Early detection and treatment of certain malignant tumors

dr. Zsolt Horváth

Ph. D. Thesis

National Institute of Oncology

Department of Chemotherapy B and Clinical Pharmacology
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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, germ cell testicular cancer (GCTC) have become an excellent testing ground for active experimental drugs. TC has been a model for multidisciplinary care, as close cooperation between professional areas do improve the cure rate. TCs are highly curable: cure rates for good-risk disease are 90-95%, and significant even in patients with metastatic disease at diagnosis. 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.

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. 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. Poor public awareness of the disease and lack of TSE may account for late presentation. According to statistics, the delay from initial symptoms to definitive diagnosis by radical orchiectomy has averaged 4 to 5 months.

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. Disseminated disease have symptom of lymphatic or hematogenous spread. 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 (TUS) usually confirms the diagnosis, and helps distinguish between TC and other intrascrotal pathologies. The tumor tissue type cannot be reliably differentiated solely by its ultrasonographic appearance, but certain characteristics could draw the attention on seminomas (S) or nonseminomas (NS). 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.

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. Moreover, the availability of reliable tumor markers (AFP, ß-hCG, LDH) has greatly facilitated the management of GCTC. 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).

Various staging systems have been used to classify and subsequently manage patients with TC. Staging based on the TNM and the AJCC staging system, that were integrated with risk classification as well by the IGCCCG classification system. 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.

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. The main goal of the rationalized the risk-adapted treatment policy 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. 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).

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 by the analysis of the figures of TC found;
2. results after the changes in delay in the diagnosis of TC;
3. changes in mortality in TC.

3. Patients and methods

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

- physical and
- US examination of the testicles and

- 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.

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. 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. 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. 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. 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.

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%).

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. 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)

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. 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).

The volunteers 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.

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.

Table 1. 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

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.

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	

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. 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%. Among the 26 men with GCTC, 19 stage I. tumors were detected. 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 all patients were cured.

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, suggesting a greater awareness of the need for treatment, especially among stage III patients.

The data shows that there were a clear decrease between 1985-1994, 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.

5. Discussion

The results of the early detection program confirm that the screening of asymptomatic patients does not necessarily lead to the detection of tumors, 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.

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 high specificity of both swelling and lump for TC, the sensitivity 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. 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 other authors. 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".The National Cancer Institute (NCI) notes 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." 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 in Hungary 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.

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.

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 –in line with the NCI statement - the use of early TUS 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 It has been pointed out that school nurses are in an ideal position to promote awareness of TC and TSE to adolescent men.

6. Thesis

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.

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

1. Introduction

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. Principles of diagnosis, treatment and follow-up of primary BC are based on well-accepted guidelines (Hungarian, ESMO, NCI, NCCN, St. Gallen Consensus). Locally advanced breast cancer (LABC) is defined as stage III disease: Stage IIIA (T3N1M0) patients are considered to have resectable LABC, whereas all other LABC is considered irresectable. Inflammatory breast cancer (IBC) as the third group of LABC defined as T4d disease.

Primary systemic chemotherapy (PSCT) –or neoadjuvant CT - is performed prior to BC surgery. It offers several advantages over standard postoperative CT, however, PSCT with classical drug of choice does not offer any survival benefits over postoperative CT to date.

IBC is the most aggressive form of BCs comprising 1-6% (most often 2-3%) of all invasive BC cases and had statistically significantly poorer 5-year disease-free survival than women with either LABC or non-T4 breast cancer. 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

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*, particulary achieving pathological complete remission (pCR) dominantly determines survival. The multidisciplinary management of IBC includes PSCT and radiotherapy (RT). In case of achieving resecablility surgery (ST) must be

performed, followed by an appropriate adjuvant treatment. An anthracycline-based (A+) regimen in combination with concomitant or sequential taxane is the standard PSCT recommended for the treatment of LABC .

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. It is not quite clear, that in case of achieving resecablity 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 given them pre- and postoperatively and survival parameters?
4. Which prognostic and predictive factors can predict the probable efficacy of PSCT?

3. Patients and methods

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 US were performed. State of malignancy was set by aspiration cytologies and/or core biopsies as well. Routine staging examinations revaled distant metastasis in 8 patient so they were dislosed 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[1]. At least, we could analyse the data of 70 patients from the point of PSCT.

In case of the evaluable 70 patients the following PSCT protocols were used: FAC/FEC or AC (, or CEF; these protocols further designated as A+. TE protocol consisted docetaxel epirubicine. Postoperative adjuvant chemotherapies were the above-mentioned A+ and TE protocols, as well as the TC (docetaxel and carboplatin) or CMF (protocols. For the improvement of local control, preoperative radiotherapy (RT) could be applied after PSCT by the physician's individual pre- or peri-treatment decision. Course of pre- and postoperative RT techniques, chemo-, endocrine and anti-HER2-treatments were in accordance with accepted institutional practice and clinical guidelines.

Table **1.** Description of patient population

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

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. Definition of other response parameterswere identical to RECIST-criteria. 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.

