DBCG

Workshop om brystbevarende
behandling
26. februar 2007

Radioterapiudvalget og Kirurgisk Udvalg

NOVARTIS ONCOLOGY

VARIAN medical systems

Workshop om brystbevarende behandling af cancer mammae

26. februar 2007 kl. 10.00 – 17.30
Ebeltoft Park Hotel

09.30-10.00 ***Kaffe og rundstykker***.

Del 1 – basis

Ordstyrer Peer Christiansen

10.00-10.05 Velkomst, indledning Marie Overgaard
10.05-10.25 Brystbevarende operation: Indikationer og kontraindikationer – Peer Christiansen
10.25-10.40 Status i DK jf. DBCG – Maj-Britt Jensen
10.40-11.00 Billeddiagnostik, specielt efter lumpektomi – Sven Erik Dettmer
11.00-11.20 Konventionel kirurgisk teknik – Jens Peter Garne
11.20-11.40 Strålebehandling: Teknik, bivirkninger m.v. Marie Overgaard
11.40-12.00 Prædiktive faktorer mht. recidiv efter brystbevarende kirurgi – Birgitte Bruun Rasmussen

Resultater:

12.00-12.20 DBCG 82TM – Mogens Blichert-Toft
12.20-12.35 DBCG 89TM – Peer Christiansen
12.35-12.50 Kosmetiske resultater efter brystbevarende behandling – Jørgen Johansen

12.50-13.50 ***Frokost***

Cases

13.50-14.20 Case 1 og 2 - Peter Wamberg og Erik Jacobsen

Del 2 - nyere aspekter

Ordstyrer Jens Overgaard

14.20-14,40 Alderens indflydelse på resultaterne efter brystbevarende beh. – Niels Kroman
14.40-15.10 Partiel mammabestråling – Birgitte Offersen og Mette Hauland

15.10-15.40 ***Kaffe***

15.40-16.00 Primær medicinsk behandling af cancer mammae – Bent Ejlertsen
16.00-16.20 Onkoplastisk kirurgi – Helle Hvid

Cases

16.20-16.50 Case 3 og 4 - Henrik Flyger og Claus Kamby

Afslutning

16.50-17.20 Fremtidige perspektiver i DBCG-regi - Marie Overgaard og Peer Christiansen

Ved mødets afslutning serveres sandwich og øl/vand.

Deltagere i Workshop i Ebeltoft den 26.2.2007

BRYSTKIRURGISK KLINIK, HØRSHOLM
Hanne Galatius
Helle Holtveg
Peer Schousen

DBCG's SEKRETARIAT
Maj-Britt Jensen
Mogens Blichert -Toft

HERLEV HOSPITAL

<u>Brystkirurgisk afd. F</u>
Mette Haulund
Henrik Flyger

<u>Plastikkirurugisk Afd.</u>
Christen Krag

<u>Onkologisk Afd.</u>
Dorte Nielsen
Peter Michael Vestlev
Anne Lene Fromm
Inge Marie Svane
Claus Kamby

<u>Radiofysisk afd.</u>
Dorte Klitgaard

HJØRRING SYGEHUS
Niels Gyldholm
Birgitte Gregersen

HOLSTEBRO SYGEHUS
Walid Adlouni

KLINIK FÜR STRAHLENTHERAPIE, FLENSBORG
Hans-Jürgen Brodersen
Thomas Vlock

MAMMAKLINIKKEN ÅRHUS
Joan Ravnsbæk

NORDSJÆLLANDS HOSPITAL HILLERØD
Birgitte Bruun Rasmussen

ODENSE UNIVERSITETSHOSPITAL

<u>Kirurgisk Afd. A</u>
Katrine L. Søe

Pia Lou-Møller
Kirsten Neckelmann

Onkologisk Afd.
Jørgen Johansen
Mette Møller Nielsen
Sune Zimmermann
Søren Cold

Radiologisk Afd.
Sven Erik Dettmer

REGIONSSYGEHUSET RANDERS

Ute Hoyer
Thor Knudsen

REGIONSSYGEHUSET VIBORG

Mammacentret, kir. afsnit

Jan Sørensen
Helle Hvid

RIGSHOSPITALET
Mammakirurgisk afd.
Esben Friis
Iver Laursen
Michael Vissing
Dorthe Theilum
Rita Jokaala
Tove Tvedskov
Niels Kroman

Onkologisk Afd.
Flemming Kjær-Kristoffersen
Andes Navrsted Pedersen
Bent Ejlertsen

RINGSTED SYGEHUS
Mammakirurgisk Afd.
Anne Pedersen
Bo Grundtmann
Gitte Rasmussen

SVS ESBJERG
Kirurgisk Afd.
Nils Ryegaard Rasmussen

VEJLE SYGEHUS

Onkologisk Afd.
Erik Jakobsen
Monika Rutzinska

Kirurgisk Mammacenter
Peter Wamberg
Christian Kjær
Susanne Bokmand

ÅBENRÅ SYGEHUS

Brystcentret
Dirk Sina
Jürgen Handler

AALBORG SYGEHUS

Mammakirurgisk Klinik
Jens Peter Garne
Lotte Jeppesen
Alex Snell Petersen

Onkologisk Afd.
Lars Stenbygaard
Claudio Caldera
Birgitte Offersen

ÅRHUS UNIVERSITETSHOSPITAL

Plastikkir. Afd. Z
Gitte Hougaard
Troels Tei

Afd. for Medicinsk Fysik
Mette Skov hus Thomsen

Onkologisk Afd.
Inger Højris
Marie Overgaard

Afd. for Eksperimentel Klinisk Onkologi
Jens Overgaard
Trine Thomsen
Marianne Kyndi
Anders Husted

Kirurgisk Afd.
Lone Fischer
Hanne Rønning
Al-SulimanNidal
Peer Christiansen

Brystbevarende operation: Indikationer og kontraindikationer

Peer Christiansen

Indikationer og kontraindikationer for brystbevarende operation ved brystkræft er grundigt gennemgået i kapitel 4 i DBCG's Retningslinier[1]. Dette kapitel er opdateret indenfor det seneste år, og indholdet ligger meget tæt op ad konsensusrapporten fra *Fifth International Consensus Conferenceof the Breast Health Institut*, som blev afholdt i Milano i 2005[2].

