Estrogen and Progesterone Receptors (ER and PR) Status of Breast Cancer Cases in Kurdistan and Their Correlation with Pathologic Prognostic Variables

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Abstract

Background: breast cancer shows different clinico-pathological features according to geographic and ethnic groups' variation. The ER and PR positive status is an indication that the patient is a good candidate for hormone therapy. Furthermore, the high percentage and intensity of ER and PR positive cells are important predictive markers for this cancer.

Aim To assess breast cancer-specific features for patients diagnosed in the north of Iraq and to assess the hormone receptors status and their relation to other pathological prognostic factors.

Patients and Methods: This study included 324 breast cancer cases diagnosed and reviewed by histopathology in the central lab of Duhok/ Iraq, from May 2007 to March 2012. Immunohistochemical markers were used to identify the ER and PR status and scoring according to Allred scoring guideline.

Results: About 68.2% of the patients included in this study were younger than 50 years. Most of them presented at stage II and III. Negative stain for ER was seen in more than half of the patients. The score proportion was decreasing with the increase in the stage, but the correlation was statistically insignificant; on contrary the correlation of ER and PR scoring with lymph node involvement was statistically highly significant

Conclusion: The young onset of breast cancer among Kurdish patients, the high stage at first presentation and the relatively high percentages of hormone insensitive cancers in both young and old patients could be attributed to the genetic predisposition modified by the revolution in life style and required additional study and analysis.

Key words: Immunohistochemistry, ER, PR, Breast, Cancer, Prognosis

الخلاصة

يشكل سرطان الثدي مشكلة كبيرة للنساء ويظهر تتغيرا في صفاته بحسب التغير الجغرافي والعرقي ، وللمُستقبِلات الهرمونيه للاستروجين و البروجسترون و لشدة ايجابيتها دور ليس في التنبئ بتطورالمرض فقط بل في التنبئ باستجابة المريض للهرمونات العلاجيه

تهدف الدراسة الحالية الى التعرف على مميزات حالات سرطان الثدي عند المرضى المصابين في شمال العراق مع دراسه مناعيه للمُستقبِلات الهرمونيه للاستروجين و البروجسترون و علاقتهم بالمميزات الأخرى في سرطان الثدي.تم جمع ٣٢٤ عينه من مرضى مصابين بسرطان الثدي من المختبر المركزي في مدينة دهوك و مستشفيات أربيل و السليمانيه منذ مايس ٢٠٠٧و حتى آذار ٢٠١٢. لقد تم تحليل صفات السرطان من نواحي مختلفه مع التركيز على درجة تميزه ، مرحلة الورم ، انتشاره في العقد اللمفاويه. وتم استخدام النسيج المُضَمَّن في البرافين لقياس المُستقبِلات الهرمونيه للاستروجين ، البروجسترون وشدة ايجابيتها

النتائج: أضهرت الدراسه أن حوالي ٦٨.٢% من المرضى في هذا البحث كانوا بعمر يقل عن الخمسين ، كما أن معظمهم كانوا في مرحله متطوره نسبيا (المرحله ٢ و ٣) **و** بدرجة تمييز قليله .كانت المُستقبِلات الهرمونيه ذات نتائج سلبيه في اكثر من نصف الحالات، ولوحظ أن شدة الصبغ المناعي كانت تتناقص مع تقدم مرحلة الورم . لقد ارتبطت بعلاقه ذات مغزى احصائي مع الانتشار في العقد اللمفاويه، وكانت عاليه في درجة التمييز العاليه

نستنتج من هذه الدراسه أن سرطان الثدي سجل بأعمار صغيره مقارنة بالدراسات من بعض مناطق العالم العربي، وأصغر بكثير من الدراسات من العالم الغربي. ان الاعمار الصغيره نسبيا بالاضافه الى النسبه العاليه من التشخيص الأولي بدرجة تميز قليله و في مرحله متطوره و نسبه متدنيه من المُستقبِلات الهرمونيه للاستروجين و البروجسترون قد يعزى الى تأثيرات جينيه معدله بتأثيرات انماط الحياة المعاصره وتحتاج الى المزيد من التحليل و الدراسه.

