodrogi István arra a kérdésre, hogyan tudják a páciensek tartós lelki sérülését elkerülni. Így a házaséletben sem következik be törés.

A hererák kiváltóokai nem ismeretesek a kutatók számára. Megelőzése lehetetlen, minél gyorsabb felismerése létérdek.

- somos -