Der er enighed om, at det er dokumenteret, at brystbevarende operation suppleret med strålebehandling giver lige så god overlevelse som mastektomi. Grundlæggende anses brystbevarende behandling som den optimale behandling ved brystkræft under forudsætning af, at der kan opnås et acceptabelt kosmetisk resultat og mikroskopisk frie resektionsrande. Det er en vigtig forudsætning, at der kan følges op med strålebehandling, men der er kun få absolutte kontraindikationer med multicentricitet som den vigtigste. Derimod er der en række faktorer, der kan påvirke resultatet og medføre relativ kontraindikation, hvilket vil blive uddybet ved workshoppen. Listen over emner, der vil blive adresseret i forbindelse diskussionen af indikationer omfatter bl.a.:

- Tumorstørrelse
- Tumor placering
- Multifokalitet
- Okkult brystkræft
- Bryststørrelse
- In situ komponent
- Histopatologiske karakteristika og biologiske markører
- Alder
- Arvelig brystkræft
- Tidligere brystaugmentation.

Referencer og supplerende litteratur

1. DBCG retningslinier http://www.dbcg.dk. 2004.
   Ref Type: Internet Communication

2. Schwartz GF et al. Consensus conference on breast conservation. *J Am Coll Surg* 2006; **203**: 198-207.

Status i Danmark; tal fra DBCGs database.

Maj-Britt Jensen, DBCGs sekretariat

Status over DBCGs registreringer af patienter med invasiv mamma cancer. Der præsenteres tal for godt 50.000 patienter registreret med en operationsdato i perioden 1990-2006, svarende til DBCG program 89, 99, 01 samt 04. Endvidere ses specielt på de ca. 10.000 patienter, der er opereret i perioden 2004-2006.

Fordeling af operationstype (lumpektomi, mastektomi) præsenteres i forhold til kirurgisk afdeling, dato for operation, præoperativ klassifikation, alder, tumorstørrelse samt kombinationer heraf. Tallene viser, at andelen af lumpektomier er steget markant i de seneste år. Endvidere præsenteres tal svarende til de to indikatorer, der specielt omhandler brystbevarende operation (se indikatorrapport på www.dbcg.dk).

Konventionel kirurgisk teknik

Jens Peter Garne

Brystbevarende kirurgi er i dag en veletableret metode i Danmark, som er vel beskrevet i DBCG's retningslinier kapitel 4.3.6.
Metodens anvendelighed er solidt dokumenteret gennem randomiserede studier med lang opfølgningstid.
I disse studier har man anvendt lidt forskellige metoder, såsom kvadrantektomi, segmentektomi eller lumpektomi. Disse metoder er ikke testet mod hinanden, men resultaterne fra de forskellige randomiserede studier er så ens, at man kan konkludere, at uanset valgt metode er brystbevarende kirurgi sikkert, når man opnår radikalitet og siden giver adekvat strålebehandling til residuale mamma.

Referencer:

Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002 Oct 17;347(16):1233-41.

Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002 Oct 17;347(16):1227-32.

Blichert-Toft M, Rose C, Andersen JA, Overgaard M, Axelsson CK, Andersen KW, Mouridsen HT. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr. 1992;(11):19-25.

Strålebehandling ved brystbevarende operation

Marie Overgaard

Strålebehandling er en vigtig del af den loko-regionære behandling ved brystbevarende behandling. Baggrunden for indførelsen af brystbevarende behandling var netop, at flere randomiserede undersøgelser i løbet af 50-60èrne havde vist, at postoperativ strålebehandling kunne kompensere for et mindre kirurgisk indgreb (simpel versus radikal mastektomi) med hensyn til lokal tumorkontrol og overlevelse. Der blev gennem 70-80èrne udført i alt 7 randomiserede forsøg, hvor brystbevarende operation inkl. axildissektion efterfulgt af strålebehandling mod residuale brystvæv blev sammenlignet med radikal mastektomi. Samtlige studier bekræftede, at disse behandlinger er ligeværdige forudsat, at det er patienter med små tumorer (T1 og T2) og fortrinsvis node negative (>80%), og hovedparten af patienterne i alle studier var > 50 år. Standard dosis var ca. 50 Gy /25 fx til hele brystet efterfulgt af boost til tumorlejet med yderligere 10-25 Gy. (1)

Resultaterne er uændrede efter længere follow up (15-20 år), sidst publiceret i EBCTCG overview i 2005 (1) og brystbevarende behandling er nu den hyppigst anvendte behandling i den vestlige verden, især hvor der også er sceeningsprogrammer.

I løbet af de sidste 20-25 år er der imidlertid sket en betydelig udvikling af den adjuverende medicinske behandling, som nu anbefales til hovedparten af brystkræft patienter, også i tidlige stadier. Dette forhold sammen med bedre diagnostiske metoder, nye kirurgiske metoder og en betydelig udvikling af stråletekniske muligheder har naturligvis medført en løbende justering af strålebehandlingen.(3, 4)

Den aktuelle standard strålebehandling, som er anbefalet af DBCG vil blive gennemgået- og en række nye problemstillinger vil blive diskuteret: Er strålebehandling nødvendig hos alle patienter? Er boost behandling nødvendig?(2) Hvilken fraktionering og dosis er optimal? Hvilke problemer er der i relation til target og timing med systemisk behandling? Strålebivirkninger, umiddelbare og persisterende? Hvilke nye tekniske muligheder er der? Hvad betyder ventetiden?

Referencer

1. Early Breast Cancer Trialists` Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrences and on 15-year survival: an overview of the randomised trials. Lancet 2005; 3666:2087-2106.
2. Bartelink H, Horiot J-C, Poortmann P, Stuikmans H, Van den Bogaert W, Barillot I, Fourquet A, Borger J, Jager J, Hoogenraad W, Collette L, Pierat M. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001; 345: 1378-1387.
3. J.Kurtz for the EUSOMA Working Party. The curative role of radiotherapy in the treatment of operable breast cancer. European Journal of Cancer 38 (2002) 1961-1974.
4. Harris, Lippman, Morrow, Osborne. Diseases of the Breast.(Lippincott, Williams & Wilkins. Second Edition 2000).

Prædiktiv faktorer mht. recidiv efter brystbevarende kirurgi.

