We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

2

Neoadjuvant Therapy in Breast Cancer

Angela Lewis Traylor[1], Nathalie Johnson[1] and Esther Han[2]
[1]*Legacy Medical Group – Surgical Oncology, Legacy Cancer Services, Portland, Oregon*
[2]*Oregon Health and Sciences University, Department of Surgery*
Sam Jackson Parkway, Portland, Oregon
USA

1. Introduction

This is an exciting time we live in. As technology has advanced at lightning speed, so has molecular science and knowledge. With the mapping of the genome, a transformation in medical science has followed. Translational application of bench research to the bedside has blossomed also at an unprecedented pace. There are many new targeted agents on the horizon and future discoveries seem limitless. Although we have advanced in technology, in many ways we have not significantly changed our therapeutic treatment approach in breast cancer. The pattern of surgery first and adjuvant therapy next remains mainstream. This chapter will start by delineating traditional thoughts on systemic therapy prior to surgery as it is currently practiced and close with thoughts on where we are headed in the future.

2. Neoadjuvant chemotherapy

Historically, neoadjuvant chemotherapy (NCT) has been used in patients with locally advanced inoperable disease. More commonly, it is used in patients with operable tumors of all stages with promising outcomes. The term "neo" is Greek for new or recent, and "adjuvant" originated from Latin, and means to assist or to help. However, neoadjuvant chemotherapy is more accurately defined as primary systemic therapy. There are advantages afforded by the use of NCT, controversial issues surrounding its use, prognostic indicators of response, and some possible disadvantages.

Several randomized and non-randomized studies have evaluated the efficacy of neoadjuvant chemotherapy (Table 1)[1]. NCT allows "in-vivo" evaluation of tumor biology and an assessment of remission rate, complete response to treatment or complete pathologic response (cPR), tumor progression, and identification of chemo- resistant tumors. Complete pathologic response (cPR) has emerged as a significant predictor of tumor response and may predict long-term outcomes. Further, NCT allows down staging of tumors by decreasing tumor size and extent of tumor mass, thereby facilitating breast conservation therapy (BCT).

Neoadjuvant chemotherapy was first used in 1973 at the Milan Cancer Institute[2,3,4]. Their goal at the time of the study was to achieve prompt tumor response or shrinkage in locally advanced inoperable disease in order to facilitate the delivery of radiation therapy. Jacquillat et al. first used NCT for operable breast cancer in 1980 in Paris, France[5]. Since then there have been multiple non-randomized trials demonstrating variable response rates of

Reference	No. of Patients	Tumour Stage	Chemotherapeutic Regimen	Follow-up (months)	Overall Response (%)	Overall Survival (%)	Disease-free Survival (months)	Breast-conserving surgery (%)	pCR (%)
13	250	I-IIIB	Vinb-thi-met-FU±adr	61	71	58-95	52-100?	–	–
14	536	>2.5cm	Cyc-met-FU, FU-adr-cyc, FU-epi-cyc	96	76	69	55	85	3
15	50	6(3-12)cm*	Infusional FU-adr-cis	–	98	–	–	62#	27
16	88	II,III	Doc	–	68	–	–	72	20
17	126	T1-3, N0-2	Adr-vinc-cys-FU± met		86	–	–	85§	–
18	50	High risk, operable	Dox-vino-cyc-FU	31	88	–	–	78	22
19	100	III + inflammatory	Cyc-met-FU± thi	27	70	43 87**	28 67**	11	–
20	122	IIB-IIIB	Pac + cis	–	91	–	–	–	42

*Values are median (range). §Depending on stage at treatment (I-IIIB); #30 per cent had no surgery; § includes 33 per cent who had radiotherapy only; ¶ non-responders; **responders. pCR, pathological complete response; vinb, vinblastine; thi, thiotepa; met, methotrexate; FU, 5-flourouracil; adr, adriamycin; cyc, cyclophosphamide; epi, epirubicin; cis, ciplatin; doc, docetaxel; dox, doxorubicin; vinc, vincristine; vino, vinorelbine; tam, tamoxifen; pac, paclitaxel.

