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Breast cancer update – analysis of knowledge of Brazilian breast surgeons

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Background: Nowadays the medical knowledge is developing fast. Because of that, there are always need for education events like congresses and meetings. However, the degree of knowledge of the participants of these events is not usually known. In this enquiry, the authors provide a panorama evaluation of the participants of one of the largest brazilian's breast congresses. The questions were compared to international guidelines.

Material and Methods: During the 3rd São Paulo Breast Congress about 600 questionnaires were distributed between the participants. The questions were about general concepts of breast cancer, including conservative surgery, diagnosis and sentinel node biopsy. 234 people have answered them. Of these 60.6% were breast specialists (BS) and 39.4% were gynecologists (G) who also perform breast surgery.

Results: The percentages of right answers are shown in the table.

Question	Correct answers		
	Total	Breast Specialist	Gynecologist
Conservative breast surgery	80.8%	81.7%	76.3%
Diagnosis	83.9%	84.2%	83.4%
Sentinel node biopsy	79.5%	80.6%	77.9%

It was also possible to notice that 46.8% of the interviewed physicians consider that there is a size limit to perform conservative breast people (39.7% of BS and 39.1% of G). Most of them use blue dye to perform sentinel node biopsy (43.8%), don't perform oncoplastic surgery (62.7%), 17.2% don't perform sentinel node biopsy and 95.9% order MRI before conservative surgery in special cases.

Conclusion: Most of the physicians who were in the congress answered the questions according to the international guidelines. There wasn't a clear difference between the groups of specialists and gynecologists. After analyzing these data we conclude that it is important to have more educational events in breast surgery, mainly in the area with higher percentage of mistakes.

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Proposal for using an international unified draft for chemotherapeutic regimen time schedule table: Chemo Box

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Most cancers require surgery and adjuvant therapy for an effective treatment. Early detection of cancer, development of standardized supplementary therapy, and the standard of treatment for cancers have all improved recently. In fact, continuous development of new anti-cancer chemotherapeutic agents is constantly improving the survival rate of cancer patients. The characteristics of cancer cells are in such a way, the composite use of anti-cancer medicines increases the effect of a treatment.

However, chemotherapy used in the current anti-cancer treatment consists of many medications and various recipe methods. Many authors and pharmaceutical companies are describing a variety of meanings in their articles and books. On the other hand, many cancer societies are announcing leaning toward the standardization of treatments and are providing guidance on the appropriate regimen for various types of cancer in an attempt to increase the effectiveness of treatments, and to increase the quality of medical managements. However, authors and cancer societies use their own notations and are yet to standardize any formats to mark the various anti-cancer chemotherapies. In future, combination of methods for administration of treatment can increase further with the development of more anti-cancer medicines.

Therefore, means to mark different kinds of anti-cancer medicines and an individual cycle will be necessary. The author proposes an anti-cancer chemotherapy notation scheme (called Chemo Box) as a simple table containing standardized notation as shown below for example of TAC regimen. This notation scheme may give direct assistance to patients receiving anti-cancer chemotherapy in addition to hospital staff and medical workers who are involved in the actual treatment process. It may also assist people learning to use the anti-cancer therapy. Many examples are presented to illustrate the usefulness of the proposed notation system.

TAC	mg/m^2	1 1	2 8	3 15	4 1	5 8	6 15	7 1	8 8	9 9	10 1	11 8	12 15	13 1	14 8	15 15	16 1	17 8	18 15
T Docetaxel	75	*			*			*			*			*			*		
A Doxorubicin	50	#			#			#			#			#			#		
C Cyclophosphamide	500	@			@			@			@			@			@		

Day 3: Start prophylactic G-CSF & antibiotics.

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Biological response and outcome

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The effect of body mass index (BMI) on disease-free and overall survival in node-positive breast cancer treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: the experience of the BIG 02-98 trial

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Background: Approximately 20% of cancer deaths in women are associated with obesity, which is also an indicator of poor prognosis for patients with primary breast cancer (BC) even after systemic therapy.