Birgitte Bruun Rasmussen

Foredraget vil være en gennemgang af de sidste ca. 10 års publikationer hvor man har undersøgt sammenhængen mellem klassiske pato-anatomiske prædiktiv/prognostiske faktorer og recidiv/overlevelse efter brystbevarende kirurgi. De prædiktive faktorer, der vil blive gennemgået er: Tumorstørrelse, type, malignitetsgrad, lymfeknudestatus, receptorstatus, vaskulær invasion, EIC (extensive introductal component), alder og forholdene omkring resektionsrande. Generelt synes ingen af de nævnte faktorer at have indflydelse på recidivraten. Hvad angår overlevelsen er denne afhængig af lymfeknudestatus og størrelse, men i de studier hvor der er randomiseret mellem lumpektomi og mastektomi er der ingen forskel i de to grupper. Den eneste faktor der synes at betyde noget for hyppigheden af lokalrecidiv er ung alder. Derimod finder man ingen effekt af tumortype, hvor det nogle gange hævdes, at de lobulære karcinomer skulle have større tendens til lokalrecidiv end andre typer. Hvad angår afstand fra tumor til resektionsrand er der heller ikke entydighed, men definitionen af fri resektionsrand er på ingen måde ens, hvilket måske kan forklare de varierende resultater.

Der er således ingen pato-anatomiske tumorkarakteristika, der skulle betinge et fravalg af lumpektomi.

Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol

Mogens Blichert-Toft

The Danish Breast Cancer Cooperative Group (DBCG) conducted the randomized trial (DBCG-82TM) from January 1983 to March 1989 recruiting 1154 patients with invasive breast carcinoma. Follow-up time ended 1st May 2006 with a potential median follow-up time of 19.6 years (time span 17.1-23.3 years). Eligibility criteria included a one-sided, unifocal, primary operable breast carcinoma, patient age below 70 years, probability of satisfactory cosmetic outcome at BCS, and no evidence of disseminated disease.

The patients accrued were grouped into three subsets, viz. 1) correctly randomized N= 793 patients, 2) suspicion of randomization error N= 131 patients, and 3) N= 209 patients who declined randomization.

The main analyses focus on the subgroup of 793 correctly randomized patients representing 70 % of the complete series. 10-year recurrence free survival (RFS) and 20-year overall survival (OS) based on intent to treat did not reveal significant differences in outcome between breast conserving surgery vs. mastectomy, p=0.95 and p=0.10, respectively. Same results came up when analyses were carried out based on treatment in fact given. Including the complete series comprising 1133 eligible patients based on treatment in fact given no significant difference between surgical options could be traced in outcome of 10-year RFS and 20-year OS, p=0.94 and p=0.24, respectively.

the occurrence of recurrence as a first event in breast conservation vs. mastectomy did not differ significantly in pattern, p=0.27. Looking into the type of local relapse, viz. new primaries vs. true recurrences, it appeared that new primaries were strongly associated to BCS, while true recurrences dominated among M treated patients. Further, true recurrences disclosed a worse final outcome compared with new primaries. Regarding location in residual breast, new primaries were mostly found in another quadrant than the quadrant of the original tumour.

In conclusion, over the long term there is evidence that BCS in eligible patients seems to be as effective as mastectomy both regarding local tumour control, RFS and OS. Local failures as a first event consistent with new primaries are strongly associated with BCS, whereas true recurrence predominates in the lapse of mastectomy.

References

1. Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomised study comparing breast-conserving surgery with radical mastectomy for early breast cancer.
   N Engl J Med 2002; 347: 1227-32.
2. Sarrazin D, Le M, Rouesse J et al. Conservative treatment versus mastectomy in breast cancer tumors with macroscopic diameter of 20 millimeters or less. The experience of the Institut Gustave-Roussy. Cancer 1984; 53: 1209-13.
3. Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347: 1233-41.
4. Dongen JAvan, Voogd AC, Fentiman IS et al. Long-term results of a randomized trial comparing breast-conserving therapy with

mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. J Natl Cancer Inst 2000; 92: 1143-50.
5. Straus K, Lichter A, Lippman M et al. Results of the National Cancer Institute Early Breast Cancer Trial. J Natl Cancer Inst Monogr 1992; 11: 27-32.
6. Blichert-Toft M, Rose C, Andersen JA et al. Danish randomized trial comparing breast conservation therapy with mastectomy: Six years of life-table analysis. J Natl Cancer Inst Monogr 1992; 11: 19-25.
7. NIH Consensus Conference. Treatment of early-stage breast cancer. JAMA 1991; 265: 391-5.
8. Voogd A, Nielsen M, Peterse JL et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: Pooled results of two European randomized trials. J Clin Oncol 2001; 19: 1688-97.
9. Kroman N, Holtveg H, Wohlfahrt J et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer 2004; 100: 688-93.

DBCG 89TM

Mette Moe Kempel, Marianne Ewertz, Maria Düring, Michael Andersson, Peer Christiansen, Niels Kroman, Marie Overgaard, Birgitte Bruun Rasmussen.

I en DBCG opgørelse af patienter, der i perioden 1989-1998 har modtaget brystbevarende behandling, indgik i alt 4240 patienter. Ved hjælp af DBCG-data suppleret med udtræk fra dødsårsagsregistret, er disse patienter fulgt til første oktober 2005 eller død, og det er registreret, om de har haft loko-regionært recidiv (LRR), fjernrecidiv (FR) eller anden malign sygdom. 322 blev tabt under forllow-up, hvorfor der kun er overlevelsesdata på 3918. Den mediane follow up mht. LRR var 8,4 år og tilsvarende 10,3 år mht. død.
*Resultater.*Ved hjælp af Kaplan Meier plots kan 15-års overlevelsen beregnes til 79%. På basis af DBCG-indberetninger viste opgørelsen, at i løbet af de første ti år efter operationen var den kumulative incidens af LRR 8,9%, og forekomsten af FR eller anden malign sygdom (dog undtaget ikke-melanom cancer cutis og c.cervicis uteri, stadium in situ) var 19,1%. 6,1% var i samme periode døde. Risikoen for LRR, FR eller anden malign sygdom forøgedes med stigende tumorstørrelse og ved tilstedeværelse af 4 eller flere lymfeknudemetastaser. Yngre patienter under 50 år havde oftere LRR i for hold til ældre patienter. I materialet indgår en lille gruppe på 169 patienter, der ikke modtog postoperativ strålebehandling (årsagerne hertil er ikke klarlagt). I den gruppe var hyppigheden af LRR stærkt forøget (hazard ratio [HR] 2.95 (95% CI 1.89-4.61). Der kunne i dette materiale ikke påvises nogen sammenhæng mellem risikoen for recidiv eller død og tilstedeværelse af frie resektionsrande.
Diskussion. I den seneste oversigt fra EBCTCG (2005) over de randomiserede studier var hyppigheden af isoleret LRR 10,3 % efter 10 år hos 7311 patienter, der efter brystbevarende operation havde fået strålebehandling. Tilsvarende opgjordes den samlede overlevelse til 79,3 % efter 10 år. Den manglende sammenhæng mellem frie resektionsrande og sygdomsfri overlevelse i vores studium forekommer lidt overraskende, da det er påvist i en række andre lignende opgørelser (Harrold et al., 1998; Elkhuisen et al., 1999; Touboul et al., 1999; Bartelink et al., 2001; Mirza et al., 2002). Perez' opgørelse (2003) viste dog heller ikke nogen sådan sammenhæng. En del af forklaringen kan være, at der desværre var relativt mange patienter, hvor der manglede informationer om resektionsrandene (273), så vi har måske underestimeret antallet af patienter med positive marginer (i alt 5,3%). Væsentligt for den tilsyneladende manglende effekt af tilstedeværelse af positive resektionsrande er det uden tvivl også, at patienter med positiv margin fik boost (10-16 Gy) mod lumpektomi-kaviteten.

