

**A NOVEL APPROACH FOR LOCAL TREATMENT OF
BREAST CANCER**

DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

JAYANT SHARAD VAIDYA

AT

UNIVERSITY COLLEGE LONDON

1996-2001

©Jayant S Vaidya FRCS MS DNB PhD
Department of Surgery
University College London
67-73 Riding House Street
London W1W 7EJ
j.vaidya@ucl.ac.uk

CHAPTER 8

Conclusion

Breast cancer treatment has undergone immense changes in the last century-these have been prompted mainly by changing models of disease. In addition, change was brought about by developments in other fields of medicine, for example, availability of good anaesthetic technique allowed Halsted to perform major surgery. More recently, patient advocacy groups have prompted change. Paradoxically this was less relevant for the development of conservative breast surgery but is becoming increasingly important in the demand for sentinel node biopsy in today's patient/ consumer/ client led world.

Breast cancer treatment is mainly directed towards achieving two goals- local tumour control with cosmetic outcome as an important secondary aim and systemic control with personal cure of the disease as the final goal. This thesis deals with the former- the optimal local control of disease.

The history of breast cancer treatment and the concept of local recurrence are dealt with in detail in the first chapter. It appears from various clinical trials of breast conserving surgery that clinically relevant invasive duct carcinoma is to some extent a "focal" disease that is limited to one quadrant of the breast. This may be related to the suggestion that chromosomal abnormalities arise at an early age and are therefore distributed in a segmental fashion along the primary branches of the duct system. These chromosomal abnormalities are probably more important in developing a milieu that is conducive

for transformation rather than actual transformation itself because, the segmental nature is restricted to clinically expressed invasive ductal carcinoma rather than occult or latent cancers. The spatial distribution of latent *in situ* cancer, as described in the second chapter, is on the other hand not segmental in nature, i.e., occult cancers are distributed evenly in all quadrants of the breast with no difference in such distribution between individual cancer types. It appears that for development of invasive ductal cancer, the local milieu of the surrounding breast tissue is very important and when a conducive milieu is present in any one area of the breast, it promotes the growth of tumours, both primary and recurrent. For lobular cancers and for breasts harbouring extensive intra-ductal cancer, it appears that the surrounding milieu is either less important or, is already conducive to cancer growth in all areas, so that clinically important cancers can develop in all areas of the breast. In addition invasive lobular cancers have been characterized by their ability to secrete proteolytic enzymes allowing an alternative mechanism of local progression to the expansile growth of invasive duct cancers. Further studies in breast cancer should involve investigating the characteristics of breast milieu commonly called 'field change' that induces or promotes cancer growth in particular quadrants.

The next phase in this project was to test the hypothesis that there might be a pre-clinical test that could characterise the clinical relevance of occult cancers. We hypothesised that Magnetic resonance imaging- which relies on tumour vascularity for producing contrast enhanced images, might be able to detect tumours that are more

vascular and therefore, more clinically relevant. However, contrast enhanced MRI proved to be perhaps too sensitive and was able to detect almost all occult cancers that we could subsequently detect using detailed histopathology. We concluded that we should use this new tool with caution and not allow ourselves to be precipitated into a mastectomy for the majority of patients thus overthrowing the wisdom gleaned from the robust results of breast conservation trials.

These being the biological implications of our findings, the clinical implications were rather straightforward, albeit going against the current dogma of breast conservative surgery. The argument for whole breast radiotherapy after breast conservative therapy arose from the idea that breast cancer is a multifocal/multicentric disease, with most (90%) of the multifocality in proximity to the primary tumour. This was the explanation given for the increased incidence of local recurrence near the primary tumour. Our whole organ analysis in 3-dimensions found that occult tumours were present in all quadrants and not related to the spatial distribution of the primary tumour and are thus not relevant for early local recurrence – which occurs most commonly in the index quadrant rather than anywhere else, for reasons yet to be elucidated. If the widespread multifocality is not clinically relevant, then the standard whole breast radiotherapy after breast conserving surgery is of questionable value.