Material and Methods: This is a retrospective analysis of 2,887 node-positive BC patients enrolled in the BIG 02-98 adjuvant trial, a randomised phase III trial whose primary objective was to evaluate disease-free survival (DFS) by adding docetaxel to doxorubicin-based chemotherapy (CT) (J Natl Cancer Inst 2008; 100: 121–133). Our study evaluated the effect of BMI on DFS and overall survival (OS). BMI was obtained before the first cycle of CT. Obesity was defined as a BMI $\geqslant 30\ kg/m^2$. Cox model and Log-rank tests were used to compare DFS and OS between obese and non-obese patients.

Obese vs non-obese

Subgroup	DFS (HR)	Interaction P value	OS (HR)	Interaction P value
ER and/or PgR positive	1.29	0.79	1.46	0.91
ER and PgR negative	1.22		1.42	
1−3 positive nodes	1.22	0.94	1.44	0.91
$\geqslant$4 positive nodes	1.24		1.40	
Premenopausal	1.30	0.99	1.68	0.69
Postmenopausal	1.24		1.26	
Age <50	1.37	0.52	1.96	0.022
Age $\geqslant$50	1.22		1.15	

Results: In total, 547 (19%) patients were obese at baseline while 2,340 (81%) patients were non-obese. Estimated 5-years DFS was 75.9% for non-obese and 70.0% for obese patients (HR 1.29; 95% CI 1.08−1.52; P = 0.005). Estimated 5-year OS was 87.5% for non-obese and 82.9% for obese patients (HR 1.48; 95% CI 1.18−1.85; P = 0.0007). These differences were also evident when the population was divided according to the 5 subgroups WHO criteria (trend log-rank test P = 0.004 for DFS and P = 0.00002 for OS). The detrimental effect of obesity on OS was greater for younger patients than for older women (see table). The effect of the docetaxel versus no docetaxel appeared to differ between obese and non-obese patients for OS (HR 1.28 and 0.83, respectively, interaction test = 0.087) but not for DFS (HR 0.96 and 0.84, respectively, interaction test = 0.49).

Conclusions: In this study, obesity was associated with poorer outcome in node-positive BC patients. The role of CT dosing and/or patient co-morbidities in obese patients is currently being studied. Given the increasing prevalence of obesity worldwide, more research on improving the treatment of obese BC patients is needed.

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Relevance of histological and molecular subtypes in the outcome of primary systemic therapy for operable breast cancer

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Objective: To analyse the relevance of histological subtypes, ductal versus lobular, and molecular subtypes using immunohistochemical profiles: luminal (estrogen-receptor positive and HER2-negative), basal (hormone receptor and HER2 negative) and HER2 positive, in the outcome of primary systemic therapy (PST).

Methods: Retrospective analysis of 254 patients treated with PST between 2000 and 2007 in the Netherlands Cancer Institute. Inoperable patients (T4, N3) were excluded. The majority of patients (70%) were initially treated with doxorubicin and cyclophosphamide and participated in two randomized studies in which antracycline and taxane based regimens were compared. Since 2005 HER2-positive patients received chemotherapy in combination with trastuzumab. The type of surgery feasible prior to neoadjuvant chemotherapy was compared to the actual surgery performed. Pathological complete remission (pCR) was defined as no evidence of invasive cancer in either breast and axilla.

Results: The increase in BCT was 32% (63/195) in patients with ductal carcinoma, and 17% (7/35) in patients with lobular carcinoma. Secondary mastectomy was required because of irradical resection in 2% and 33%, respectively. The pCR rate in ductal and lobular carcinoma was 12% and 2%, respectively. The overall pCR rate was 11%. The pCR rate in luminal, basal and Her2 positive patients treated with trastuzumab was 2%, 28% and 35%, respectively. Multivariate analysis indicated that molecular subtype was the only independent predictor of pCR. (P 0.004).

Conclusion: There is a clear difference in tumor response and surgical downstaging between histological and molecular subtypes. This result provides us another argument to select patients for PST on the basis of these subtypes in future trials.