Konklusion. Den foreliggende opgørelse viser, at brystbevarende operation med efterfølgende strålebehandling, efter DBCG-standard giver sammenlignelige resultater med tidligere publicerede randomiserede studier.

Referencer og supplerende litteratur

1. *Bartelink H, Horiot J-C, Poortmans P, Stuikmans H, Van den Bogaert W, Barillot I, Fourquet A, Borger, J, Jager J, Hoogenraad W, Collette L, Pierat M.* Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001; 345:1378-1387.
2. *Blicher-Toft M, Rose C, Andersen JA, et al*. Danish randomized trial comparing breast conervation therapy with mastectomy: six years of life table analysis. In: Consensus development conference on the

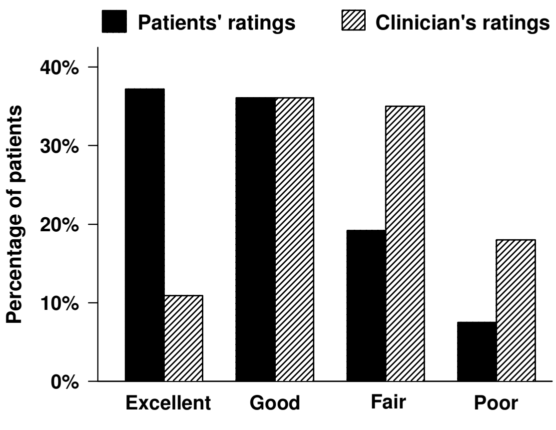
treatment of early-stage breast cancer. Journal of the National Cancer Institute monographs. No.11. Bethesda, Md: National Cancer Instutute, 1992:19-25. (NIH publication no.90-3187.)

3. *Early Breast Cancer Trialists' Collaborative Group*. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and on 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087-2106.
4. *Elkhuisen PH, Voogd AC, van den Broek LC, et al*. Risk factors for local recurrence after breast-conserving therapy for invasive carcinomas: a case-control study of histological factors and alterations in oncogene expression. Int J Radiat Oncol Biol Phys 1999; 45: 73-83.
5. *Harrold EV, Turner BC, Matloff ET, et al*. Local recurrence in the conservatively treated breast cancer patient: a correlation with age and family history. Cancer J Sci Am 1998; 4: 302-307.
6. *Kroman, N., Holtveg, H., Wohlfahrt, J., et al*. Effect of Breast Conserving Therapy versus Radical Mastectomy on Prognosis for Young
7. Women with Breast Carcinoma. Cancer 2004; 100: 688-693.
8. *Mirza NQ, Vlastos G, Meric F, et al*. Predictors of locoregional recurrence among patients with early-stage breast cancer treated with breast-conserving therapy. Ann Surg Oncol 2002; 9: 256-265.
9. *Perez, C.A*. Conservation Therapy in T1-T2 Breast Cancer: Past, Current issues and Future Challenges and Opportunities. Cancer J 2003; 9:6, 442-453.
10. *Touboul E, Buffat L, Belmacemi Y, et al.* Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. Int J Radiat Oncol Biol Phys 1999; 43: 25-38.

Kosmetiske resultater efter brystbevarende behandling

Jørgen Johansen

Formål: Med henblik på at vurdere affekten af forskellige behandlingsmodaliteter på de kosmetiske resultater efter brystbevarende behandling gennemførtes en efterundersøgelse af patienterne i DBCG-82TM protokollen.
Patienter og Metoder: Alle recidivfri kvinder i tumorektomi-armen i DBCG-82TM blev tilbudt at deltage i undersøgelsen, som omfattede en enkelt ambulant klinisk undersøgelse og et struktureret interview. Både kosmetiske og funktionelle forhold samt normalvævsreaktioner i og omkring brystet blev vurderet. Morbiditet og det kosmetiske resultat blev graderet på en skala fra 0-3. Klinisk foto indgik i vurderingen. Kvinderne blev desuden udspurgt om eventuelle ændringer i påklædningsvaner, kropsopfattelse samt evt. brystrekonstruktion som følge af den brystbevarende behandling. Resultaterne blev analyseret i forhold til indrapporterede behandlingsdata til DBCG-sekretariatet.
Resultater: 266 kvinder i alderen 24 -70 år (med. 50 år) deltog efter median follow-up på 6,6 år (3,5-10,5). De kirurgiske indgreb var blev foretaget på 21 forskellige afdelinger (1 - 83 patienter), strålebehandlingen på 6 onkologiske afdelinger. 73% af patienterne var særdeles tilfreds/tilfreds med det kosmetiske resultat; modsvarende 47% efter lægens vurdering (figur). Elektronbestråling medførte signifikant flere normalvævsreaktioner end fotonbehandling: Dyspigmentering 32% vs. 9% ($p<0,001$); telangiektasier 42% vs. 3% ($p<0,001$), fibrose 29% vs. 18% ($p<0,05$). Mammaretraktion (≥ 10%) forekom hos 37% og var relateret til bryststørrelse, tumorstørrelse og lokalisation i øvre kvadranter. I multivariatanalyse var det kosmetiske resultat signifikant associeret med elektronbestråling, større bryster og systemisk behandling. I analyserne af præ- og postmenopausale patienter var CMF stadig signifikant associeret med det kosmetiske resultat i modsætning til tamoxifen.