Table 1. Non-Randomized trials of Neoadjuvant Chemotherapy.[1]

large operable and inoperable tumors to NCT. The reported pCR (complete pathologic response) rates vary from 3 % to 24 %[1]. In multiple randomized clinical trials the pCR observed varies between 4% and 34 %[1].

The largest prospective randomized trial of NCT was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18. This trial showed an overall response rate of 79%, and a pCR of 13%[6,7]. 1493 patients with operable breast cancer were stratified by age, clinical tumor size, and clinical nodal status to preoperative versus postoperative administration of Adriamycin/cyclophosphamide (AC) q 21 days x four cycles. Patients older than 50 years old were also given Tamoxifen 10mg BID x 5 years after completion of chemotherapy.

Updated results from B-18 continue to demonstrate the significant correlation between pCR and DFS. The trial also demonstrated the equivalence between preoperative and postoperative chemotherapy. Breast conservation therapy (BCT) rates were 67% versus 60%.

Another landmark trial, NSABP B-27, enrolled 2411 patients in a randomized prospective trial to compare the efficacy of docetaxel in the preoperative versus postoperative setting after neoadjuvant AC x four cycles[7]. The patients were randomized into three groups (Figure 1). All patients received Tamoxifen 20mg PO daily x 5 years.

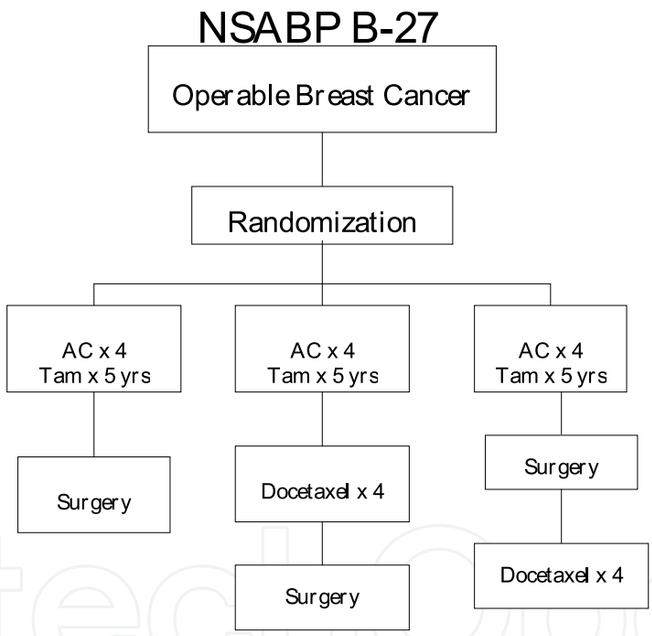


Fig. 1.[7]

The overall response rate was 91 % for those who received preoperative AC and docetaxel vs. 85.7 % for those who received preoperative AC alone ($p < 0.001$). The pCR was 26 % vs. 13.7 % ($p < 0.001$). Preoperative AC-docetaxel also significantly downstaged the axillary lymph nodes. 50.7% of the AC- alone group had negative lymph nodes vs. 58.1 % of the AC-docetaxel group ($p< 0.01$). Both B-18 and B-27 demonstrate tumor response to NCT as a significant predictor of pathologic nodal status.

Studies on tumor growth and kinetics also support the use of neoadjuvant chemotherapy[8]. Several investigators have demonstrated the inhibitory effect that the "in-situ" or undisturbed primary tumor with intact vasculature has on metastatic deposits and the development of spontaneous metastases after removal of the primary tumor[9,10]. In past

studies, tumor growth was often measured grossly. However, Gunduz et al. used cytokinetic parameters to evaluate tumor growth[8]. The parameters included: Labeling index, primer-dependent DNA polymerase index or growth fraction, DNA synthesis time, and cell cycle time. It was shown that following tumor removal changes were observed, specifically, accelerated growth in the residual tumor focus within 24hrs. The labeling index and growth fraction were increased with a decrease in tumor doubling time. There was minimal change in DNA synthesis and cell cycle time. Minimal changes in these last two parameters suggest increased growth was not the result of increased DNA synthesis and cell cycle times, but increased growth secondary to conversion of non-cycling cells in G0 phase into proliferation. Could the intact or "in-situ" primary tumor cause quiescence or down regulation of non-cycling cells and thus inhibit metastatic deposits? This is a very interesting question that may be answered in future studies on NCT.