Progression-free survival (PFS) and overall survival (OS) was defined as time from starting PSCT until progression or death from any cause. Censoring

[1] Data of these 4 patients were only considered in PSCT + adjuvant CT in the combined analysis.

time for living patients was 01.09.2008. or the last contact closest to this date. Time to locoregional progression, named LPFS, was defined as time from starting chemotherapy to first local recurrence of breast cancer in the mentioned areas.

Statistical analyses were conducted with using Statistica® 7.1 software (StatSoft® Inc., Tulsa, OK, USA). Descriptive stastistics,matched pair univariate analysis (Pearson's $\chi 2$-test were performed on qualitative data. For quantitative data we used Wilcoxon's rank sum test and Kruskal-Wallis test. Non-parametric comparisons between two groups were made with Mann-Whitney U-test and log-rank 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. p of 0,05 or lower was considered statistically significant.

4. Results

1. Comparing the anthracycline-containing, but docetaxel non-containing PSCT with the docetaxel-epirubicine PSCT protocol in terms of 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 2. Detailed results comparing the two types of PSCT can be seen on Table. 3.

Table **2.** 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 **3.** 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 (5 pCRs were seen on the non-taxane arm vs nil on the TE arm), however the objective RR and the clinical benefit were not different.

2. Relationship between response to PSCT and survival parameters

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. 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.

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. 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; $\chi 2$=1.13; p=0,29), and without BC or relapsed (A:15/33 vs. TE: 8/14; $\chi 2$=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 were identical in both arms.

Table **4.** 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)

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.

3. Relationship between response to PSCT and adjuvant CT and survival parameters

Fourty-one patients recieved postoperative andjuvant CT and 33 did not[2]. Three patients were excluded from the analysis: 2 recieved TC pre- and postoperatively, and 1 recieved CMF as PSCT, but nil postoperatively. Two groups were formed: in the first group pateints recieved only A+ protocols (N=43; 60,56%); in the second they recieved both anthracycline and taxane (docetaxel) (N=28; 39,44%). However, in the further statistics, we did not take 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 then 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).

Table 5. 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

At the censoring time, proportion of patients dead or alive (A+:27/16 vs. TE: 22/6; $\chi 2$=1,77; p=0,16), and without BC or relapsed (A+:13/30 vs. TE: 10/18; $\chi 2$=0,23; p=0,63) was not different. There was no comparisons which demonstrated any significant difference between the two types of PSCT. Similarly, median overall survival and 3 year survival rates were identical in both arms.

4. Effect of PSCT or PSCT *and* adjuvant treatment cycles given on survival parameters

Most patient 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

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

same survival parameters, than those who had 6 cycles or more: PFS: $\chi 2$= 5.28, p=0.15; LPFS: $\chi 2$=1,15, p=0.77; OS: $\chi 2$=4.01, p=0.26.

5. Discussion

1. Introduction of doxorubicin-based chemotherapy significantly improved results in IBC. 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. Changing 5FU to taxane (i.e. TEC vs. FEC) in the third generation concomitant protocol, showed further significant improvement in the neoadjuvant therapy of operable breast cancer. Despite these observations, we could not detect significant difference between the A+ and TE protocols, in terms of clinical response parameters. An unexpected elevation was seen in pCR rate after A+, probably that is due to statistical terms.
2. The problem of clinical response evaluation is reflected in the observed difference in cCR and pCR. Definition of pCR has profound effect on further clinical decisions. We found, that cCR was approximately three-fold higher, than pCR in our patient population, that may reflect the definition of pCR. Other studies demonstrated less (approximately 1,5-2-fold) or the same differences.

Achieving resecability leading to longer survival is the key point in the management of IBC, so the most effective protocols must be chosen.. 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. The median survival of our patients achieved pCR is one year longer than patients reaching only cCR. We could also confirm, that achieving pCR renders a greater probability of longer PFS and LPFS, but not significant tendency in OS data. Comparing the taxane non-containing protocols to concomitant TE protocol in our study, response rates and survival data were equivalent. 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, that could explain the unexpected lower response and survival rates on TE arm was the higher PR content in this group.

In a further analysis, we practically could not demonstrate any meaningful difference between A+ and docetaxel-containing protocols irrespectively given them as PSCTor split them pre- and postoperatively. The practice in which therapeutic decisions – i.e. continue or change the inital protocol - based on the early response, were evaluated in different trials and the results were conflictingDividing the CT into pre- and postoperative parts also seems to be equally effective. This setup has slightly improved the relapse-free survival on non IBC population, but it was not demonstrated in IBC series so far.

Overall, in our selected IBC patient group, we did not detect any meaningful differences between A+ and the concomitant TE protocols suggesting, that we

should utilize a more intense third generation concomitant or sequential taxane-antracycline regimens with integrating novel targeted therapies.

3. Concerning to the question of cycle numbers: results of the studies that are in line with this field are non-equivocal. More cycles of CT was an independent predictor of pCR in ABCSG-14 trial. 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 has not IBC. – 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) of CT could be enough for patients achieving cCR. However for patients not achieving cCR after 3-4 cycles of PSCT, following decision making should make on changing the original PSCT to a non-cross-resistant one. This can be given either PSCT or splitting as pre-and postoperative treatment. This approach could serve better the patient's interest, than using a fixed 6 cycles of PSCT.

6. Thesis

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.

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