Yngre kvinder var generelt mindre tilfredse med det kosmetiske resultat end ældre. 8% af alle havde ændret 'Body Image' som flg. af brystbevarende behandling, hvilket var relateret til telangiektasier, brystretraktion og tumorer i nedre kvadranter. 21% havde ændret vaner mht. beklædning pga. forandringer i brystet, og 21% havde enten fået foretaget rekonstruktion eller udtrykte ønske herom.

Konklusion: DBCG-TM82 bekræfter, at det kosmetiske resultat efter brystbevarende behandling er relateret til både det kirurgiske indgreb, stråleterapi, systemisk behandling samt visse patientfaktorer (1-5).

Referencer

1) Johansen J, Overgaard J, Rose C et al. Cosmetic outcome and breast morbidity in breast-conserving treatment. Results from the Danish DBCG-82TM national randomized trial in breast cancer. Acta Oncol 2002; 41(4):369-380.

2) Johansen J, Overgaard J, Blichert-Toft M, Overgaard M. Treatment morbidity associated with the management of the axilla in breast-conserving therapy. Acta Oncol 2000; 39(3):349-354.

3) Vrieling C, Collete L, Forquet A et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. Radiother Oncol 2000; 55(3):219-232.

4) Cardoso MJ, Cardoso J, Santos AC et al. Factors determining aesthetic outcome after breast cancer conservative treatment. The Breast Journal. 2007 (in press).

5) Johansen J, Overgaard J, Blichert-Toft M, Overgaard M. Effect of adjuvant systemic treatment on cosmetic outcome and late normal-tissue reactions after breast conservation. Acta Oncol 2007 (accepteret)

Case 1 & 2

Peter Wamberg, Erik Jakobsen

Case 1:
Genetisk disposition og mammacancer.
Yngre kvinde med påvist BRACA 1 mutation udvikler mamacancer. Gennemgang af kirurgiske behandlingsalternativer og præsentation af den aktuelt valgte kirurgisk behandling med baggrund i litteraturen.

Case 2:
Onkoplastisk kirurgi og strålebehandling.
Med udgangspunkt i onkoplastikken og den dermed mulige diskrepans mellem cikatriceplacering og tumor-"bed" udfordres de onkologiske retningslinier specielt vedrørende stråle-target.

Referencer:

1. Ann Oncol 2006 Mar;17(3):391-400
2. Eur J Cancer 2005 Oct;41(15):2304-11
3. Br J Cancer Aug 8;93(3):287-92
4. British Journal of Surgery 2006;93:961-968

Alderens indflydelse på resultaterne efter brystbevarende behandling

Niels Kroman

Det er velkendt, at mammacancer blandt yngre kvinder generelt har et mere aggressivt vækstmønster sammenlignet med midaldrende og ældre kvinder. Dette ses også ved BCS hvor lokalrecidivrater på 30% er rapporteret blandt yngre patienter sammenlignet med en forventet rate på generelt under 10%. Metaanalyser antyder at op til hver femte lokalrecidiv på lang sigt kan være fatalt. Et stort multicenter studie med dansk bidrag har vist, at den relative risiko for lokalrecidiv er næsten ti gange større blandt kvinder under 35 år sammenlignet med kvinder over 60 år. Således kunne man teoretisk set påstå at BCS burde være kontraindiceret blandt unge.

Tal fra DBCG viser ikke overraskende, at kirurgerne strækker sig langt for at tilbyde BCS til den yngste patientgruppe. En ny cancer i et opereret bryst registreres principielt som et som et recidiv, men det er ikke entydigt, om det reelt er et recidiv eller en ny primær cancer. Kvinder under 35 år ved diagnosen har en livstidsrisiko for kontralateral mammacancer, sv. t. kvinder der kan tilbydes profylaktisk mastektomi. Hvis man fravælger BCS alene p. gr. a. alder må man således overveje om denne patientgruppe skal tilbydes kontralateral profylaktisk mastektomi.

Det vil blive diskuteret hvordan de foreliggende data kan fortolkes, samt hvordan man skal forholde sig til ønsket om BCS hos yngre kvinder.

Partiel mammabestråling: aktuel status

Birgitte Offersen, Mette Haulund

Brystbevarende behandling er en bredt accepteret behandling til stadie I og II mammacancer, hvor der bl.a. gives adjuverende strålebehandling til hele mamma for at mindske risikoen for lokale recidiver, og dermed også øge den sygdomsspecifikke overlevelse. I hht. DBCG´s retningslinier gives 48 Gy på 24 fraktioner, evt. suppleret med boost på 10 Gy over 5 fraktioner.
Det er en generel opfattelse, at de fleste lokale recidiver forekommer i eller tæt på området for den oprindelige tumor. Det kan derfor umiddelbart virke oplagt at rette strålebehandlingen mod dette område, og samtidig skåne det øvrige "raske" mammavæv for bestråling. Ved at bestråle et mindre volumen antages det at være acceptabelt at øge dosis pr. fraktion, og man kan derved hypofraktionere strålebehandlingen, hvilket som sidegevinst forventes at forkorte ventelisterne til strålebehandling.
I det lys er der indenfor de senere år blevet præsenteret forskellige stråleteknikker, hvor adjuverende strålebehandling af mammacancer bliver givet efter helt nye retningslinier.
I foredraget vil der bl.a. blive omtalt rationale for partiel mammabestråling, herunder lokalisation af de lokale recidiver. Der vil blive vist stråleteknik og data på studier med IORT[1], TARGIT[2], MammoSite[3], Interstitiel HDR og LDR[4] samt 3D-CRT[5,6]. Det vil fremgå, at der anvendes forskellige kriterier for udvælgelse af patienter til partiel mammabestråling, forskellige stråledoser og fraktioneringer samt volumina, som skal have behandling, og endelig forskellig behandlingsvarighed. Generelt har studierne kort follow-up, så effekten af behandlingen (såvel den anti-neoplastiske som den kosmetiske) er indtil nu ikke veldokumenteret. Der vil ydermere blive påpeget tumorbiologiske problemstillinger.