Unfortunately, NCT is not a panacea. There are a small number of patients who will have have disease progression while receiving neoadjuvant therapy. In theory, for this group, NCT may be delaying delivery of effective surgical treatment to those with chemo-resistant tumors. DeLana et al. showed six patients (5.5%) who had disease progression in response to induction chemotherapy. However, the percentage of people with disease progression remains miniscule in most studies. No patients in Jacquillat's study had disease progression[5]. In the current era of thinking of breast cancer as a systemic disease, it also begs the question as to whether or not nonresponders to NCT are a group of biologically more aggressive tumors whose outcome is poor, regardless of pre or post operative therapy.

NCT may also increase local recurrence rates in those treated with BCT. Mauriac et al. demonstrated an initial BCT rate of 63% at 34 months follow-up, which decreased to 45% at 124 months follow-up[1,11]. This effect may be partially due to the non-uniform and varied response patterns of the primary tumor to NCT (Figure 2)[12].

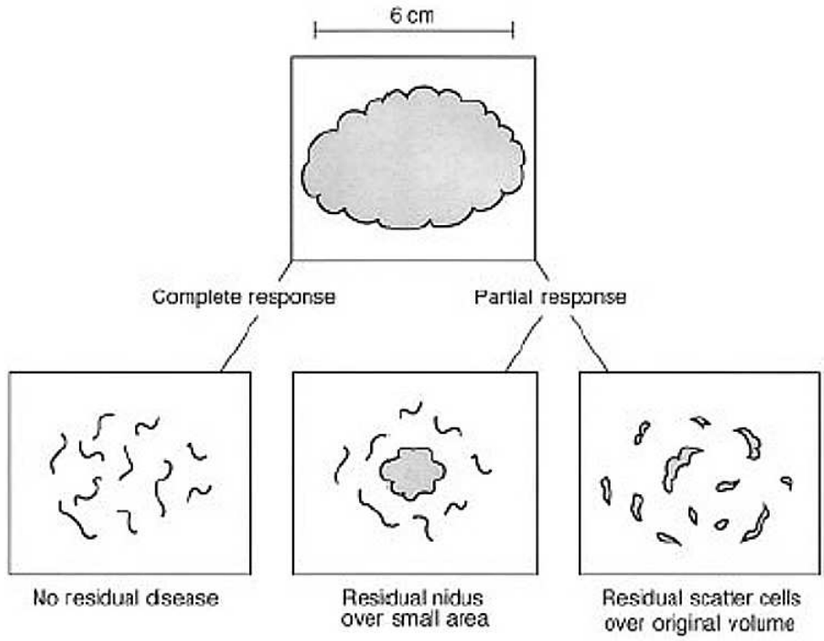


Fig. 2.[2]

Examples of the various pathologic responses observed after neoadjuvant chemotherapy. In some instances, malignant cells are clustered around a residual nidus after disease response. In other cases, residual tumor cells are scattered over the residual volume of disease. A breast-conserving surgical procedure directed toward a central nidus may leave different volumes of residual disease in these two clinical scenarios.

NSABP B-18 showed ipsilateral recurrence rates of 10.7% for NCT versus 7.6% for the adjuvant chemotherapy group. This discrepancy may be attributable to those mastectomy candidates who were converted to BCT candidates after tumor response to NCT. The European Organization for Research and Treatment of Cancer (EORTC) 10902 trial showed no difference in local recurrence rates between NCT and adjuvant chemotherapy[13].

Although NCT has not yet been shown to improve OS or DFS, it has led to the elucidation of pCR as a significant prognostic indicator. Due to the lack of standardization of the definition of pCR, a new measure of response has been proposed, called residual cancer burden (RCB) [14]. This is a calculated index that combines tumor size and cellularity with the size and number of lymph node metastases. RCB may predict recurrence-free survival and identify a group of high-risk patients and those with chemo-resistant tumors.