Introduction

Breast cancer, the most terrifying cancer for females, is the commonest malignancy and the second leading cause of cancer death in women. [1] Since the discovery of the ER and PR in 1950s, the ER, and to a lesser extent PR, have become important prognostic and predictive markers for breast cancer. [2] They act as DNA-binding transcription factors and regulate the activity of different genes mediating breast cell proliferation and DNA replication leading to mutations. [3, 4] Survival and response to hormonal therapy such as tamoxifen or aromatase inhibitors are most favorable among patients with hormone sensitive cancers. [5] The advance in the production of monoclonal antibodies and in antigen retrieval methods has greatly improved the detection of ER/PR in sections from formalin-fixed paraffin imbedded tissue.[6] Many investigators shed light upon the importance of using one of the semiquantitative immunohistochemistry (IHC) methods (Allred-score, Q-score, or an H-score like method) [7] because large amount of information is lost when one labels a tumor as a mere ER positive one.

Although IHC scoring of ER and PR is recommended by the American Society of Clinical Oncology to guide breast cancer treatment, [8] unfortunately, inter-laboratory variability and diversity in IHC assessment are relatively high in clinical practice. Rhodes et al showed that in hormone sensitive cancers about 73% of laboratories demonstrate mere ER positivity, and only 27% demonstrate the ER low-expressing tumors. [9, 10] Epidemiologic studies have shown that the hormone sensitive cancers are associated with other indicators of favorable prognosis include; low-grade, negative nodes, [11] low S-phase fraction, normal complement of DNA and low proliferative index, [7] in addition to other variables like older age, white (vs. black) race, and nulliparity. [12] According to our knowledge this is the first wide research on breast cancer cases and hormone status in Kurdistan.

Patients and Methods

This study was conducted from the first of May 2007 to the first of March 2012 and included 324 patients diagnosed and reviewed in the central lab of Dohuk as patients having breast cancer. Cases were referred from Dohuk, Arbil and Sulaymani for diagnosis and to assess the hormonal status of cancer. The breast cancer was classified histologically according to the World Health Organization classification, [13] graded using the Bloom-Richardson grading system [14] and staged according to American Joint Committee on Cancer Staging. [15]

The paraffin embedded blokes (PEBs), containing representative breast cancer tissue, were used to perform immunohistochemical analysis for ER and PR according to the Avidin Bioin Complex (ABC) detection system.[16] Sections of 4 microns thickness, obtained from the PEBs, placed on positively charged slides, together with adjacent parallel control sections, were processed with each set of staining for the IHC. Primary and secondary antibody kits

were used, provided by the DAKO Company detected with the Envision+ system that employs peroxidase-labeled polymer conjugated to anti-mouse immunoglobulin antibodies. Immune complexes were identified by using a peroxidase reaction with DAB+ as chromogen.

The IHC scoring was assessed by examining 100 malignant cells (at X 40 objective) according to Allred scoring guideline by assessing the proportion score (PS) and intensity score (IS) as follow.

PS	0	1	2	3	4	5
	0	> 0 to 1/100	> 1/100 to 1/10	> 1/10 to 1/3	> 1/3 to 2/3	> 2/3 to 1
IS	0	1	2	3		
	Negative	weak	intermediate	strong		

A total score (TS) = sum of PS and IS (0 or 2 – 8). A positive result is defined as TS = or > 3 which was validated in numerous studies. [17, 18]

Results

In this study only 8 out of the 324 breast cancer cases were males (2.5%), all the rest cases were females (97.5%). The age ranged from 19 to 72 years, with a mean age of 46.8 years. About 68.2% of the patients were younger than 50 years (table1). Histopathological analysis revealed that non invasive carcinoma was found only in 2.5% of the patients, representing stage 0, while infiltrating carcinoma were reported in the majority of patients (97.5%); among them infiltrating ductal carcinoma comprises the commonest type (89.5%), followed by infiltrating lobular carcinoma (5.9%). Other types including mixed infiltrating ductal and lobular carcinoma, medullary carcinoma, papillary, mucinous and tubular carcinoma reported in lower percentages. The results of tumor grading showed that 25.9% of cases were in grade I, 38.3% were in grade II and 35.8% were in grade III (table2). The TNM staging revealed that stage 0 formed only 2.5% and most of the patients included in this study (83.9) presented at stage II and III (table4). Axillary lymph-node could not be assessed (Nx) in the 64 cases. In 260 cases the lymph node involved in 37.1% of patients (table5).