We present the problems faced by patients undergoing breast

conserving therapy and health care systems delivering it. The 6-wk course of radiotherapy is costly and inconvenient at best and prohibitive at worst. Many women living in geographically remote areas, far from a radiotherapy centre, cannot take the 6-wk holiday in the metropolis to take the radiotherapy course, and not many welfare states can provide for their accommodation or transport. Frequently these women have to choose between mastectomy and breast conservation, on the basis of, not the nature of the cancer, but on whether they can afford commute daily, or to live near the radiotherapy centre for the 30 visits during the course of radiotherapy. A solution to these problems is to deliver radiotherapy only to the quadrant of primary tumour with a technique that can do it in one sitting- preferably in the operating theatre at the time of the primary surgery. We describe one such technique of delivering therapeutic radiation in a standard operating theatre. The machine is called Photon Radiosurgery System (PRS). This technique directs soft x-rays generated with a portable lightweight electron-beam-driven device. These x-rays are generated at the centre of an applicator that can be placed in the tumour bed. So the radiation is from within the breast and as the pliable breast tissue wraps around the applicator, true conformal radiotherapy dosimetry is achieved. The highest dose is delivered to the tissues immediately adjacent to the applicator and normal tissues like skin do not get significant radiation damage. Since the high dose region is of a small volume we expect that the late fibrosis, if any, will not be disfiguring.

We had two tasks- first to test the novel radiotherapy technique and then to test then novel approach of single dose

index quadrant radiation. In the first phase, we substituted the conventional 1wk course of tumour bed boost with intra-operative radiotherapy using the PRS device; the remaining 5-wk course of whole breast radiotherapy (50Gy, #25) was delivered as usual. In the pilot phase we tested the feasibility of conducting the clinical trial- patient acceptability, the logistics of co-ordination between the radiotherapy, radiation physics and surgical departments and the clinical results. We found the usual resistance to change in the administrative circles- but the business proposition of possible saving money for NHS was attractive to the management. The patient acceptability was the least difficult area- only 2 of the patients offered the novel treatment refused to take part in the pilot study. Many patients were keen not to take the 5wk course, suggesting to us that recruitment in the next phase of the project would be relatively easy. The pilot study and the operative technique are described in the 4th and 5th chapters. There has been no local recurrence in any of the patients on the pilot study at the median follow up of 34 months and the cosmetic outcome is good and the patients are satisfied. The results of the pilot study were instrumental in getting FDA approval for the PRS device.

We also used the PRS device in another increasingly common clinical situation. Elderly patients who are not fit for surgery, but are nevertheless known to benefit from local treatment are frequently treated with tamoxifen alone for the want of suitable local therapy. We tested the use of PRS radiotherapy as the

primary treatment in these cases. We used the Fischer Mammothest prone table- for stereotactic localisation of the primary tumour and Mammothome vacuum biopsy for limited excision under local anaesthetic. After calibrating the Fischer table for the PRS device, we placed the tip of the bare PRS probe in the centre of the tumour. The radiation dose of over 130 Gy was achieved at the centre with the periphery of the tumour receiving about 20 Gy. We found remarkable response to this treatment. The contrast-enhanced MRI, just 6 days after treatment revealed an almost absence of vascular enhancement in the tumour. All these patients with other co-morbid conditions and short life expectancy have lived the rest of their life without suffering from the morbid sequelae of breast cancer.

Encouraged by the results of the pilot phase, we started the randomised trial in March 2000, to test the hypothesis that radiotherapy to the peri-tumoural tissues alone is adequate local treatment. We called it TARGeted Intraoperative radioTherapy (TARGIT) trial. The randomisation procedure was much easier than expected. We were able to recruit more than 90% of patients eligible for the trial. Only 3-4 patients have refused to take part- mainly because the option of entry into trial is usually given early in the discussions about treatments and it was too much to take in for the patient. The early cosmetic results are good and there has not been any recurrence although the follow up time is short. Since the numbers needed to prove equivalence are 850 in each arm, a multicentre trial was deemed a necessity. A recent modification will change the trial from an equivalence trial to a trial to test whether a strategy

using Targit for all patients and additional whole breast radiotherapy for high-risk patients reduces local recurrence rates compared with conventional postoperative radiotherapy. Such a trial will need 419 patients in each arm to show a reduction in local recurrence from 9% to 4%.

This trial has attracted worldwide interest and several investigators from Australia, India, UK, Italy and USA are keen to join in. The protocol of the randomised study has been peer-reviewed and published on the Lancet Website.

The implications of proving TARGIT equal to 6-wk course of radiotherapy are far reaching. Firstly, it will save the ordeal that these women have to face to come daily for the 'radiotherapy shot'. As one woman in our trial described it to BBC's Tomorrow's world- 'I felt a bit of a fraud... have I really had cancer treatment? I had finished all my treatment and was back at work in 2 days'. In the more 'prosperous' countries, it will mean saving millions of pounds and radiotherapy resources and for the thousands of women in the developing countries and remote areas of developed world, it will mean they can preserve their breasts!