Current studies in NCT are looking at ways to predict tumor response to chemotherapy. For instance, it is rare that treatment with chemotherapy of a strongly estrogen receptor positive (ER +), progesterone receptor (PR+) ,Her 2 neu negative tumor will result in a cPR. [15] More and more studies are evaluating response to chemotherapy based on multiple identified subtypes. For instance, lobular cancers (loss of e-cahedrin expression) may not respond well to chemotherapy. Luminal A subtypes (strongly ER+ PR+) tumors often express very low growth rate patterns and may also not respond well to chemotherapy. On the other hand, ER+PR- (luminal B) type tumors and ER-PR-Her2neu- (basal type) tumors respond far better to chemotherapy and more often will result in cPR.[15].Novel chemotherapeutic agents such as the antiangiogenic agent, bevacizumab, and monoclonal antibody, trastuzumab, are now being tested in neoadjuvant clinical trials. The future lies in the ability to tailor NCT according to predictable prognostic indicators such as tumor subtype , and molecular therapeutic markers and in the development of specific NCT regimens with individualization based on tumor biology.

3. Neoadjuvant endocrine therapy

Systemic chemotherapy (NCT) was first used in the neoadjuvant setting in trials to downstage locally advanced tumors. Quite naturally it became the popular treatment modality for patients with locally advanced breast cancer considered inoperable or for those with operable breast cancer who desired breast conservation therapy. Since the development of prognostic markers that can be reliably tested the idea of preoperative endocrine therapy based on estrogen and progesterone receptor has also come into question. Initial studies of this approach have been most often performed in postmenopausal women.

A number of clinical trials have compared surgery with primary endocrine therapy in older postmenopausal women with large ER+ tumors destined for mastectomy in whom neoadjuvant chemotherapy was deemed inappropriate due to age and comorbidities. It was clear that many had an initial response to therapy and were able to achieve breast conservation but not all. Unfortunately, some experienced disease progression.

Tamoxifen has for many years been the mainstay of endocrine therapy. Rightfully so, more recent trails have compared Tamoxifen to the newer aromatase inhibitors both in the

adjuvant and neoadjuvant setting. It is clear from the BIG- I 98 (letrazole vs Tamoxifen) and ATAC (Arimidex vs Tamoxifen Alone or in Combination) trials that aromatase inhibitors have slightly superior disease free survival rates (DFS) (about 4-6%) Armed with that knowledge, Ingle et al, recently published a series comparing tamoxifen versus letrazole in the neoadjuvant setting, and found letrazole had superior clinical response rates.[16]

It has, however, become increasingly clear that the strongly ER+PR+HER 2 neu – (luminal A tumors) are the ones that respond best to endocrine therapies. Much energy is now being spent on looking for markers to predict response to endocrine therapy. Multigene prognostic assay tools such as Recurrence Score (Oncotype Dx) and the Amsterdam 70 gene assay (Mammaprint) define a low risk population and also seem to predict response to therapy. Other genomic measurements also hold promise. One is a panel of genes co - expressed with ESR1 that could predict sensitivity to endocrine therapy (SET) and improved relapse free survival.[17] Patients with a high SET had few relapses with Tamoxifen alone.

Another measure of response to endocrine therapy is a decrease in Ki-67 with treatment. Ki-67 is a measure of proliferation and studies are showing that patients who have a decrease in expression of Ki-67 after two weeks of endocrine therapy will go on to have a good response. The American College of Surgeons – Oncology Group study Z 1031 is looking at this measure in post menopausal women with stage 2 or 3 breast cancer be studying it with repeat tumor sampling two weeks after start of therapy for ER+ tumors.

One of the advantages that appear to be offered by neoadjuvant endocrine therapy over chemotherapy is concentric shrinkage of the tumor, thereby making it far more likely to yield negative margins at the time of surgery. This seems to translate into better local control rates with breast conservation therapy and additive radiation.

3.1 Timing of the sentinel node biopsy in the neoadjuvant setting

There is controversy on the timing of the sentinel node biopsy in the setting of neoadjuvant therapy. Should sentinel node (SNB) evaluation occur before or after induction of chemo or endocrine therapy? There are salient points for both sides of this controversy. Lymph node status has been and still is a strong predictor of outcome . However, cPR after neoadjuvant therapy is also a very strong predictor of outcome, even in the setting of positive nodal disease.