The association of the ER score with the age is seen in table 1. Negative stain for ER (which is also considered as score 0) was seen in more than half of our patients (51.9), and in 44.4% for PR stain. Among the negative ER cases, 67.3% were younger than 50 years. A similar interpretation can be given for PR results with slight ineffective differences form ER results.

Regarding the grading; positive hormonal receptors status were significantly high in grade I only (Table 2). For scoring of ER and PR there were increase in percentages of patients in grade I with strong staining, (Table 3) but unlike the results in(table 2) there was no statistical significant for the score in this observation.

Table 4 analyzes the association of ER and PR scoring with the stage of the tumor. The percentage of total score proportion is decreasing with the increase in the stage. The decrease is more obvious in strong staining (44.4% - 39.5% – 8.4%). To a lesser extent, the PR scoring had a slight decrease with the increase in the stage. But these figures were

statistically insignificant for both ER and PR.

The correlation of ER scoring with the lymph node involvement was statistically highly significant in most of the scoring ($p<0.005$). Negative ER staining was seen in 80 out of 120 cases with positive lymph node and only 8 patients with positive lymph node show strong ER score. The same association was seen in PR hormonal receptor scoring and lymph-node involvement (Table 5)

Discussions

The relatively low mean age of breast cancer patients reported in this study (46.8) is close to that reported by other authors in Baghdad (46.5 years), [19] Egypt (46 years), [20] Kingdom of Saudi Arabia (45 years). [21] Slightly higher mean ages reported in Morocco, Algeria, Tunisia and Libya (48 years) with 55 % of breast cancer cases being younger than 50 years [22]. Higher mean ages reported in Palestinian Arab kindred and Jewish population (51.5 and 55.9 years respectively). [23]

The median age of onset of our patients is more than ten years younger than that reported in Europe and USA (excluding the African-Americans). While numerous theories have been proposed to explain this difference, including age at menarche, time of first delivery, parity, socio-demographic factors and genetic difference, none are completely satisfactory and more researches are needed in this area. [24, 25, 26, 27]

About 51.9% of our patients had negative ER staining. Nearly 29.6% of the ER positive cases had strong positive stain (score 7-8). In Baghdad higher occurrences of these receptors reported in malignant breast tissues (61.9% for ER and 52% for PR). [28] Even higher figures recorded in Western studies. [7, 29] Unexpectedly the ER negative cases in this study were higher than the positive cases for both before and after 50 years. Opposite results reported in several studies, which suggested that low ER values in premenopausal women might represent a true lack of the receptor protein, [30] or the tumors among elderly women tend to be better differentiated and hence have higher receptor content [31] After these debatable findings of hormonal status, we may say that the young onset of breast cancer among patients in the north of Iraq and the relatively high percentages of hormonally insensitive cancer in young and old patients could be attributed to the genetic predisposition

Most of patients included in this study (83.9) presented for the first time at stage II and III**.** Detection at early stages of the cancer formed only 7.4% (for stage 0 and stage1). The positive hormonal receptors status was significantly high in grade I and in negative lymph node. It was mentioned in the 1st World Conference on breast cancer that in Iraq breast cancer incidence is increasing and the diagnosis is mostly at late stage. Furthermore it has been pointed to a high rate of malignant breast tumors in Iraq with poorly differentiated cells (aneuploid). [28]

A tumor in which 15% of cells exhibiting weak ER staining is biologically different from a tumor demonstrating strong intensity staining in 90% of cells. This fact has been demonstrated not only by IHC and ligand binding assay, but also by quantitative RT-PCR assays. [32, 33] Moreover, the greater benefit from tamoxifen is seen in patients with stronger ER expression. A similar interpretation can be given for PR results with slight ineffective differences form ER results. [34]

The correlation of ER scoring with the lymph node involvement was statistically highly significant in most of the scoring. Similar results have been documented by many authors. [6, 35, 36]

Simpson, PT 2005 hypothesized that low and high-grade breast cancers may represent separate pathways of oncogenesis, thus the absence of low grade tumors the advance in the stage is not explained by delay in diagnosis allowing 'progression' to a higher grade. [11] This may explain the few cases in our study with positive hormone receptors and strong total score in stage IV and in metastatic lymph nodes.

Conclusion

The criteria of patients with breast cancer at first presentation including; the low age, the excess of high-grade, the advanced stage, and the substantially low hormone receptor status, may suggest a role of genetic predisposition in addition to environmental risk factors in developing the cancer in this population. These criteria are closer to that of eastern than the western world. The relatively low hormone sensitive cancers could be attributed to the overall low age at presentation, but the particular low ER in patients older than 50 years required additional analysis. The ER and PR positive status and scoring correlate significantly with the negative lymph node involvement and there were decreasing in strong staining with the increase in the stage.

Table 1 The association of ER and PR scoring with the age.

Scoring	Before 50		After 50		Total		P value
	No.	%	No.	%	No.	%	
ER* Negative (0-2)	**113**	**34.9**	**55**	**17.0**	**168**	**51.9**	**>0.05**
Weak (3-4)	**22**	**6.8**	**6**	**1.9**	**28**	**8.7**	
Intermediate (5-6)	**23**	**7. 1**	**9**	**2.8**	**32**	**9.9**	
Strong (7-8)	**63**	**19.4**	**33**	**10.2**	**96**	**29.6**	
Total	**221**	**68.2**	**103**	**31.8**	**324**	**100**	
PR* Negative (0-2)	**97**	**29.9**	**47**	**14.5**	**144**	**44.4**	**>0.05**
Weak (3-4)	**23**	**7. 1**	**13**	**4.0**	**36**	**11.1**	
Intermediate (5-6)	**37**	**11.4**	**15**	**4.6**	**52**	**16.0**	
Strong (7-8)	**64**	**19.8**	**28**	**8.6**	**92**	**28.4**	
Total	**221**	**68.2**	**103**	**31.8**	**324**	**100**	

* Total score proportion score (PS) + intensity score (IS)

Table 2 The association of ER and PR with the grade of the tumor

Grade	ER +/- PR				Total No	%	P value
	Positive	%	Negative	%			
I	**64**	**76.2**	**20**	**23.8**	**84**	**25.9**	**<0.05 only in grade I**
II	**68**	**54.8**	**56**	**45.2**	**124**	**38.3**	**>0.05**
III	**56**	**48.3**	**60**	**51.7**	**116**	**35.8**	**>0.05**
Total	**188**		**136**		**324**	**100%**	

Table 3 The association of ER and PR scoring with the tumor grade.

Scoring	Grade						Total
	I	%	II	%	III	%	
ER Negative (0-2)	**28**	**8.64**	**68**	**20.99**	**72**	**22.22**	**168**
Weak (3-4)	**4**	**1.23**	**8**	**2.47**	**16**	**4.94**	**28**
Intermediate (5-6)	**16**	**4.94**	**12**	**3.70**	**4**	**1.23**	**32**
Strong (7-8)	**36**	**11.11**	**36**	**11.11**	**24**	**7.41**	**96**
Total	**84**	**25.93**	**124**	**38.27**	**116**	**35.80**	**324**
PR Negative (0-2)	**24**	**7.41**	**56**	**17.28**	**64**	**19.75**	**144**
Weak (3-4)	**4**	**1.23**	**16**	**4.94**	**16**	**4.94**	**36**
Intermediate (5-6)	**16**	**4.94**	**20**	**6.17**	**16**	**4.94**	**52**
Strong (7-8)	**40**	**12.35**	**32**	**9.88**	**20**	**6.17**	**92**
Total	**84**	**25.93**	**124**	**38.27**	**116**	**35.80**	**324**

Table 4 The association of ER and PR scoring with tumor stage.

Scoring	Stage									%	Total	P value
	0	%	I	%	II	%	III	%	IV			
ER Negative	0	0	4	1.2	64	19.8	88	27.2	12	3.7	168	
Weak	0	0	0	0	12	3.7	8	2.5	8	2.5	28	
Intermediate	0	0	4	1.2	20	6.2	4	1.2	4	1.2	32	>0.05
Strong	8	2.5	8	2.5	48	14.8	28	8.6	4	1.2	96	
Total	8	2.5	16	4.9	144	44.4	128	39.5	28	8.6	324	
PR Negative	0	0	4	1.2	64	19.8	72	22.2	4	1.2	144	
Weak	0	0	0	0	12	3.7	16	4.9	8	2.5	36	>0.05
Intermediate	0	0	4	1.2	20	6.2	20	6.2	8	2.5	52	
Strong	8	2.5	8	2.5	48	14.8	20	6.2	8	2.5	92	
Total	8	2.5	16	4.9	144	44.4	128	39.5	28	8.6	324	

Table 5 The association of ER and PR scoring with lymph-node involvement

Scoring	Lymph nodes involvement				Total		P Value
	positive	%	Negative	%	Total	%	
ER scoring Negative	80	30.8	32	12.2	112	43.0	<0.005
Weak	20	7.7	8	3.1	28	10.8	<0.005
Intermediate	12	4.6	20	7.7	32	12.3	>0.05
Strong	8	3.1	80	30.8	88	33.9	<0.005
Total	120	46.2	140	53.8	260	100%	
PR scoring Negative	80	30.8	32	12.3	112	43.1	<0.005
Weak	20	7.7	12	4.6	32	12.3	
Intermediate	16	6.2	24	9.2	40	15.4	>0.05
Strong	4	1.5	72	27.7	76	29.2	<0.005
Total	120	46.2	140	53.8	260	100%	

References

1. "World Cancer Report". International Agency for Research on Cancer. 2008. Retrieved 2011-02-26
2. Greene G L, Sobel N B, King W J, and Jensen E V. (1984). Immunochemical studies of estrogen receptors. J. Steroid Biochem, 20: 51-56.
3. Deroo BJ, Korach KS. (2006). "Estrogen receptors and human disease". J. Clin. Invest. 116 (3): 561–7.
4. Levin ER. (2005). "Integration of the extranuclear and nuclear actions of estrogen". Mol. Endocrinol. 19 (8): 1951–9.
5. Clemons M, Danson S, Howell A. (2002). "Tamoxifen (Nolvadox): A Review". Cancer Treat. Rev. 28 (4): 165–180.
6. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Azorides R. Morales

MD. (2005). Immunohistochemistry of Estrogen and Progesterone Receptors Reconsidered: Experience With 5,993 Breast Cancers. Am J Clin Pathol; 123(1):21-27.

7. Goldstein NS, Ferkowicz M, Odish E, Mani A, Hastah F (2003). Minimum formalin fixation time for consistent estrogen receptor immunohisto-chemical staining of invasive breast carcinoma. Am J Clin Pathol, 120:86-92
8. Bast RC Jr, Ravdin P, Hayes DF, et al (2000). Update of recommendations for the use of tumor markers in breast and colorectal cancer: Clinical practice guidelines of the American Society of Clinical Oncology. J Clin Onco; 19:1865-1878.
9. Harvey JM, Clark GM, Osborne CK, Allred DC (1999). Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol; 17:1474-81.
10. Rhodes A, Jasani B, Barnes DM, et al. (2000). Reliability of immunohistochemical demonstration of oestrogen receptors in routine practice: Interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. J Clin Pathol, 53:125-130.
11. Simpson PT, Reis-Filho J, Gale T, Lahani SR. (2005). Molecular evolution of breast cancer. J Pathol. ; 205:248–254.
12. Habel LA, Stanford JL. (1993). Hormone receptors and breast cancer. Epidemiol Rev;15:209–19
13. Tavassoli: Tumours of the Breast and Female Genital Organs. World Health Organization (WHO, 2003).
14. Genestie C, Zafrani B, Asselain B, Fourquet A, Rozan S, Validire P, Vincent-Salomon A, Sastre-Garau X. (1998). "Comparison of the prognostic value of Scarff-Bloom-Richardson and Nottingham histological grades in a series of 825 cases of breast cancer: Major importance of the mitotic count as a component of both grading systems". Anticancer research 18 (1B): 571–576.
15. AJCC Cancer Staging Manual, 6th ed. New York, Springer, 2002
16. Urika V. Mikel. (1994). Advanced laboratory methods in histology and pathology. Armed Force. Institute of pathology. America registry of pathology, Washington, DC.
17. Allred DC. (1993). Should immunohistochemical examination replace biochemical hormone receptor assays in breast cancer? Am J Clin Pathol; 99:1–3.
18. Qureshi A, Pervez S, (2010). Allred scoring for ER reporting and its impact in clearly distinguishing ER negative from ER positive breast cancers. JPMA. 60; 5, May 351-2
19. Al-Janabi A.A. (2003). Immunohistochemical study of p53-onco-suppressor gene in correlation to other biochemical markers in breast cancer (a prospective study) Thesis.
20. Omar S, Khaled H, Gaafar R, Zekry AR, Eissa S, el-Khatib O, et al. (2003). Breast cancer in Egypt: a review of disease presentation and detection strategies. Eastern Mediterranean Health Journal May; 9(3):448-63.
21. Elkum N, Dermime S, Ajarim D, Al-Zahrani A, Alsayed A, Tulbah A; (2007). Being 40 or younger is an independent risk factor for relapse in operable breast cancer patients: The Saudi Arabia experience BMC Cancer.; 7: 222.
22. Uhrhammer N, Abdelouaha A, Lafarge L, Feillel V, Ben Dib A, Bignon Y. (2008) BRCA1 mutations in Algerian breast cancer patients: high frequency in young, sporadic cases. Int. J. Med. Sci. , 5197
23. Nissan A, Spira RM, Hamburger T, Badriyyah M, Prus D, Cohen T, Hubert A, Freund HR, Peretz T. (2004).

Clinical profile of breast cancer in Arab and Jewish women in the Jerusalem area. Am J Surg, 188:62-67.
24. Vorobiof DA, Sitas F, Vorobiof G. (2001). Breast cancer incidence in South Africa. Journal of Clinical Oncology. Sep 15; 19 (18 Suppl): 125S-7S.
25. Adebamowo CA, Ajayi OO. (2000). Breast cancer in Nigeria. West African Journal of Medicine Jul; 19 (3): 179-91.
26. Newman LA, (2005). Breast cancer in African-American women. Oncologist Jan; 10 (1): 1-14.
27. Polite BN, Olopade OI. (2005) Breast cancer and race: a rising tide does not lift all boats equally. Perspect Biol Med. 48(1) (suppl):S166-S175.
28. Al-Alwan NAS. (2000). DNA Proliferative Index as a marker in Iraqi Aneuploid Mammary Carcinoma. EMHJ. WHO Eastern Mediterranean Regional office. Vol: 6, Issue5/6 p: 1062-72
29. Rutqvist LE. (1996). Breast cancer registry, Stockholm, Gotlandregionen, 1977-1992. Stockholm Gotland, Onkologiskt Centrum.
30. Wilking N. (1989). Steroid receptor levels in breast cancer: relation with age and menopausal status. Acta oncologica, 28:807-10.
31. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S. (1994). Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J. Clin. Oncol. 12: 888-94.
32. Lacroix M, Querton G, Hennebert P, Larsimont D, Leclercq G. (2001). Estrogen receptor analysis in primary breast tumors by ligand-binding assay, immunocytochemical assay, and northern blot: a comparison. Breast Cancer Res Treat, 67:263-271.
33. Cronin M, Pho M, Dutta D, Stephans JC, Shak S, Kiefer MC, et al. (2004). Measurement of gene expression in archival paraffin-embedded tissues: development and performance of a 92-gene reverse transcriptase-polymerase chain reaction assay. Am J Pathol, 164:35-42.
34. Baehner FL, Watson D, Shak S, Habel LA, Quesenberry CP, Capra A, Tang G, Paik S, Wolmark N. (2004). Quantitative RT-PCR analysis of ER and PR by Oncotype DX indicates distinct and different associations with prognosis and prediction of tamoxifen benefit [abstract 45]
35. Baehner FL, Habel LA, Quesenberry CP, et al: (2006). Quantitative RT-PCR analysis of ER and PR by Oncotype DX indicates distinct and different associations with prognosis and prediction of tamoxifen benefit. Presented at the 29th Annual San Antonio Breast Cancer Symposium, December 14-17.
36. Goldstein LJ, O'Neill A, Sparano J, et al: (2005). E2197 Phase III AT(doxorubicin/ docetaxel) vs AC (doxorubicin/ cyclophosphamide) in the adjuvant treatment off node positive and high risk node negative breast cancer.