References

- Ahsan H, Neugut AI (1998) Radiation therapy for breast cancer and increased risk for esophageal carcinoma. *Ann Intern Med* 128: 114-117
- Amichetti M, Busana L, Caffo O (1995) Long-term cosmetic outcome and toxicity in patients treated with quadrantectomy and radiation therapy for early-stage breast cancer. *Oncology* 52: 177-181
- Anastassiades O, Iakovou E, Stavridou N, Gogas J, Karameris A (1993) Multicentricity of breast cancer A study of 366 cases. *Am J Clin Oncol* 99: 238-243
- Assersohn L, Powles TJ, Ashley S, Nash AG, Neal AJ, Sacks N, Chang J, Querci della RU, Naziri N (1999) Local relapse in primary breast cancer patients with unexcised positive surgical margins after lumpectomy, radiotherapy and chemoendocrine therapy [see comments]. *Ann Oncol* 10: 1451-1455
- Astor MB, Hilaris BS, Gruerio A, Varricchione T, Smith D (2000) Preclinical studies with the photon radiosurgery system (PRS). *Int J Radiat Oncol Biol Phys* 47: 809-813
- Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR (2000) Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst* 92: 269-271
- Atkins H, Hayward JL, Klugman DJ, Wayte AB (1972) Treatment of early breast cancer: a report after ten years of a clinical trial. *Br Med J* 2: 423-429
- Axelsson CK, Mouridsen HT, Zedeler K (1992) Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). *Eur J Cancer* 28A: 1415-1418
- Axelsson CK, Rank F, Blichert-Toft M, Mouridsen HT, Jensen MB (2000) Impact of axillary dissection on staging and regional control in breast tumors < or = 10 mm--the DBCG experience. The Danish Breast Cancer Cooperative Group (DBCG), Rigshisoutalet, Copenhagen, Denmark. *Acta Oncol* 39: 283-289
- Bates T, Fennessy M, Latteier J, MacRae K, Riley DL, Houghton J, Baum M. Surgery for early breast cancer improves survival in the elderly: result of a randomized trial of tamoxifen alone versus surgery plus tamoxifen. *Br.J.Surg.* 88[41], Suppl 41-41. 1-5-2001.
- Bates T, Riley DL, Houghton J, Fallowfield L, Baum M (1991) Breast cancer in elderly women: a Cancer Research Campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. The Elderly Breast Cancer Working Party. *Br J Surg* 78: 591-594
- Baum M, Vaidya JS, Mitra I (1997) Multicentricity and recurrence of breast cancer [letter; comment]. *Lancet* 349: 208
- Beck RM, Gotz L, Heywang-Kobrunner SH (2000) Stereotaxic vacuum core breast biopsy--experience of 560 patients. *Swiss Surg* 6: 108-110
- Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, Di Palma S, Simony-Lafontaine J, de M, I, van de Vijver MJ (2001) Risk factors for recurrence and metastasis after

breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol* 19: 2263-2271

Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnattelli L, Brambilla C, De Lena M, Tancini G, Bajetta E, Musumeci R, Veronesi U (1976) Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 294: 405-410

Boyages J, Recht A, Connolly JL, Schnitt SJ, Gelman R, Kooy H, Love S, Osteen RT, Cady B, Silver B (1990) Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiother Oncol* 19: 29-41

Brenner DJ, Leu CS, Beatty JF, Shefer RE (1999) Clinical relative biological effectiveness of low-energy x-rays emitted by miniature x-ray devices. *Phys Med Biol* 44: 323-333

Buadu LD, Murakami J, Murayama S, Hashiguchi N, Sakai S, Masuda K, Toyoshima S, Kuroki S, Ohno S (1996) Breast lesions: correlation of contrast medium enhancement patterns on MR images with histopathologic findings and tumor angiogenesis. *Radiology* 200: 639-649

Butler WE, Piaggio CM, Constantinou C, Niklason L, Gonzalez RG, Cosgrove GR, Zervas NT (1998) A mobile computed tomographic scanner with intraoperative and intensive care unit applications. *Neurosurgery* 42: 1304-1310

Chan KC, Knox WF, Sinha G, Gandhi A, Barr L, Baildam AD, Bundred NJ (2001) Extent of excision margin width required in breast conserving surgery for ductal carcinoma in situ. *Cancer* 91: 9-16

Clark RM, McCulloch PB, Levine MN, Lipa M, Wilkinson RH, Mahoney LJ, Basrur VR, Nair BD, McDermot RS, Wong CS (1992) Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 84: 683-689

Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, Lipa M, Wilkinson RH, Mahoney LJ (1996) Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 88: 1659-1664

Clark RM, Wilkinson RH, Mahoney LJ, Reid JG, MacDonald WD (1982) Breast cancer: a 21 year experience with conservative surgery and radiation. *Int J Radiat Oncol Biol Phys* 8: 967-979

Clarke DH, Le MG, Sarrazin D, Lacombe MJ, Fontaine F, Travagli JP, May-Levin F, Contesso G, Arriagada R (1985) Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. *Int J Radiat Oncol Biol Phys* 11: 137-145

Cosgrove GR, Hochberg FH, Zervas NT, Pardo FS, Valenzuela RF, Chapman P (1997) Interstitial irradiation of brain tumors, using a miniature radiosurgery device: initial experience. *Neurosurgery* 40: 518-523

Cosgrove R, Spiro I, I, Loeffler J, Biggs P, Beatty J, Zervas NT (1999) Stereotactic interstitial radiosurgery for malignant brain tumors. *Stereotact Funct Neurosurg* 73: 37

Craft PS, Primrose JG, Lindner JA, McManus PR (1997) Surgical management of breast cancer in Australian women in 1993: analysis of Medicare statistics. *Med J Aust* 166: 626-629

Cuzick J, Stewart H, Peto R, Baum M, Fisher B, Host H, Lythgoe JP, Ribeiro G, Scheurlen H, Wallgren A (1987) Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. *Cancer Treat Rep* 71: 15-29

- Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, Peto R, Baum M, Fisher B, Host H (1994) Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy [see comments]. *J Clin Oncol* 12: 447-453
- Dale RG, Jones B, Price P (1997) Comments on Inadequacy of Iridium Implant as sole radiation treatment for operable breast cancer, Fentiman et al., *Eur J Cancer* 1996, 32A, pp 608-611. *Eur J Cancer* 33: 1707-1708
- Deng G, Lu Y, Zlotnikov G, Thor AD, Smith HS (1996) Loss of heterozygosity in normal tissue adjacent to breast carcinomas. *Science* 274: 2057-2059
- Douglas RM, Beatty J, Gall K, Valenzuela RF, Biggs P, Okunieff P, Pardo FS (1996) Dosimetric results from a feasibility study of a novel radiosurgical source for irradiation of intracranial metastases. *Int J Radiat Oncol Biol Phys* 36: 443-450
- Early Breast Cancer Trialists' Collaborative Group (1988) Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. Early Breast Cancer Trialists' Collaborative Group [see comments]. *N Engl J Med* 319: 1681-1692
- Early Breast Cancer Trialists' Collaborative Group (1995) Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med* 333: 1444-1455
- Early Breast Cancer Trialists' Collaborative Group (2000) Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. [see comments]. *Lancet* 355: 1757-1770
- Egan RL (1982) Multicentric breast carcinomas: clinical-radiographic-pathologic whole organ studies and 10-year survival. *Cancer* 49: 1123-1130
- Egan RL, Ellis JT, Powell RW (1969) Team approach to the study of diseases of the breast. *Cancer* 23: 847-854
- Ewing J (1928) *Neoplastic Diseases*. W B Saunders: Philadelphia
- Fentiman, I. S. Long-term follow-up of the first breast conservation trial (Guy's Wide Excision Study). *Eur J Cancer* 34[Suppl 5], S37-S38. 1998.
- Fentiman IS (2000) Long-term follow-up of the first breast conservation trial: Guy's wide excision study. *Breast* 9: 5-8
- Fentiman IS, Matthews PN, Davison OW, Millis RR, Hayward JL (1985) Survival following local skin recurrence after mastectomy. *Br J Surg* 72: 14-16
- Fentiman IS, Poole C, Tong D, Winter PJ, Mayles HM, Turner P, Chaudary MA, Rubens RD (1991) Iridium implant treatment without external radiotherapy for operable breast cancer: a pilot study. *Eur J Cancer* 27: 447-450
- Fentiman IS, Poole C, Tong D, Winter PJ, Gregory WM, Mayles HM, Turner P, Chaudary MA, Rubens RD (1996) Inadequacy of iridium implant as sole radiation treatment for operable breast cancer [see comments]. *Eur J Cancer* 32A: 608-611
- Fisher B (1980) Laboratory and clinical research in breast cancer--a personal adventure: the David A. Karnofsky memorial lecture. *Cancer Res* 40: 3863-3874

Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, Mamounas EP, Deutsch M, Margolese R (1991a) Significance of ipsilateral breast tumour recurrence after lumpectomy [see comments]. *Lancet* 338: 327-331

Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM (1995) 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 [see comments]. *N Engl J Med* 333: 1456-1461

Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, Fisher E, Wolmark N, Deutsch M, Montague E (1985) Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 312: 665-673

Fisher B, Gunduz N, Costantino J, Fisher ER, Redmond C, Mamounas EP, Siderits R (1991b) DNA flow cytometric analysis of primary operable breast cancer. Relation of ploidy and S-phase fraction to outcome of patients in NSABP B-04. *Cancer* 68: 1465-1475

Fisher B, Wolmark N, Redmond C, Deutsch M, Fisher ER (1981) Findings from NSABP Protocol No. B-04: comparison of radical mastectomy with alternative treatments. II. The clinical and biologic significance of medial-central breast cancers. *Cancer* 48: 1863-1872

Fisher B, Gebhardt MC (1978) The evolution of breast cancer surgery: past, present, and future. *Semin Oncol* 5: 385-394

Fisher ER, Anderson S, Redmond C, Fisher B (1992) Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. *Semin Surg Oncol* 8: 161-166

Fisher ER, Costantino J, Fisher B, Palekar AS, Paik SM, Suarez CM, Wolmark N (1996) Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Five-year observations concerning lobular carcinoma in situ. *Cancer* 78: 1403-1416

Fisher ER, Sass R, Fisher B, Wickerham L, Paik SM (1986) Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). I. Intraductal carcinoma (DCIS). *Cancer* 57: 197-208

Forrest AP, Stewart HJ, Everington D, Prescott RJ, McArdle CS, Harnett AN, Smith DC, George WD (1996) Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group [see comments]. *Lancet* 348: 708-713

Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL (1990) Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment [see comments]. *Int J Radiat Oncol Biol Phys* 19: 833-842

Gallager HS, Martin JE (1969) Early phases in the development of breast cancer. *Cancer* 24: 1170-1178

Gazet JC, Ford HT, Coombes RC, Bland JM, Sutcliffe R, Quilliam J, Lowndes S (1994) Prospective randomized trial of tamoxifen vs surgery in elderly patients with breast cancer. *Eur J Surg Oncol* 20: 207-214

Gross SW (1880) *Practical Treatise on Tumours of the Mammary Gland*. Appleton & Co.: New York

- Haffty BG, Harrold E, Khan AJ, Pathare P, Smith TE, Turner BC, Glazer PM, Ward B, Carter D, Matloff E, Bale AE, Alvarez-Franco M (2002) Outcome of conservatively managed early-onset breast cancer by BRCA1/2 status. *Lancet* 359: 1471-1477
- Halsted WS (1894a) The results of operations for the cure of cancer of the breast performed at The Johns Hopkins Hospital from June 1889 to January 1894. *Johns Hopkins Hospital Reports* 4: 297-350
- Halsted, W. S. (1894b) The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Ann.Surg.* 20, 497-555.
- Harris JR, Botnick L, Bloomer WD, Chaffey JT, Hellman S (1981) Primary radiation therapy for early breast cancer: the experience at The Joint Center for Radiation Therapy. *Int J Radiat Oncol Biol Phys* 7: 1549-1552
- Harris JR, Osteen RT (1985) Patients with early breast cancer benefit from effective axillary treatment. *Breast Cancer Res Treat* 5: 17-21
- Haybittle JL, Brinkley D, Houghton J, A'Hern RP, Baum M (1989) Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. *BMJ* 298: 1611-1614
- Heywang-Kobrunner SH, Viehweg P, Heinig A, Kuchler C (1997) Contrast-enhanced MRI of the breast: accuracy, value, controversies, solutions. *Eur J Radiol* 24: 94-108
- Holland R, Hendriks JH, Vebeek AL, Mravunac M, Schuurmans Stekhoven JH (1990) Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. *Lancet* 335: 519-522
- Holland R, Veling SH, Mravunac M, Hendriks JH (1985) Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 56: 979-990
- Houghton J, Baum M, Haybittle JL (1994) Role of radiotherapy following total mastectomy in patients with early breast cancer. The Closed Trials Working Party of the CRC Breast Cancer Trials Group. *World J Surg* 18: 117-122
- Hunter MA, McFall TA, Hehr KA (1996) Breast-conserving surgery for primary breast cancer: necessity for surgical clips to define the tumor bed for radiation planning. *Radiology* 200: 281-282
- Hutter RVP, Dim DU (1971) The problem of multiple lesions of the breast. *Cancer* 28: 1591-1607
- Johansson, B., Karlsson, L., and Liljegren, G. PDR brachytherapy as the sole adjuvant radiotherapy after breast conserving surgery for T1-2 breast cancer. Program and abstracts -10th International Brachytherapy Conference, Madrid, Nucletron, 127. 2000.
- Keynes GL (1937) Conservative treatment of cancer of the breast. *BMJ* 2: 643-647
- Keynes GL (1952) Carcinoma of breast. *St Bart Hosp Rep* 56: 462-466
- King TA, Bolton JS, Kuske RR, Fuhrman GM, Scroggins TG, Jiang XZ (2000) Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg* 180: 299-304