One of the concerns with performing the SNB after neoadjuvant treatment is related to the technical ability to find the SNB and its accuracy. Several studies now have demonstrated that, in patients who are clinically node negative at diagnosis, the SN can be identified over 97% of the time with low false negative rates.[17,18] Several studies also support the view that performing the SNB after NCT allows downstaging of the axilla and results in fewer patients being subjected to full axillary node dissection (ALND), with its attendant risk of chronic lymphedema.

Proponents of performing the SNB prior to NCT believe that knowledge of the state of the axilla prior to the initiation of chemotherapy is critical for prognostication. In addition, there are times that knowledge of the number of lymph nodes involved may influence the regimen of chemotherapy delivered or whether radiation is administered after mastectomy. In some cases, only one SN is removed for evaluation and post NCT the SNB technique is repeated. This particular approach (removing only one SN), however, negates the arguments of needing to know number of involved nodes. If only one SN is removed then it is unclear if this was the only involved node. After treatment, it is also unclear whether or

not nodal disease would have cleared with treatment. The authors do not recommend this approach. Instead, if SNB is performed prior to NCT then patients with a positive intraoperative SN should proceed with full axillary evaluation (ALND).
The axilla should be evaluated clinically and if there is any concer, should have axillary ultrasound and needle biopsy of suspicious nodes.
The current recommendation for those with known nodal involvement prior to inception of NCT is to proceed with ALND after chemotherapy.
There are currently trials evaluating the safety of SNB in node positive women who have an excellent response to chemotherapy.

4. The new paradigm

Clinical research in cancer is resulting in a shift towards a new paradigm. In the past, new agents or combinations have been studied in the adjuvant or postoperative setting. The tumor has been removed and the only way to measure success or failure of a treatment is to wait years to document treatment failures. Any studies that were performed prior to tumor extirpation required that all patients, regardless of tumor response, were to receive the same chemotherapeutic drugs. Recently, there has been recognition that performing drug studies prior to removal of the tumor provides instant feed back on response to therapy.
Tumor regression in response to therapy can be gauged by examination of the tumor. In addition, the treatment plan can be altered based on which drugs are eliciting tumor response.
The best example of this new change in trial design and concept is seen in the I-SPY 2 trial (**I**nvestigation of **S**erial studies to **P**redict **Y**our **T**herapeutic **R**esponse with **I**maging **A**nd mo**L**ecular analysis). On this study patients are randomized to standard NCT or investigational drugs with imaging and repeat core biopsies to restudy the tumor molecular changes as treatment progresses. The investigational drugs given in the neoadjuvant setting allows immediate feedback on drug efficacy by measuring tumor response to treatment. This we believe will be the future of cancer clinical trials and will allow us to move forward much more quickly with studies of drug efficacy alone or in combination.
It's a brave new world!

5. References

[1] Charfare, H., Limongelli, S., and Purushotham, A.D. *Neoadjuvant chemotherapy in breast cancer*. British Journal of Surgery 92:14-23, 2005.

[2] De Lena, M., Zucali, R., Viganotti, G., Valagussa, P., and Bonadonna, G. *Combined Chemotherapy-Radiotherapy Approach in Locally Advanced (T3b-T4) Breast Cancer*. Cancer Chemotherapy and Pharmacology 1: 53-59, 1978.

[3] Valagussa, P., Zambetti, P., Bignami, M., De Lena, M., Varini, R., Zucali, R., Rovini, D., and Bonadonna, G. *T3b-T4 Breast Cancer: Factors Affecting Results in Combined Modality Treatments.* Clin. Expl. Metastasis vol 1, No.2:191-202, 1983.

[4] Bonadonna, G., De Lena, M., Brambilla, C., Zucali, R., Uslenghi, C., Valagussa, P., and Veronise, U. *Combination Chemotherapy and Combined Treatment Modality In Disseminated and Locally Advanced Breast Cancer*. Breast Cancer p.437-458, 1977.

[5] Jacquillat, C., et al. *Results of Neoadjuvant Chemotherapy and Radiation Therapy in the Breast-Conserving Treatment of 250 Patients With All Stages of Infiltrative Breast Cancer*. Cancer 66:119-129, 1990.