		N	pCR	P value	Odds Ratio	95% CI
Age	<45 yrs	137	22	0.31	R	
	>45 yrs	114	7		0.42	0.077−2.27
Menopausal status	post	59	3	0.56	R	
	pre/peri	187	26		1.87	0.23−15.3
Histology	lobular	42	1	0.69	R	
	ductal	195	23		1.61	0.16−16.11
Molecular subtype	luminal	138	3	0.004*	R	R
	basal	57	16	0.01*	14.8	2.79−78.4
	Her2+	56	10	0.06	11.9	2.28−63.6
pN category prechemo	N1	169	13	0.10	R	R
	N0	43	13		3.07	0.95−9.94
T category	T1	12	2	0.27	R	R
	T2	151	19	0.76	0.33	0.04−2.76
	T3	88	8	0.11	0.16	0.02−1.62

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Systematic validation of novel breast cancer progression-associated biomarkers via high-throughput antibody generation and application of tissue microarray technology

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Background: There now exist vast quantities of DNA microarray data defining differences in gene expression between different subtypes of breast cancer, including variations in invasiveness and metastatic capabilities. However, this type of genetic assay is of limited prognostic or predictive value in most clinical settings due to general requirements for fresh/frozen tissue. The aim of this project is to translate the genetic data available into a more clinically relevant form – that of immunohistochemistry – identifying from these gene datasets any independent biomarkers that may be potential biomarkers and/or drug targets.

Materials and Methods: Our approach involves the high-throughput validation of the affinity-purified, mono-specific antibodies created by the Swedish Human Proteome Resource (SHPR, www.proteinatlas.com) against candidate breast cancer progression-associated biomarkers selected from publicly available and in-house transcriptomic and proteomic datasets. Initial validation of these antibodies was performed by the SHPR using a variety of normal and cancer tissues. Of the 137 targets selected for production, 32 have begun specificity validation by Western blot analysis. Those that are successful are moved forward to immunohistochemical (IHC) validation using cell pellet arrays derived from different human breast tumour cell lines. Successful IHC validation leads to the use of tissue microarrays (TMAs) of clinical samples to assess the clinical relevance of the putative biomarkers, either individually or as a panel. For efficient validation of the candidate biomarkers a TMA is being used, constructed from a cohort of 512 consecutive breast cancer cases diagnosed between 1988 and 1992.

Results: PDZK1, an estrogen-responsive gene, was previously found to be associated with good prognosis (interval to distant metastasis) at the transcript level in breast tumours. Our TMA IHC results showed PDZK1 protein to be associated with improved breast cancer-specific survival ($p = 0.0247$), ER positivity ($p = 0.041$) and low grade ($p = 0.002$). Another promising putative biomarker undergoing validation according to this schema is PDZ-binding kinase (PBK).

Conclusion: We have developed a comprehensive biomarker pathway that extends from discovery through to validation on TMA and is yielding clinically relevant biomarkers.

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Down regulation of angiogenesis antagonist EFEMP1 is associated with unfavourable prognosis in sporadic breast cancer patients

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Background: EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1) was recently described to be an angiogenesis antagonist and to act as a suppressor of formation and progression of human malignancies.

Materials and Methods: Immunohistochemistry on tissue microarrays of 203 clinically well characterized primary breast carcinomas was used to assess the potential clinical relevance of reduced EFEMP1 protein expression regarding patient outcome. Cox regression for multivariate survival modelling as well as univariate analyses were performed. Next to immune reactivity score for EFEMP1 expression, tumor grade, hormone receptor status, lymph node status, Her-2 status, tumor size, and type of adjuvant systemic therapy were included into analysis.

Results: Multivariate regression analyses in the 186 node-positive cases revealed that next to tumour size and grade EFEMP1 expression remained in the survival model as relevant factor influencing disease-free- and overall survival at borderline significance (DFS: $p = 0.14$; OS: $p = 0.077$). Further analysis of patient subgroups with homogeneous adjuvant systemic therapy revealed a significant correlation of low EFEMP1 expression with poor DFS and OS survival ($p = 0.037$ and $p = 0.032$) only in those node-positive patients who had received adjuvant anthracycline-containing