- Koniaris LG, Chan DY, Magee C, Solomon SB, Anderson JH, Smith DO, De Weese T, Kavoussi LR, Choti MA (2000) Focal hepatic ablation using interstitial photon radiation energy. *J Am Coll Surg* 191: 164-174
- Krawczyk JJ, Engel B (1999) The importance of surgical clips for adequate tangential beam planning in breast conserving surgery and irradiation. *Int J Radiat Oncol Biol Phys* 43: 347-350
- Krishnan L, Jewell WR, Tawfik OW, Krishnan EC (2001) Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer. *Breast J* 7: 91-96
- Kurita H, Ostertag CB, Baumer B, Kopitzki K, Warnke PC (2000) Early effects of PRS-irradiation for 9L gliosarcoma: characterization of interphase cell death. *Minim Invasive Neurosurg* 43: 197-200
- Kurtz JM, Amalric R, Brandone H, Ayme Y, Jacquemier J, Pietra JC, Hans D, Pollet JF, Bressac C, Spitalier JM (1989a) Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. *Cancer* 63: 1912-1917
- Kurtz JM, Jacquemier J, Torhorst J, Spitalier JM, Amalric R, Hunig R, Walther E, Harder F, Almendral A, Brandone H (1989b) Conservation therapy for breast cancers other than infiltrating ductal carcinoma. *Cancer* 63: 1630-1635
- Lacour J, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C (1983) Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. *Cancer* 51: 1941-1943
- Lacour J, Le M, Rumeau C, Bucalossi P, Caceres E, Koszarowski T, Jacobelli G, Veronesi U (1976) [International therapeutic trial comparing the value of radical mastectomy (Halsted) and extended mastectomy (Halsted plus internal mammary node dissection in the treatment of breast cancer. 5-year results]. *Chirurgie* 102: 638-649
- Lagios MD (1977) Multicentricity of breast carcinoma demonstrated by routine correlated serial subgross and radiographic examination. *Cancer* 40: 1726-1734
- Latteier J, Bates T, Riley DL, Houghton J, Baum M, Closed Trials Working Party of the CRC Breast Cancer Trials Group L (1997) The addition of surgery to tamoxifen as primary treatment of early breast cancer in women over 70, a multicentre trial. *Breast* 6: 224
- Lewis D, Rienhoff WFJr (1932) A study of results of operations for the cure of cancer of the breast. *Ann Surg* 95: 336
- Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, Adami HO (1999) 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial [see comments]. *J Clin Oncol* 17: 2326-2333
- Lu Q, Nakamura J, Savinov A, Yue W, Weisz J, Dabbs DJ, Wolz G, Brodie A (1996) Expression of aromatase protein and messenger ribonucleic acid in tumor epithelial cells and evidence of functional significance of locally produced estrogen in human breast cancers. *Endocrinology* 137: 3061-3068
- Machtay M, Lanciano R, Hoffman J, Hanks GE (1994) Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 30: 43-48
- Mai KT, Yazdi HM, Isotalo PA (2000) Resection margin status in lumpectomy specimens of infiltrating lobular carcinoma. *Breast Cancer Research and Treatment* 60: 29-33

- McDermott MW, Cosgrove GR, Larson DA, Sneed PK, Gutin PH (1996) Interstitial brachytherapy for intracranial metastases. *Neurosurg Clin N Am* 7: 485-495
- Meier P, Ferguson DJ, Karrison T (1985) A controlled trial of extended radical mastectomy. *Cancer* 55: 880-891
- Meier P, Ferguson DJ, Karrison T (1989) A controlled trial of extended radical versus radical mastectomy. Ten- year results. *Cancer* 63: 188-195
- Moore C (1867) On the influence of inadequate operations on the theory of cancer. *R Med Chir Soc Lond* 1: 244-280
- Moore MM, Borossa G, Imbrie JZ, Fechner RE, Harvey JA, Slingluff CL, Adams RB, Hanks JB (2000) Association of infiltrating lobular carcinoma with positive surgical margins after breast-conservation therapy. *Annals of Surgery* 231: 877-881
- Morrow M, White J, Moughan J, Owen J, Pajack T, Sylvester J, Frank Wilson J, Winchester D (2001) Factors Predicting the Use of Breast-Conserving Therapy in Stage I and II Breast Carcinoma. *J Clin Oncol* 19: 2254-2262
- Nakamura J, Savinov A, Lu Q, Brodie A (1996) Estrogen regulates vascular endothelial growth/permeability factor expression in 7,12-dimethylbenz(a)anthracene-induced rat mammary tumors. *Endocrinology* 137: 5589-5596
- Nattinger AB, Kneusel RT, Hoffmann RG, Gilligan MA (2001) Relationship of distance from a radiotherapy facility and initial breast cancer treatment. *J Natl Cancer Inst* 93: 1344-1346
- Neugut AI, Murray T, Santos J, Amols H, Hayes MK, Flannery JT, Robinson E (1994) Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers [see comments]. *Cancer* 73: 1615-1620
- Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA (1987) Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. *Br J Cancer* 56: 814-819
- O'Neill JS, Elton RA, Miller WR (1988) Aromatase activity in adipose tissue from breast quadrants: a link with tumour site. *Br Med J (Clin Res Ed)* 296: 741-743
- Obedian E, Haffty BG (2000) Negative margin status improves local control in conservatively managed breast cancer patients. *Cancer J Sci Am* 6: 28-33
- Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial [see comments]. *N Engl J Med* 337: 949-955
- Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB, Blichert-Toft M, Mouridsen HT (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial [see comments]. *Lancet* 353: 1641-1648
- Park CC, Mitsumori M, Nixon A, Recht A, Connolly J, Gelman R, Silver B, Hetelekidis S, Abner A, Harris JR, Schnitt SJ (2000) Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol* 18: 1668-1675

Perera F, Engel J, Holliday R, Scott L, Girotti M, Girvan D, Chisela F, Venkatesan V (1997) Local resection and brachytherapy confined to the lumpectomy site for early breast cancer: a pilot study. *J Surg Oncol* 65: 263-267

Polgar, C., Major, T., and Mangel, L. C. Sole HDR brachytherapy after breast conserving surgery: 4-year results of a pilot study and initial findings of a randomised phase III trial. *Radiother. Oncol.* 55 (suppl 1), 31. 2000.

Porter R (1998) In *The Greatest Benefit to mankind*, pp 73-82. Harper Collins:

Potyka I, Houghton J, Baum M, Odling W, CRC Breast Cancer Trials Group (1999) The role of postoperative radiotherapy after breast conserving surgery in the presence of systemic therapy. *Br J Cancer* 80: Suppl 2:11

Qualheim RE, Gall EA (1957) Breast carcinoma with multiple sites of origin. *Cancer* 10: 460-468

Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, Wilson KS, Knowling MA, Coppin CM, Paradis M, Coldman AJ, Olivotto IA (1997) Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer [see comments]. *N Engl J Med* 337: 956-962

Rauschecker HF, Sauerbrei W, Gatzemeier W, Sauer R, Schauer A, Schmoor C, Schumacher M (1998) Eight-year results of a prospective non-randomised study on therapy of small breast cancer. The German Breast Cancer Study Group (GBSG). *Eur J Cancer* 34: 315-323

Ribeiro GG, Magee B, Swindell R, Harris M, Banerjee SS (1993) The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol (R Coll Radiol)* 5: 278-283

Robertson JF, Ellis IO, Elston CW, Blamey RW (1992) Mastectomy or tamoxifen as initial therapy for operable breast cancer in elderly patients: 5-year follow-up. *Eur J Cancer* 28A: 908-910

Rosen PP, Fracchia AA, Urban JA, Schottenfeld D, Robbins GF (1975) "Residual" mammary carcinoma following simulated partial mastectomy. *Cancer* 35: 739-747

Samuel LM, Dewar JA, Preece PE, Wood RAB (1999) A pilot study of radical radiotherapy using a perioperative implant following wide local excision for carcinoma of the breast. *Breast* 8: 95-97

Sarnelli R, Squartini F (1986) Multicentricity in breast cancer: a submacroscopic study. *Pathol Annu* 21 Pt 1: 143-158

Schnitt SJ, Connolly JL, Harris JR, Hellman S, Cohen RB (1984) Pathologic predictors of early local recurrence in Stage I and II breast cancer treated by primary radiation therapy. *Cancer* 53: 1049-1057

Sedlmayer F, Rahim HB, Kogelnik HD, Menzel C, Merz F, Deutschmann H, Kranzinger M (1996) Quality assurance in breast cancer brachytherapy: geographic miss in the interstitial boost treatment of the tumor bed. *Int J Radiat Oncol Biol Phys* 34: 1133-1139

Shah JP, Rosen PP, Robbins GF (1973) Pitfalls of local excision in the treatment of carcinoma of the breast. *Surg Gynecol Obstet* 136: 721-725

Shukla HS, Melhuish J, Mansel RE, Hughes LE (1999) Does local therapy affect survival rates in breast cancer? [see comments]. *Ann Surg Oncol* 6: 455-460

Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, Gamagami P, Colburn WJ (1999) The influence of margin width on local control of ductal carcinoma in situ of the breast [see comments]. *N Engl J Med* 340: 1455-1461

Solomon SB, Koniaris LG, Chan DY, Magee CA, DeWeese TL, Kavoussi LR, Choti MA (2001) Temporal CT changes after hepatic and renal interstitial radiotherapy in a canine model. *J Comput Assist Tomogr* 25: 74-80

Spinelli C, Berti P, Ricci E, Miccoli P (1992) Multicentric breast tumour: an anatomical-clinical study of 100 cases. *Eur J Surg Oncol* 18: 23-26

Turner BC, Glazer PM, Haffty BG (1999a) BRCA1/BRCA2 in breast-conserving therapy [letter; comment]. *J Clin Oncol* 17: 3689

Turner BC, Harrold E, Matloff E, Smith T, Gumbs AA, Beinfield M, Ward B, Skolnick M, Glazer PM, Thomas A, Haffty BG (1999b) BRCA1/BRCA2 germline mutations in locally recurrent breast cancer patients after lumpectomy and radiation therapy: implications for breast-conserving management in patients with BRCA1/BRCA2 mutations [see comments]. *J Clin Oncol* 17: 3017-3024

Urban J (1978) Management of operable breast cancer: the surgeon's view. *Cancer* 42: 2066

Vaidya JS, Baum M (1998) Clinical and biological implications of the milan breast conservation trials. *Eur J Cancer* 34: 1143-1144

Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, Metaxas M, Harte KJ, Sliski AP, Thomson E (2001) Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 12: 1075-1080

Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mitra I (1996) Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 74: 820-824

van Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, van der SE, Sylvester R, Winter J, van Zijl K (1992) 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* 15-18

van Tienhoven G, Voogd AC, Peterse JL, Nielsen M, Andersen KW, Mignolet F, Sylvester R, Fentiman IS, van der Schueren E, van Zijl K, Blichert-Toft M, Bartelink H, van Dongen JA (1999) Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. *Eur J Cancer* 35: 32-38

Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, Rilke F, Sacchini V, Saccozzi R, Savio T (1993) Radiotherapy after breast-preserving surgery in women with localized cancer of the breast [see comments]. *N Engl J Med* 328: 1587-1591

Veronesi U, Orecchia R, Luini A, Gatti G, Intra M, Zurrada S, Ivaldi G, Tosi G, Ciocca M, Tosoni A, De Lucia F (2001) A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 37: 2178-2183

Vicini FA, Baglan KL, Kestin LL, Mitchell C, Chen PY, Frazier RC, Edmundson G, Goldstein NS, Benitez P, Huang RR, Martinez A (2001) Accelerated treatment of breast cancer. *J Clin Oncol* 19: 1993-2001

Wazer DE, Lowther D, Boyle T, Ulin K, Neuschatz A, Ruthazer R, DiPetrillo TA (2001) Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 50: 107-111

Weidner N, Semple JP, Welch WR, Folkman J (1991) Tumor angiogenesis and metastasis--correlation in invasive breast carcinoma. *N Engl J Med* 324: 1-8

Westman-Naeser S, Bengtsson E, Eriksson O, Jarkrans T, Nordin B, Stenkvist B (1981) Multifocal breast carcinoma. *Am J Surg* 142: 255-257

Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML (2000) Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 18: 1220-1229

Willner J, Kiricuta IC, Kolbl O (1997) Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. *Int J Radiat Oncol Biol Phys* 37: 853-863

Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW (2001) Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *JAMA* 285: 885-892