[6] Fisher, B., et al. *Effect of Preoperative Chemotherapy on the Outcome of Women With Operable Breast Cancer*. Journal of Clinical Oncology vol 16, No. 8:2672-2685,1998.

[7] Mamounas, E., et al. *NSABP Breast Cancer Clinical Trails: Recent Results and Future Directions*. Clinical Medicine and Research vol 1, No. 4:309-326, 2003.

[8] Gunduz, N., et al. *Effect of Surgical Removal on the Growth and Kinetics of Residual Tumor*. Cancer Research 39:3861-3865, 1979.

[9] Ketcham, A.S., et al. *The Development of Spontaneous Metastases after the Removal of a Primary Tumor II. Standardization protocol of five animal tumors*. Cancer 14:875-882, 1961.

[10] Ketcham, A.S., et al. *The effect of removal of a "Primary" tumor on the development of spontaneous metastases I. Development of a standardized experimental technique*. Cancer Research 19:940-944, 1959.

[11] Mauriac, L., et al. *Effect of Primary Chemotherapy in Conservative Treatment of Breast Cancer patients with Operable tumors larger than 3 cm. Results of a randomized trial in a single center*. Annals of Oncology 2:347-354, 1991.

[12] Buchholz, T., et al., *Neoadjuvant Chemotherapy for Breast Cancer. Multidisciplinary Considerations of Benefits and Risks*. Cancer vol 98, No. 6:1150-1160, 2003.

[13] van der Hage, Jos A., et al., *Preoperative Chemotherapy in Primary Operable Breast Cancer:Results from the European Organization for Research and Treatment of Cancer Trial 10902*. Journal of Clinical Oncology vol 19, No. 22:4224-4237, 2001.

[14] Budzar, A., et al., *Preoperative Chemotherapy Treatment of Breast Cancer-A Review*. Cancer vol 110, No. 11:2394-2407, 2007.

[15] Lips, E ,et al, Neoadjuvant chemotherapy in ER+,Her2neu – breast cancer : response predication based on immunohistochemical and molecular characteristics. Breast Cancer Res Treat, DOI 10.1007/s10549-011-1488-0 , on line April 07, 2011

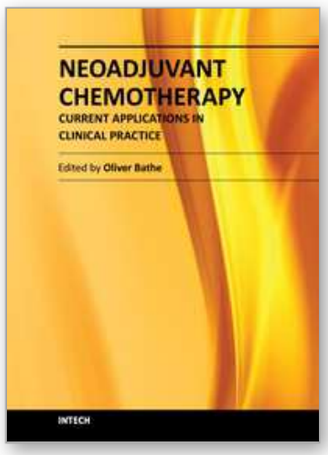
[16] Ingle, J.N. et al, Aromaatase Inhibitors vs Tamoxifen for management of post menopausal breast cancer in the advanced neoadjuvant setting, J Steroid Biochem Mo Biol ,Sept:86(35) 313-9

[17] Chung A., Guiliano A.

[18] Stell V.H., et al, Sentinel Node after neoadjuvant chemotherapy in breast cancer : Breast J 2011 Jan 17(1):71-4

[19] Symmans,W.F., et al ,Genomic index of sensitivity to endocrine therapy for breast cancer,J Clin Oncol,2010 Sept 20:28(27)4101-3

[20] I SPY 2, breast cancer trials. gov web site



Neoadjuvant Chemotherapy - Current Applications in Clinical Practice

Edited by Dr. Oliver Bathe

ISBN 978-953-307-994-3
Hard cover, 268 pages
Publisher InTech
Published online 01, February, 2012
Published in print edition February, 2012

The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Angela Lewis Traylor, Nathalie Johnson and Esther Han (2012). Neoadjuvant Therapy in Breast Cancer, Neoadjuvant Chemotherapy - Current Applications in Clinical Practice, Dr. Oliver Bathe (Ed.), ISBN: 978-953-307-994-3, InTech, Available from: http://www.intechopen.com/books/neoadjuvant-chemotherapy-current-applications-in-clinical-practice/neoadjuvant-therapy-for-breast-cancer

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen