CARCINOMA OF THE BREAST : TIME TO PRACTICE EVIDENCE BASED MEDICINE

Timilsina D S

ABSTRACT

Breast cancer is a common, dangerous and to some extent curable disease. Mortality from this disease has just now beginning to fall after remaining stagnant for 40 years. Screening and multimodal therapy based on our paradigm changes are responsible for this happy trend. There is a very individualistic trend among surgeons to manage such cases, based on their own personal experiences. We are in a situation where same staged disease is managed very differently and thus comparison of results and national guidelines are very far off. We have very few indexed publications listed on this subject from Nepal.^{1,2,3} Here an attempt is made to review the recent publications and rationalizations from the abundance of information available.

Key Words: Carcinoma, breast, screening, mammography, radiotherapy, mastectomy.

INTRODUCTION

Breast cancer causes 400,000 deaths in women each year.⁴ Management of such a killer disease cannot be based on anecdotal experience but on the results of prospective randomized clinical trials. Screening, adjuvant chemotherapy and radiotherapy have been clearly showing reduction in mortality and improvement in the quality of life of patients with breast cancer. There has been an explosion of publications in the last 10 years, leading to terrible confusion among surgical societies. Time and again we come across same stage disease being managed differently among institutes and indeed among different surgeons of same institute. Rationalization of the information available is a very pressing need. Especially in Nepal management must also consider feasibility on grounds of socioeconomic reasons before offering the patient one. Sayami P et al⁵ have a large and the well documented series of over 10 years from Nepal.

MATERIALS AND METHODS

Medline search was done for publications after 1985. The most

frequently cited publications were isolated using key words Carcinoma, breast, screening, mammography, chemotherapy, radiotherapy, and mastectomy.

Special emphasis was given to more widely read publications and text. The topics were grouped under key points.

Literature considered as landmarks, which lead to major paradigm shifts are specially studied in detail.

The conclusions of the studies are put under key points.

KEY POINT 1 : SURGICAL COMMUNITY IS DIVIDED AS TO THE NATURAL HISTORY OF BREAST CANCER AND ITS IMPLICATIONS

The true effect of locoregional therapy on the natural history of breast cancer is a very controversial issue^{6,7} mainly because of two opposing but well established views on the natural history of breast cancer.⁸ One group firmly believes that the disease is systemic at inception and surgery will have no effect on the risk of death. The other group equally firmly believes

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Address for correspondence : Dr. Digvijay S. Timilsina
Manipal Teaching Hospital
5 Madan Ashrit Marg, Batulechaur, Madaan
Pokhara 16, Nepal
Email: digvijay@cnet.wlink.com.np

that the disease is localized at diagnosis and timely removal of primary tumor will reduce risk of death. Four hundred years ago Hippocrates had warned "It is better not to excise hidden cancer, because those who are excised quickly perish; while they who are not live longer."⁹ Galen also believed in the same theory¹⁰ and said that woman's monthly menstrual flow relieved her of excess black bile and this accounted for the increased incidence of carcinoma of breast in postmenopausal women. Galen did advocate excision of the primary tumor till the borders of healthy tissue. LeDran¹¹ was the first to challenge the humoral theory and also the first to advocate lymph node dissection. Virchow's¹² anatomical studies gave us the concept of tumor arising from epithelial cells and spreading along fascial planes and lymphatics. Halsted greatly influenced by Virchow¹³ was the first to champion radical mastectomy as the optimal treatment for carcinoma of the breast.¹⁴ Surgeons till the end of 19th century accepted his principles. The results of large randomized trials of recent times have been interpreted to mean that locoregional therapy has no effect on survival. Fisher¹⁵ argues convincingly that "operable breast cancer is a systemic disease and involves complex spectrum of host-tumor interactions and thus local/regional therapy is unlikely to affect survival." Hellman¹⁶ equally convincingly argues that "persistent disease locally or regionally gives rise to distant metastases and thus loco-regional management is important." Undoubtedly this debate of the last 2500 years still divides surgical communities. This controversy can only be resolved by comparing surgery and no surgery groups of patients, but such a study would be totally unethical. Bloom¹⁷ has come nearest to this study when he reported the outcome of 250 patients with diagnosis of primary breast cancer who received no treatment from 1805-1933. Tissue diagnosis was obtained from autopsy. Henderson¹⁸ compared the survival of these patients with those who received mastectomy from 1889-1933 from the same hospital. The survival rates were identical. This conclusively proved that surgery had no impact on survival. This coupled with the fact that 30% of node negative patients offered radical mastectomy eventually die for metastatic breast cancer.¹⁵ Halsted's hypothesis of carcinoma of the breast as a locally progressive disease and has a centrifugal and contiguous spread implies that extent of mastectomy should influence survival. NSABP-04 (National Surgical Adjuvant Breast Project-04)¹⁹ and the King's/Cambridge trial²⁰ have proved that the delayed treatment of the axilla does not influence survival. Six prospective randomized trials²¹⁻²⁶ have shown that even though local recurrence is more common with breast conservation surgery, the extent of mastectomy does not effect survival. Thus the argument of the Halstedian surgeons of 20th century surgeons that resection of node negative breast cancer is curative^{27,28} is no longer valid. Now nodal involvement is not considered merely an indicator of delayed presentation but as a marker of breast cancer phenotype.²⁹ The only rational

explanation to these findings is that at Halsted's time women usually presented with locally advanced diseases and surgery alone did not offer survival advantage. Present day women with more awareness and having the advantage of screening present much earlier and these findings may not necessarily hold true.

KEY POINT 2 : DEFINITIONS OF CURE STILL LACK

At which state of the disease management should we call the patient cured, is a very debatable issue and the closest we can get is Langland's³⁰ classification. He has classified cure in 3 categories

2a) PERSONAL CURE

A situation when a patient of carcinoma breast eventually dies of other cause. Typically a 65 year old patient of carcinoma breast who dies of myocardial infarction at 67 years. Such a patient always has the disease.

2b) CLINICAL CURE

Any end point arbitrarily set by physician. The typical example will be the Halsted's 5-year disease free survival. Here the incidence of cure will depend on the end point (more cures at 5 years than at 10) and the aggressiveness with which disease is searched for (more cures with clinical examination alone and less if mammogram, bone scans etc are used). This is the most commonly used and attainable situation.

2c) STATISTICAL CURE

This is the one that can be used to compare results and is also the most difficult to attain. Here the risk of death in the treated group equals age matched control population. Brinkley and Haybittle³¹ and Karrison³² report increased risk of death upto 25 years after mastectomy. Only after 25 years will the mortality rate of treated carcinoma breast patients' equal general population. Considering that the average age of diagnosis of carcinoma breast is above 50 years, we need a significant population of women above the age of 75 to be able to call our breast cancer patients cured. This does not appear to be attainable at all.

KEY POINT 3 : STAGING SYSTEM MUST BE REVIEWED

The value of any staging system is to a) Prognosticate. b) Help plan management. c) Help exchange of information. d) Help compare results. TNM was conceived in 1950s and since then needless to say there has been major paradigm changes in our understanding of breast carcinoma. TNM does not help prognosticate. The most important indicator of prognosis is the number of lymph nodes involved and this is given no

weightage in TNM. Tumor size of T2 can be anywhere between 2-5 cm. The difference in 5 year survival rate (5YSR) between these 2 extremes is 20%.³¹ It also does not help plan management. The fourth edition of TNM considered supraclavicular nodal involvement as M1 disease. This is in direct conflict with the accepted definition of locoregional field of breast cancer in which the supraclavicular glands are inclusive and the RT for breast whenever indicated for locoregional control always includes supraclavicular fossa. This has been mitigated by more recent revision where ipsilateral supraclavicular nodes are given N3c status. TNM does not help in exchange of information and comparing of results. This is mainly due to the broad classification encompassed in TNM. I have to agree with Barr and Baum³⁴ that the TNM system is less than relevant in fulfilling the goals that were set out in its first edition in 1950s, mainly because of rapid changes in our understanding of the disease.

KEY POINT 4 : SCREENING AND ITS IMPLICATIONS

KEY POINT 4a : Efficacy of screening is difficult to measure

Proving the benefits of screening implies showing of improvement in health of an apparently healthy population. It also means that a small number of women will benefit but all will pay the cost. The question that needs to be asked for any screening program is whether it will deliver a reduction in mortality from breast cancer? For breast cancer this will mean a wait of 6-7 years from the start of the screening program. The estimation of the likely effects of the screening program must begin at the start itself, before mortality results are available mainly to rectify any faults and to reduce the subsequent loss of life. The criteria for a screenable disease will be A) Not rare. B) Serious. C) Treatable. D) Have a preclinical phase when it can be detected. E) Management at the preclinical stage must yield better results than at manifest stage of the disease. Breast cancer must be considered as an excellent example of a disease that can be screened. There are some genuine problems with interpreting the results of screening for breast cancer

- ? **Disease specification :** We should make it clear if we consider breast cancer at the first appearance of a malignant cell or after 30 billion replications when it gets to 1 cm mass³⁵. This renders the efficacy of screening

difficult to measure.

- ? **Who benefits is not clear :** Even-though randomized controlled trials (RCT's) have shown the benefit of screening on mortality, it is very unclear which age groups benefit.
- ? **DCIS confounds results :** Screening picks up an increasing percentage of DCIS and this has a distinct natural history.
- ? **Costs :** Cost of widespread screening will reduce the resource allocation for preventive service programs for other conditions.

All are agreed that the effect of a screening program on the incidence rate of advanced cancers is a definitive measure of its effectiveness. Since insitu cancers do not kill early, the greatest benefit of survival will be due to detection of invasive carcinomas at an early stage. Day and Williams et al³⁶ have put a quick checklist of the targets for early evaluation of a screening program.

1. Prevalence at first screen should be at least 3 times the annual incidence in the absence of screening.
2. Interval cancers in the first 2 years after a negative screen should be less than 25% of the expected incidence in the absence of screening.
3. More than 50% of the screen detected invasive cancers should be less than 15 mm.
4. More than 30% of the grade III invasive tumors should be less than 15 mm.
5. More than 70% of the screen-detected cancers should be node negative.
6. CIS should be less than 20% of all the screen-detected cancers.

Achieving target 4 means that program is working, but achieving all the targets may not mean that mortality will be reduced. Breach of 1-2 means that the program has poor sensitivity and breach of 3-6 means that there is a poor lead time/differential.

KEY POINT 4b : Screening implications are different for different age groups

RCT do indicate that periodic screening by mammography will reduce mortality from breast cancer it is unclear, which age

Table I : Differential implication of screening on different age groups.³²

Age group	40 - 49	> 50
Number of women enrolled	1000	1000
Abnormal first mammogram	65	70
Excision biopsy	16	24
Diagnosis of cancer	3	9
% DCIS	50%	25%

groups benefit.³⁷ Abnormal mammograms will be reported in ~ 10% of the screened population. The frequency with the first screen will report an abnormal mammogram will be same for all age groups. The positive predictive value declines from ~ 19% for >60 age group to ~ 4% for 40-49 age group. Screening implications for the 2 age groups is outlined in table I

KEY POINT 4c : 40-49 year age group women benefit less

There are 7 RCT for results of breast cancer screening. All report distinct advantage for women 50-64 age 9 years after enrollment in screening, all report insignificant benefit for women enrolled for screening at 40-49 years age group. Health Insurance Plan Project (HIP) the first RCT reported 29% breast cancer mortality reduction for women invited for screening compared to controls over a 9-year follow-up.³⁸ Women 50-64 years at study entry the 35% reduction in relative risk (RR) was significant but it was insignificant for women 40-49 years at enrollment. The Swedish Two County Trial³⁹ reported a 31% overall mortality reduction at 6 years follow-up. They too found this benefit to be isolated to 50-64 year age group. No trial could show benefit to women at 40-49 years from screening upto a 10-year follow-up. Combining data from all RCT Kerilowske⁴⁰ showed 23% reduction in the risk of dying from breast carcinoma when 50-74 year women are enrolled. Those enrolled at 40-49 years showed an insignificant 8% reduction. Thus the benefit to the 40-49 age groups will be more manifest when the incidence of carcinoma breast increases in this age group, to make the 8% a large figure.

KEY POINT 4d : Explanation for the decreased benefit to women 40-49 years

There is only one meta-analysis by Hendrik,⁴¹ which showed benefit of screening women 40-49 years and that too after a 13-year follow-up. The present literature throws up 2 facts unequivocally.

1. The risk reduction from breast cancer screening is less for 40-49 year age group.
2. The appearance of survival benefits is delayed for this group.

Publications for these data are available again from the Swedish Two County trials where it was proved that screening will have poor efficacy in reducing mortality from highly aggressive breast cancers.⁴² There was identical mortality reduction for grade II invasive carcinomas for all age groups. But for grade III tumors > 50 year group showed 39% benefit in mortality reduction but no benefit for the < 50 age patients. Younger women have denser breasts and this reduces the accuracy of

mammography screen. In a population-based mammography screening program the group in whom mammography was least sensitive at 70% was

- ? Less than 50 years.
- ? Positive history of breast cancer.

For the rest the sensitivity was 83.6%.⁴³ The delayed mortality reduction in 40-49 years age group puts up 2 explanations and 2 different implications

- a) Screening through early detection and treatment of prevents death caused by progression of indolent cancers – Screening must start at an earlier age.
- b) Delayed benefit results from the women reaching 50 during the screening program – Screening after 50 will not mean loss of the beneficial effects.

In all this confusion one distinct benefit from screening has not been given adequate attention: Even if no direct benefits on mortality can be proved for screening women less than 50, the screened population is detected at smaller stages and gets less aggressive treatment.⁴⁴

KEY POINT 4e : Screening will over diagnose DCIS

14% of new diagnosis of cancer after screening will be DCIS⁴⁵. 50% to 60% of these will regress spontaneously. Thus half of the DCIS patients detected by screening are never a health problem at all.^{46,47} The over diagnosis of DCIS leading to overdiagnosis of true disease and treatment is an unquantifiable risk. This is truer for women at 40-49 years in whom DCIS represents a higher percentage of breast cancer diagnosis.

KEY POINT 4f : Clinical Breast Examination (CBE) in a screening program gives no additional benefit

Even-though approximately 60% of the 29% reduction in mortality seen in the HIP trial has been attributed to CBE, NO STUDY has demonstrated any additional benefit on survival from inclusion of CBE to the screening program.^{48,49,50} In developing countries like Nepal mammographic screening for entire population of women above 50 is not possible CBE is the only cost effective screening tool.

KEY POINT 4g : Non benefit situation from screening mammogram

1. False negative mammography

The BCDDP (Breast Cancer Detection and Demonstration Project)⁵¹ showed 10.8% of breast cancer in women 40-49 were detected by CBE and BSE alone compared to 5.2% at 50-59 year group and 4.7% >60 year group.

2. Cost burden

I do not think that the hidden costs could ever be analyzed. Salzmann et al⁵² reported that biennial screening of women 50-69 compared with no screening leads to a cost per year of life saved at USD 21,400. If screening is added to 40-49 year age group each 18 months then the cost per year of life saved spirals to USD 105,000.

RATIONALIZING INFORMATION ABOUT SCREENING with all the data scrutinized we can finally put come definite conclusions regarding screening and its implications

- ? Mammography can reduce breast cancer mortality.
- ? Observed benefits from screening will not be same for all women.
- ? Benefits for women less than 50 and more than 70 will be less and delayed.
- ? Unless further RCT give some definite answers disagreements will persist.

KEY POINT 5 : Mass, Nipple discharge, Abnormal mammogram, Breast pain are the new presentations of breast cancer all with different implications.

KEY POINT 5a : MASS

Morrow⁵³ et al reviewed 605 women <40 referred for surgical consultation for evaluation of breast masses. The information is outlined in Table II

- ? Premenopausal women with palpable mass should go in for FNAC.
- ? Post menopausal women should go for mammography before FNAC to define the extent of possible malignancy, identify non palpable lesions (mass/calcifications) which might influence therapy.⁵⁴
- ? Routine cytology of cysts is not indicated as shown by both Morrow⁵⁵ and Giatto.⁵⁶ Giatto analyzed 6782 cyst aspirates and found atypical cells in 1677 cases and no cancer cell could be identified.
- ? Younger women, with non-worrisome masses on CBE; should be screened by USG rather than mammogram.
- ? FNAC of breast masses give a sensitivity and specificity of 100-96%.
- ? Controversy exists in the management of patients with palpable masses, which have a benign FNA result. When

physical examination (PE), Mammography, FNA are all benign the so called TRIPLE NEGATIVE TEST an incidence of carcinoma will be present in 0.6 – 3.4 % cases.^{57,58}

Do not be misled by triple negative test if a mass is not seen in mammography and there is no epithelial cell in cytology. We can put the patient in planned observation only if

- ? Epithelial cell is seen on FNAC but report is benign.
- ? Mammography shows a classic benign mass.
- ? CBE also diagnoses benign lesion.

KEY POINT 5b : NIPPLE DISCHARGE

- ? 3% to 11% women with cancer of breast have nipple discharge and this likelihood increases with age.⁵⁹ Seltzer et al⁶⁰ had shown that 32% of women presenting with nipple discharge an no mass had cancer compared to 6% if less than 65 years of age.
- ? Pathological discharge is spontaneous, unilateral and usually from on duct. Even-though 70%-85% of nipple discharges secondary to carcinoma will have blood, any pathological but non-bloody discharge should undergo full evaluation.
- ? Like cystic fluids the cytology of nipple discharges are not useful.
- ? Galactography is very controversial and it never alters the surgical regimen. Dawes⁶¹ has reported 4/20 patients with pathological discharges with normal galactography results who had intraductal cancer. I totally agree with him that there is no replacement for duct excision for pathological nipple discharge.
- ? Duct fiberoscopy and nipple discharge for tumor markers are upcoming tools.

KEY POINT 5c : BREAST PAIN

This is a distinctly unusual symptom of carcinoma. 7% of 240 women with carcinoma breast had pain as their sole symptom.⁶²

KEY POINT 5d: ABNORMAL MAMMOGRAM

- ? Generally 20% to 35% of lesions suspicious on mammography will have carcinomas.⁶³
- ? Most of the mammographically detected lesions do not have clinical correlates. They will need further clinical/

Table II : Mode of Detection⁵³

Mode of detection	CBE Prim Health Worker	Breast Self Exam
Number	121	484
Surgeon confirmed mass	20%	36%
Positive Predictive value	19%	29%
HPR proven Cancer	5%	5%

imaging workup. Morrow⁶⁴ has already reported that 67% of the 267 consecutive women referred for surgical evaluation after abnormal mammogram had incomplete radiological workup. After completing the radiological workup only 150 of the 267 patients needed biopsy.

- ? The BI-RADS is the only quality assurance tool devised for standardizing mammographic reporting, which is repeatedly cited and quoted.⁶⁵
- ? Discordance between needle biopsy and mammographic reporting should warrant an excision biopsy.

KEY POINT 6 : IMPLICATIONS OF MENSTRUAL CYCLE AND TIMING OF SURGERY ON PROGNOSIS

Estrogen remains unopposed during the follicular phase; upto day 12, during the rest of the menstrual cycle (MC) progesterone opposes the effects of estrogen. It was Ratajczak⁶⁶ et al who first reported the resection of tumors during the preoestrous phase was associated with 2.5 times better survival rate than in the metestrous phase mainly due to influence of lung metastases. There are 3 states when women experience unopposed estrogen and if our theory should be true then deleterious effects should be seen in each of these three states. The works of Badwe deserve to be credited here.

- a) D3-D12 of MC.
- b) Post menopausal women.
- c) Obese women (They produce more estrogen)

Badwe⁶⁷ has compared the survival of women on whom surgery was performed during the D3-D12 of MC (unopposed estrogen) with that of women in the remainder part of their cycle. The result is summarized in Table III. Here the fact that women will have poor survival if operated in D3-D12 phase was highlighted with statistical significance of ($p=.001$).

Badwe⁶⁸ has also done a metanalysis of 22 published series, which have examined the effect of menopausal status/age at diagnosis on survival. 15 of the 22 studies revealed better survival in premenopausal women (<50). Seven showed equivocal results. With odds reduction of 24% and $2P < 0.0000001$ these figures cannot be ignored.

Badwe⁶⁹ has also metanalyzed 18 studies related to obesity and breast cancer survival. Here 12 studies showed non-obese women having better survival rates and 6 showed equivocal results. None showed obese women to have better survival. Odds reduction of 35.6 ± 3.7 and $2P < 0.000001$ are very

powerful reminders.

Tumor cells under the influence of estrogen have an increased ability to produce proteases. Other prognostic factors of breast cancer notably EGF⁷⁰ and Cyclin D⁷¹ are also unfavorably modulated by estrogen. Finally the natural killer cell activity is lowest during this phase.⁷²

KEY POINT 7 : EXAMINING THE Surgical Dissemination Autonomy CONCEPT

This concept implies that surgery itself could influence the dissemination or autonomy of distant metastasis. The only way to test this concept would be to compare surgery with no surgery. This could be very unethical and the best compromise would be to examine randomized trials where is surgery is delayed in the control group by 18-24 months (lead-time). Conventional theory implies that since the metastasis is determined by micrometastases unrecognized at the time surgery; the event of surgery would not influence the natural history of disease. If this were true then death rate would be same for both groups for the first several years. The meta-analysis of Eldwood⁷³ has reported excess mortality in the second group in the first few years. This excess mortality was seen in the first 7 years for <50 and for first 1 year for >50 women. For the first few years early surgical intervention had deleterious effect for other cancers too.^{74,75} Conventional theory also assumes that tumor size determines preexisting micrometastases. Then T1 tumors should enjoy a lead time = transition from T1-T2. This could not be shown from the Kings/Cambridge Study.⁸ Most studies including an excellent one from Tata Memorial Cancer Center, Mumbai, India using life table analysis show the expected difference in survival for T1 and T2 tumors. 5YSR of 72% and 52%. But the time to relapse is same for T1 and T2 tumors. The difference is only in the number of patients who relapse. Examining the life table curve of patients who relapsed: showed a median relapse free survival (RFS) of 22 and 21 months for T1 and T2 respectively. Thus smaller tumors do not recur later but recur in less smaller numbers than larger tumors during the same time span.⁷⁶

KEY POINT 8 : MANAGING THE AXILLA

Present surgeons do not validate the Halstedian principles. We do not consider regional or nodal spread a pre-requisite for distant metastases. Long term follow-up of node negative

Table III : 10 YSR of women operated in different phases of MC.⁶⁷

Phase of MC	Number	10 Year Survival Rate
D3 - D12	75	54%
Other	174	84%

patients who underwent radical mastectomy with axilla clearance has shown that 30% died due to metastatic breast cancer.⁷⁷ Dissection internal mammary and supraclavicular chains also did not improve survival.^{78,79} Veronesi⁸⁰ studied 539 node positive patients who underwent complete ALND (axillary lymph node dissection) and reported skip lesions in 4% cases. He also reports that levels II ALND will correctly stage 96% of cases. Removal of level III increases risk of edema without any additive prognostic information. Axillary treatment is still integral to invasive cancers but not for in situ lesions. Surgery and radiation can manage the axilla. Surgery is indicated for node positive cases due to the larger doses needed by radiation therapy for clearing for such an axilla. Surgery is also valued more for its staging contribution. The much-hyped sentinel lymph node biopsy (SLNB) should be viewed very carefully. I agree with McMasters⁸² that comments on SLNB are meaningless till the NSABP-32 trial results are made public as its false negative rates are still to be computed.

CONCLUSION

Controversy still reigns among surgical societies even after 2500 years of experience with this disease. Practicing on anecdotal teachings handed out to us rather than evidence based approach explains why surgeons have ranged their treatment from lumpectomy to radical mastectomies for the same stage disease. Avoiding surgery during D3-D12 of MC, Optimizing breast conservation, adjuvant and neoadjuvant therapies along with multidisciplinary approach are the only solutions. Top priority is needed to form a task force to create feasible and effective guidelines for our country.

REFERENCES

1. Tan, Z.B., et al.: How we perform chest wall reconstruction: Analysis of 31 cases. *Indian J Cancer*, 2003; 40: 27-30.
2. Singh, Y., et al.: Nepalese breast in relation to reproductive factors: Comparison between Nepalese and Japanese cases. *Anticancer Res* 2002, 22: 319-23.
3. Braun, C.M., I tano, J.K. Cancer care in Nepal: Variables that effect diagnosis, treatment and prognosis; a case study. *Cancer Nurs.* 2001, 24: 137-42.
4. Ismail, J.: Editorial, *Surg Clin North Am*, 1999; 79.
5. Sayami, P et al.: Retrospective analysis of breast cancer cases and surgical treatment in a period of 10 years. *J Nepal Med Assoc.*, 2001; 40:112-19.
6. Fletcher, G.H., McNeese, M.D., Oswald, M.J.: Long range results for breast cancer patients treated with radical mastectomy and post operative radiation without adjuvant chemotherapy: An update: *Int J Radiat Oncol Biol Phys*, 1989; 17:11-14.
7. Levi tt, S.H.: The importance of loco-regional control in the treatment of breast cancer and its impact on survival. *Cancer*, 1994; 74:1804-806.
8. Jaoti, I.: Breast cancer a systemic or a local disease? *Am J Clin Oncol*, 1997; 20: 536-39.
9. Wood, W.C.: Progress from clinical trials on breast cancer. *Cancer*, 1994; 74: 2606-09.
10. Ariel, I.M.: Breast cancer a historical review: Is the past prologue? In Ariel I.M., Cleary, J.B., (eds) *Breast Cancer Diagnosis and Treatment*. New York, McGraw Hill, 1987; 3-26.
11. LeDran, H.F.: Memoires avec un precis du peusieurs observations sur le chirurgie, 1757; 3:1-54.
12. Virchow, R: Cellular Pathology. Philadelphia, J.B. Lippincott, 1863.
13. Halsted, W.S.: A clinical and histological study of certain adenocarcinoma of the breast and a brief consideration of the supraclavicular operation and results of operations of cancer of the breast from 1889 to 1898 at the John Hopkins Hospital. *Ann Surg*, 1898; 28: 557-76.
14. Halsted, W.S.: The results of operations for the cure of cancer of the breast performed at the John Hopkins Hospital from June 1889 to Jan 1894. *Ann of Surg*, 1894; 20: 497-555.
15. Fisher, B.: Personal contributions to progress in breast cancer research and treatment. *Semin Oncol*, 1996; 23: 414-27.
16. Hellman, S.: Natural history of small breast cancers. *J Clin Oncol*, 1994; 12: 2229-54.
17. Bloom, H.J.G., Richardson, W.W., Harries, E.J.: Natural history of untreated breast cancer (1805-1933). *BMJ*, 1962; 2: 213-21.
18. Henderson, I.C., Canellos, E.P.: Cancer of the breast: The past decade. *N Engl J Med*, 1995; 302: 951-52.
19. Fisher, B., Redmond, C., Fisher, E.R., et al.: Reanalysis and results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med*, 1995; 332: 674-81.
20. Cancer Research Campaign Working Party: Cancer Research Campaign (King's/Cambridge) trial for early breast cancer. *Lancet* ii, 1980; 55-60.
21. Blichert-Toft, M., Rose, C., Anderson, J.A., et al.: Danish randomized trial comparing breast conservation therapy with mastectomy. *J Natl Cancer Inst Monogr*, 1992 11: 19-25.
22. Fisher, B., Anderson, S., Redmond, C.K., et al.: Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*, 1995; 333: 1456-61.
23. Jacobson, J.A., Cowan, K.H., D'Angelo, T., et al.: Ten-year results of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med*, 1995; 332: 907-11.

24. Sarrazin, D., Le, M., Arriagada, R., et al.: Ten year results of a randomized trial comparing conservative treatment to mastectomy in early breast cancer, *Radi other Oncol*, 1989; 14: 177-84.
25. Van Donegen, J.A., Bartelink, H., Fentiman, I.S., et al.: Randomized clinical trial to assess the value of breast conserving therapy in stage I and II breast cancer, EORTC 10801 trial, *J Natl Cancer Inst Monogr*, 1992; 11: 15-18.
26. Vernosi, U., Sacrozi, R., Del Vecchio, M., et al.: Comparing radical mastectomy with quadrantectomy, axillary dissection and radiotherapy in patients with small cancers of the breast. *N Engl J Med*, 1981; 305: 6-11.
27. Eggers, C.: Cancer Surgery: The value of radical operations for cancer after lymphatic drainage area has become involved. *Ann Surg*, 1937; 106: 668-89.
28. Karri son, T.G., Ferguson, D.J., Meier, P.: Dormancy of mammary carcinoma after mastectomy. *J Natl Cancer Inst Monogr*, 1999; 91: 80-85.
29. Jatoi, I., Hilsenbeck, S.G., Clark, G.M., et al.: The significance of axillary lymph node dissection in primary breast cancer. *J Clin Oncol*, 1999; 17: 2334-40.
30. Langlands, A.O.: Prognostic factors in the curability of breast cancer. *Aust NZ J Surg*, 1995; 65: 630-33.
31. Brinkley, D., Haybittle, J.L.: Long term survival in women with breast cancer. [letter] *Cancer Res*, 1988; 48: 2314-24.
32. Karri son, T.G., Ferguson, D.J., Meier, P.: Dormancy of mammary carcinoma after mastectomy. *J Natl Cancer Inst*, 1999; 91: 80-85.
33. Carter, C.L., Allen, G., Henson, D.E.: Relation of tumor size, lymph node status and survival in 24740 breast cancer cases. *Cancer*, 1989; 63: 181-87.
34. Barr, L.C., Baum, M.: Time to abandon TNM staging for breast cancer? *Lancet*, 1992; 339: 912-15.
35. Black, W.C., Welch, H.G.: Screening for disease. *Am J Roentgenol*, 1997; 168: 3-11.
36. Day, N.E., Williams, D.R.R., Khaw, K.T.: Breast Cancer Society Program: The development of a monitoring and evaluation system, *Brit J of Cancer*, 1989; 59: 954-58.
37. Singh, G.K., Kochanek, K.D., MacDorman, M.F.: Advance report of final mortality statistics, 1994. Monthly vital statistics report; vol 45 no 3 supp. Hyattsville, MD, Centers for Disease Control and Prevention, National Cancer Health Statistics, 1996. Layfield, L.J., Glasgow, B.J., Cramer, H.: FNAC in the management of breast masses. *Pathol Annu*, 1989; 24:23.
38. Saphiro, S., Venet, W., Strax, S., et al.: Periodic screening for breast cancer: The Health Insurance Plan Project and its sequel, 1983-1986. Baltimore, M.D. The John Hopkins University Press, 1988.
39. Tabar, D.B., Gao, D.L., Sel f, S.G., et al.: Reduction in mortality from breast cancer after screening with mammography. *Lancet*, 1985; 325: 829-32.
40. Keri lowske, K., Grady, D., Rubin, S.M., et al.: Efficiency of screening mammography: A meta-analysis. *JAMA*, 1995; 273: 149-54.
41. Hendrik, R.E., Smith, R.A., Rutledge, J.H., et al.: Benefit of screening mammography in women aged 40-49 years: A new meta-analysis of randomized trials. *Monogr Natl Cancer Inst*, 1997; 22: 87-92.
42. Tabar, L., Chen, H.-H., Fagerberg, G., et al.: Recent studies from Swedish Two County Trials: The effect of age, histology type and mode of detection of efficiency of breast cancer screening. *Monogr Natl Cancer Inst*, 1997; 22: 43-47.
43. Keri lowske, K., Grady, D., Bracley, J., et al.: Effect of age, breast density and family history on the sensitivity of first screening mammography. *JAMA*, 1996; 276: 33-38.
44. Fletcher, S.W., Black, W., Harris, R., et al.: Report of the international workshop on the screening of breast cancer. *J Natl Cancer Inst*, 1993; 85: 1644-56.
45. Surveillance Epidemiology and End Results [SEER] Program Cancer Statistics Review (1973-1995), Bethesda, M.D., National Cancer Institute, Division of Cancer Prevention and Control, Surveillance, Cancer Statistics Branch, 1998.
46. Page, D.L., Dupont, W.D., Rogers, L.W., et al.: Intraductal carcinoma of the breast - Follow-up after biopsy only. *Cancer*, 1982; 49: 751-58.
47. Rosen, P.P., Braun, D.W., Kuri e, D.E.: The clinical significance of pre-invasive breast cancer. *Cancer*, 46:919-925, 1980. [Baines, C.J., Miller, A.B.: Mammography versus clinical examination of the breasts. *Monogr Natl Cancer Inst*, 1997; 22: 125-29.]
48. Miller, A.B., Baines, C.J., To, T., et al.: Canadian National Breast Screening Study: 1 Breast Cancer detection and death rates among women aged 40-49 years. *Can Med Assoc J*, 1992; 147: 1477-88.
49. Miller, A.B., Baines, C.J., To, T., et al.: Canadian National Breast Screening Study: 2 Breast Cancer detection and death rates among women aged 40-49 years. *Can Med Assoc J*, 1992; 147: 1477-88.
50. Saphiro, S., Venet, W., Strax, S., et al.: Ten to fourteen year effect of screening on breast cancer mortality. *J Natl Cancer Inst*, 1982; 69: 349-55.
51. Smart, C.R., Bryne, C., Smith, R.A.: Twenty year follow-up of breast cancer diagnosed during the Breast Cancer Detection and Demonstration Project, *CA Cancer J Clin*, 1997; 47: 134-49.
52. Salzman, P., Keri lowske, K., Philip, S.K.: Cost effectiveness of extending screening mammography to include women 40-45 years old. *Ann Int Med*, 1997; 127: 966-72.
53. Morrow, M., Wong, S., Venta, L.: The evaluation of breast masses in women younger than 40 years. *Surgery*, 1998; 124: 634.
54. Morrow, M., Wong, S., Venta, L.: Patient selection for breast conservation therapy with magnification mammography. *Surgery*, 1988; 124: 364.

55. Morrow, M.: Indications and techniques for breast biopsy. In Kavanagh, J.J., Singletary, S.E., Einhorn, N., et al.: (eds): *Cancer in Women*, London, Blackwell Science, 1998; 103.
56. Giatto, S., Caricaggi, P., Bulgaresi, P.: The value of routine cytological examination of cyst fluids. *Acta Cytol*, 1987; 31: 301.
57. Donegan, W.L.: Evaluation of palpable breast masses. *N Engl J Med*, 1992; 327: 937.
58. Bell, D.A., Hajdu, S.I., Urban, J.A., et al.: Role of aspiration cytology in the diagnosis and management of mammary lesions in office practice. *Cancer*, 1983; 51: 1182.
59. Urban, J., Egeli, R.: Nonlactational nipple discharge. *CA Cancer J Clin*, 1978; 28: 3.
60. Seltzer, M., Perloff, L., Kelley, R., et al.: The significance of age in patients with nipple discharge. *Surg Gynecol Obstet*, 1970; 131: 519.
61. Dawes, L.G., Bowen, C., Venta, L.A., et al.: Ductography for nipple discharge: No replacement for duct excision. *Surgery*, 1998; 124: 685.
62. Pearce, P.E., Baum, M., Manse, R.E., et al.: Importance of mastalgia in operable breast cancer. *Br Med J*, 1982; 284: 1299.
63. Knutzen, A., Givold, J.: Likelihood of malignant disease for various categories of mammographically detected nonpalpable breast lesions. *Mayo Clin Proc*, 1993; 68: 454.
64. Morrow, M., Schmidt, R., Cregar, B., et al.: Preoperative evaluation of abnormal mammographic findings to avoid unnecessary breast biopsies. *Arch Surg*, 1994; 129: 1090.
65. American College of Radiology: Breast Imaging Reporting and Data System (BI-RADS), ed 2. Reston VA, *American College of Radiology*, 1995.
66. Ratajczak, H.V., Sothorn, R.B., Hrushesky, W.M.: Estrogen influence on surgical cure of mouse breast cancer. *J Exp Med*, 1988; 168: 73-83.
67. Badwe, R.A., Gregory, W.M., Chaudhary, M.A., et al.: Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer. *Lancet*, 1991; 337: 1261-64.
68. Badwe, R.A., Fentiman, I.S., Richards, M.A., et al.: Bodyweight and vascular invasion in postmenopausal women and breast cancer. *Br J Cancer*, 1997; 75: 910-13.
69. Badwe, R.A., Hawaldar, R.: Timing of surgery and breast cancer. *Ann Oncol*, 1991; 5: 29-31.
70. Marques, L.A., Franco, E.L.: Association between timing of surgery during the menstrual cycle and prognosis in premenopausal breast cancer. *Cancer*, 1993; 53: 707-708.
71. Altucci, L., Addeo, R., Cicciello, L., et al.: 17beta-estradiol induces cyclin D1 gene transcription p36D1-p34cdk4 complex activation and phosphorylation during mitogenic stimulation of G1 arrested human breast cancer oncogene. *Cancer*, 1996; 12: 2315-24.
72. Hanna, W., Schnieder, M.: Enhancement of tumor metastases and suppression of KNC cell by beta-estradiol treatment. *J Immunol*, 1973; 130: 974-914.
73. Eldwood, J.M., Cox, B., Richardson, A.K.: The effectiveness of breast cancer screening by mammography for younger women. *Online J Curr Clin Trials Doc*, 1993; 32.
74. Fontana, R.S.: Screening for lung cancer. In Miller AB (ed): *Screening for Cancer*. Orlando FL, Academic Press, 1985; 377-95.
75. Kubik, A., Parkin, D.M., Khat, K., et al.: Lack of benefit from semiannual screening for cancer of the lung. Follow-up report of a randomized control trial of a population of the high risk males in Czechoslovakia. *Int J Cancer*, 1990; 45: 26-33.
76. Rajendra, A. et al.: Timing of surgery with regards to menstrual cycle in women with breast cancer. *Surg Clin North Am*, 1999; 79: 1047-59.
77. Bonnadonna, G., Valagussa, P.: The contribution of medicine to primary treatment of cancer. *Cancer Res*, 1988; 48: 2314-24.
78. Urban, J., Marjoni, M.A.: Significance of internal mammary lymph node metastases *AJR Am J Roentgenol* 111; 1971; 130-36.
79. Wangwinsteen, O.h.: Another look at supraductal operation for breast cancer. *Surgery*, 1957; 41: 857-61.
80. Veronesi, U., Rilke, F., Lunnin, A., et al.: Distribution of axillary node metastases by level of invasion. *Cancer*, 1987; 59: 682-87.
81. McMasters, K.M., Giuliano, A.R., Ross, M.I., et al.: Sentinel lymph node biopsy for breast cancer - not yet standard of care. *N Engl J Med*, 1998; 339: 990-95.