Referencer:

[1]Veronesi et al., Ann. Surg. 2005, 242: 101-6
[2]Vaidya et al., IJROBP 2006, 66: 1335-8
[3]Vicini et al., Cancer 2005, 104: 1138-48
[4]Vicini et al., JNCI 2003, 95: 1205-10
[5]Vicini et al., IJROBP 2005, 63: 1531-7
[6]Formenti et al., IJROBP 2004, 60: 493-504

Primær medicinsk behandling af cancer mammae

Bent Ejlertsen

Medicinsk behandling anvendes i stigende grad, som første behandlingsmodalitet til patienter med nydiagnosticeret brystkræft. Hos patienter med lokal- og regional fremskreden brystkræft er primær medicinsk behandling nu den etablerede standard. Disse patienter kan være operable, fx ved indvækst i hud eller et konglomerat af lymfeknuder i aksillen, men hos andre vil radikal kirurgi ikke være mulig trods et omfattende og måske mutilerende indgreb. Afhængig af hormonreceptorstatus, HER2 status, ko-morbiditet og alder vil patienter med lokal- og regional fremskreden brystkræft blive tilbudt primær kemoterapi, evt. i kombination med trastuzumab, eller en aromatase inhibitor.

Hos patienter med operabel brystkræft er der gennemført forsøg med randomisering til kemoterapi før versus efter den definitive operation. Resultaterne fra en del af disse forsøg er samlet i en meta-analyse, og den viser samme overlevelse uafhængigt af om kemoterapien gives før eller efter operationen. Meta-analysen viser også at præoperativ kemoterapi øger risikoen for lokal- og regional recidiv, medens der er en insignifikant reduktion i risikoen for fjernmetastaser. Via EBCTCG er der påbegyndt indsamling af data fra samtlige forsøg mhp. på en meta-analyse baseret på individuelle patientdata. Præoperativ kemoterapi kan hos udvalgte patienter være den eneste mulighed for brystbevarende operation. Andre fordele ved præoperativ kemoterapi kan være individualisering af kemoterapien afhængig af effekten og en reduktion i risikoen for fjernmetastaser. Progression af tumoren ses hos mindre end 5% af patienterne i forbindelse med primær kemoterapi, men kan i sjældne tilfælde føre til inoperablitet. Der er også en potentiel øget risiko for operationskomplikationer. Der er ikke udført forsøg der kan belyse om primær endokrin terapi influerer på den recidivfrie eller den samlede overlevelse. Indirekte sammenligninger tyder dog på en sammenlignelig effekt af præoperativ endokrin- og kemoterapi hos patienter med hormonreceptor positive tumorer.

Hvad er onkoplastisk brystkirurgi

Helle Hvid

Ved onkoplastisk brystkirurgi forstås et spektrum af operationsmetoder, der er onkologisk sikre, men samtidig tilsigter et godt kosmetisk resultat. Der er talt om en række indgreb der spænder fra simple indgreb til sjældnere langvarige operationer, der omfatter lapplastik.

De forskellige operationsmetoder vil blive vist, illustreret ved tegninger og fotos.
Fordele og ulemper ridses op.

Alle operationer er foretaget på Regionshospitalet Viborg og Århus Sygehus.

Referencer:

1. Audretch,W . Is mastectomy Still Justified- And if, in Which patients ? Oncologie 2006; 29:243-245.

2. Rachel Bright-Thomas.What is oncoplastic breast surgery ?.BMJ Career Focus 2006;332:23-24

3. Kollias, J .Breast conservation by volumen reduction surgery. Aust. NZ (…?)

4. Sneeuw K.A., Aaronson N, Yarnold J et al. Cosmetic and functionel outcomes of breast conserving treatment for early stage breast cancer. Comparison of patients´ratings,observers´ratings and objective assessments. Radiother. Oncol. 1992;25: 153-159

5. Rose M. A., Olivotto I., Cady B. Conservative surgery and radiation terapy for early breast cancer- Long term cosmetic result. Arch.surg. 1998;124;153-157.

6. Baildam A.D. Oncoplastic surgery of the breast. British Jounal of Surgery 2002;89;532-533

7. J.Johansen. Cosmetic outcome and breast Morbidity in Breast-Conserving Treatment. Acta Oncol.Vol 41 no 4, pp 369-380,2202.

Postlumpektomibestråling - sygehistorier

Claus Kamby & Henrik Flyger

1. En patient, der er "måske egnet" til intraoperativ strålebehandling (IORT)

Hos over 60 % af patienter med cancer mammae findes cancer foci andre steder i det opererede bryst. Af disse vil ca. 80 % af områderne ligger uden for indexkvadrantet. Således burde brystbevarende kirurgi ikke være mulig. Alligevel ligger over 90 % af lokalrecidiverne i indexkvadrantet. Der findes forandringer i det tumornære væv som ikke ses i den øvrige del af mamma; høj aromatase aktivitet (1), loss of heterozygosity (2), genetisk instabilitet, p53 mutationer (3) og BRCA1/2 mutationer (4). Disse forhold er summeret i (5). Dette har ført til teoretiske overvejelser om, at det er det omkringliggende væv (stromaet) og ikke blot tilstedeværelsen af tumorceller, der har betydning for opståen af recidiv (*soil vs. seed teorien*).

Der er i de sidste fem år etableret flere protokoller, der afprøver hypotesen om at IORT kan reducere risikoen for lokalrecidiv lige så meget grad som konventionel ekstern bestråling. Postlumpektomi-strålebehandling er nemlig en omkostningstung - men effektiv - behandling, som foruden at reducere lokalrecidiv raten med en tredjedel, også reducerer de brystkræftspecifikke mortalitet (6). Den første sygehistorie omhandler en 69 årig kvinde med lav-risiko cancer fundet ved "gråzone" screening, og som har 6-9 % risiko for lokalrecidiv. Patienten vil blive tilbudt behandling i henhold til "TARGIT" protokollen.

Hos ældre kvinder er fundet relativt store 'omkostninger' både mht. recidiv rater og komplikationer i forhold til gavnlig effekt af stråleterapi (7-9); IORT, er måske derfor en særlig gunstig mulighed hos ældre patienter, idet der gives høj stråledosis til områder der ligger nærmest operationskaviteten, mens vævet længere væk (især hud, hjerte og lunger) ikke modtager betydende stråledosis. En anden fordel ved IORT er at man undgår '*geografic miss'* (behandlingen gives præcis hvor tumor sidder).

2. Kommunikation mellem kirurg og radioterapeut

Optimal gennemførelse af postoperativ strålebehandling hviler blandt andet på god kommunikation mellem kirurgisk og onkologisk afdeling. Kirurgen må kende arten og omfanget (feltgrænser) af den postoperative strålebehandling, for at undgå at placering af cicatricer ikke giver vanskeligheder ved f. eks. afgrænsning af boostfeltet. For at stråleplanlægning kan gennemføres korrekt er det derfor vigtigt, at der i journalen fra kirurgisk afdeling er en grundig anamnese (herunder tidligere operationer på mammae), objektive fund og operationsbeskrivelse.

Gennem sygehistorier demonstreres, at dette især har betydning ved planlægning af boostfelters afgrænsning, valg af strålekvalitet og dosering. Der fremlægges et tilfælde, hvor multiple cicatricer på brystet (nogle formentlig hidrørende fra en ikke beskrevet *papil/areola re-placering*) giver anledning til problemer med boostfeltets afgrænsning. Retningslinjernes krav om at clips og lumpektomicicatrice skal inkludere med en margen på mindst 1

cm kunne således ikke tilgodeses uden at næsten hele mamma inkluderes i feltet. I et andet tilfælde blev en lang lumpektomicicatrice yderligere forlænget op i aksillen (4/26 tumorpositive lymfeknuder). Ved boostanlæggelse blev store dele af denne cicatrice ikke inkluderet i boostfeltet for at 'skåne' aksil og store dele af processus aksillaris. Efter få fraktioner påvises recidiv i relation til cicatricen (implantationsmetastase?/ lokalrecidiv) og boostfeltet udvides samtidig dosis øges fra 10 til 16 Gy (á 2 Gy).
Litteratur

1. O'Neill JS, Elton RA, Miller WR. Aromatase activity in adipose tissue from breast quadrants: a link with tumour site. *Br.Med.J (Clin Res Ed)* 1988;296:741-3.

2. Deng G, Lu Y, Zlotnikov G, Thor AD, Smith HS. Loss of heterozygosity in normal tissue adjacent to breast carcinomas. *Science* 1996;274:2057-9.

3. Turner BC, Gumbs AA, Carbone CJ, Carter D, Glazer PM, Haffty BG. Mutant p53 protein overexpression in women with ipsilateral breast tumor recurrence following lumpectomy and radiation therapy. *The Cancer* 2000;88:1091-8.

4. Turner BC, Harrold E, Matloff E, Smith T, Gumbs AA, Beinfield M et al. 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. *Journal of Clinical Oncology* 1999;17:3017-24.

5. Vaidya JS, Tobias JS, Baum M, Keshtgar M, Joseph D, Wenz F et al. Intraoperative radiotherapy for breast cancer. *Lancet Oncol* 2004;5:165-73.

6. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *The Lancet* 2005;366:2087-106.

7. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den BW, Barillot I et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N.Engl.J.Med.* 2001;345:1378-87.

8. Bartelink, H., Horiot, J. C., Poortmans, P., Struikmans, H., Van den Bogaert, W., and et al. Impact of radiation dose on local control, fibrosis and survival after breast conserving treatment: 10 years results of the EORTC trial 22881-10882. Breast Cancer Res and Treat SABCS 2006((suppl)), # 11. 2006.
   Ref Type: Abstract

9. Pierce SM, Recht A, Lingos TI, Abner A, Vicini F, Silver B et al. Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer(see comments). *Int.J.Radiat.Oncol.Biol.Phys.* 1992;23:915-23.

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2005; 366: 2087–2106

*Collaborators listed at end of report

Correspondence to: EBCTCG secretariat, Clinical Trial Service Unit (CTSU), Richard Doll Building, Old Road Campus, University of Oxford, Oxford OX3 7LF, UK
bc.overview@ctsu.ox.ac.uk

Summary

Background In early breast cancer, variations in local treatment that substantially affect the risk of locoregional recurrence could also affect long-term breast cancer mortality. To examine this relationship, collaborative meta-analyses were undertaken, based on individual patient data, of the relevant randomised trials that began by 1995.

Methods Information was available on 42 000 women in 78 randomised treatment comparisons (radiotherapy *vs* no radiotherapy, 23 500; more *vs* less surgery, 9300; more surgery *vs* radiotherapy, 9300). 24 types of local treatment comparison were identified. To help relate the effect on local (ie, locoregional) recurrence to that on breast cancer mortality, these were grouped according to whether or not the 5-year local recurrence risk exceeded 10% (<10%, 17 000 women; >10%, 25 000 women).

Findings About three-quarters of the eventual local recurrence risk occurred during the first 5 years. In the comparisons that involved little (<10%) difference in 5-year local recurrence risk there was little difference in 15-year breast cancer mortality. Among the 25 000 women in the comparisons that involved substantial (>10%) differences, however, 5-year local recurrence risks were 7% active versus 26% control (absolute reduction 19%), and 15-year breast cancer mortality risks were 44·6% versus 49·5% (absolute reduction 5·0%, SE 0·8, 2p<0·00001).

These 25 000 women included 7300 with breast-conserving surgery (BCS) in trials of radiotherapy (generally just to the conserved breast), with 5-year local recurrence risks (mainly in the conserved breast, as most had axillary clearance and node-negative disease) 7% versus 26% (reduction 19%), and 15-year breast cancer mortality risks 30·5% versus 35·9% (reduction 5·4%, SE 1·7, 2p=0·0002; overall mortality reduction 5·3%, SE 1·8, 2p=0·005). They also included 8500 with mastectomy, axillary clearance, and node-positive disease in trials of radiotherapy (generally to the chest wall and regional lymph nodes), with similar absolute gains from radiotherapy; 5-year local recurrence risks (mainly at these sites) 6% versus 23% (reduction 17%), and 15-year breast cancer mortality risks 54·7% versus 60·1% (reduction 5·4%, SE 1·3, 2p=0·0002; overall mortality reduction 4·4%, SE 1·2, 2p=0·0009). Radiotherapy produced similar *proportional* reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with or without systemic therapy), so large *absolute* reductions in local recurrence were seen only if the control risk was large.

To help assess the life-threatening side-effects of radiotherapy, the trials of radiotherapy versus not were combined with those of radiotherapy versus more surgery. There was, at least with some of the older radiotherapy regimens, a significant excess incidence of contralateral breast cancer (rate ratio 1·18, SE 0·06, 2p=0·002) and a significant excess of non-breast-cancer mortality in irradiated women (rate ratio 1·12, SE 0·04, 2p=0·001). Both were slight during the first 5 years, but continued after year 15. The excess mortality was mainly from heart disease (rate ratio 1·27, SE 0·07, 2p=0·0001) and lung cancer (rate ratio 1·78, SE 0·22, 2p=0·0004).

Interpretation In these trials, avoidance of a local recurrence in the conserved breast after BCS and avoidance of a local recurrence elsewhere (eg, the chest wall or regional nodes) after mastectomy were of comparable relevance to 15-year breast cancer mortality. Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality.

Introduction

In early breast cancer, surgery can remove any disease that has been detected in or around the breast or regional lymph nodes, but undetected deposits of disease may remain either locally (ie, in the residual breast tissue, scar area, chest wall, or regional lymph nodes) or at distant sites that could, if untreated, develop into life-threatening recurrence. Many randomised trials over the past half century have studied the effects of radiotherapy and of the extent of surgery on local disease control and on cause-specific mortality in early breast cancer. This report updates previous meta-analyses[1–4] of the individual patient data from those trials.

Post-BCS radiotherapy

After breast-conserving surgery (BCS), a particularly common site of local recurrence is the conserved breast itself (or the axilla, if this has not been treated effectively). The risk of recurrence in a conserved breast can be substantial even in node-negative disease that has been confirmed by axillary clearance, and it can be greatly reduced by radiotherapy.[4,5] Hence, the recent National Institutes of Health (NIH) consensus conference on early breast cancer[6] recommended that after BCS there should be radiotherapy to the conserved breast. Recent surveys in North America and Europe indicate that this treatment is generally given.[7] It is, however, not always given,[8] since later recurrence in a conserved breast can usually be removed by further surgery. Breast radiotherapy immediately after BCS could improve long-term survival (by comparison with a policy of watchful waiting for any local recurrence) only if life-threatening spread from tumour cells in the conserved breast would otherwise occur after BCS but before any clinically evident local recurrence was detected and treated, or if the local disease could then not be controlled adequately. Hence, radiotherapy is likely to have little effect on early mortality, whatever effect it might have on long-term breast cancer mortality.

Post-mastectomy radiotherapy

Even after mastectomy, an appreciable risk of local recurrence (eg, in the chest wall or lymph nodes) can remain unless some reliable method of investigation, such as axillary clearance, has found no evidence of nodal involvement. If axillary investigation reveals nodal involvement (or if the axilla has not been adequately investigated), post-mastectomy radiotherapy can produce a substantial absolute reduction in this risk of local recurrence, and previous trials[9–12] and meta-analyses[2–4] have shown that although it has little effect on breast cancer mortality during the first few years, it can produce a moderate, but definite, reduction in longer-term breast cancer mortality. Hence, the NIH consensus conference[6] recommended radiotherapy after mastectomy for women at high risk of locoregional recurrence (eg, those with four or more involved lymph nodes).

Long-term follow-up of mortality

Moderate differences in mortality that take many years to emerge can best be assessed by systematic meta-analyses of the data on every individual patient in all relevant randomised trials. Even this method of assessment, however, will yield reliable answers only if large numbers of relevant individuals have been randomised and followed up for many years. Our previous reviews of individual patient data included follow-up of the surgery trials only to 1990[3] and follow-up of the radiotherapy trials[4] only to 1995. In the latter review,[4] the effect on long-term breast cancer mortality was only marginally significant in the trials of post-BCS radiotherapy, although more clearly significant in those of post-mastectomy radiotherapy. Moreover, in the data then available, all-cause mortality was not significantly reduced by radiotherapy after either BCS or mastectomy. More recently, a review of just the published results from the post-BCS radiotherapy trials found only a marginally significant difference in all-cause mortality, but noted that an updated meta-analysis of individual patient data would be more reliable.[13]

The present review of individual patient data from randomised trials of local treatments involves substantially longer follow-up than our previous reviews.[3,4] For the post-BCS radiotherapy trials in particular, many of which started relatively recently, and for at least the most recent post-mastectomy radiotherapy trials, this longer follow-up should offer a much more reliable assessment of the long-term effects on mortality. The main results for these two particular comparisons are presented separately, before the more general analyses that bring together data from all the local treatment comparisons.

The main aim of this report is to assess quantitatively the relationship between local control and long-term breast cancer mortality. It deals only semi-quantitatively with the effects of some radiotherapy regimens on mortality several years later from other conditions (eg, heart disease and lung cancer[14–16]), and does not investigate the extent to which the long-term fatal (or non-fatal) adverse effects of local treatment can be avoided by the substantial changes that have taken place over the past few decades in radiotherapy and surgery techniques.[17–19]

Methods

Every 5 years since 1985 evidence from the randomised trials in early breast cancer has been reviewed centrally, in a worldwide collaboration between the individuals now responsible for them (as the Early Breast Cancer Trialists' Collaborative Group, EBCTCG). An EBCTCG report published earlier this year[20] gave the results up to the year 2000 from the trials that began by 1995 of systemic treatments (chemotherapy or hormonal therapy) for early breast cancer. The present report gives the corresponding results from the trials of local treatments (various types of surgery or radiotherapy, or both), using similar methods.

Treatment comparisons and main outcomes

Information was available (table 1) from several trials of post-BCS radiotherapy (mostly to the conserved breast); of post-mastectomy radiotherapy (mostly to the chest wall and locoregional lymph nodes, after axillary clearance); of more surgery versus less surgery in the absence of radiotherapy; of more surgery versus less surgery in the presence of radiotherapy; and of surgery versus radiotherapy (ie, more surgery versus less surgery plus additional radiotherapy). Only unconfounded trials were considered (ie, trials in which there was to be no

Treatments compared	Available for analysis*			Not yet available†	
	Trials	Deaths	Women	Trials	Women
RT versus no RT, but the same surgery					
BCS, generally with AC, then RT versus no RT‡	10	1940	7311	3	1150
Mastectomy+AC, then RT versus no RT	25	6265	9933	2	165
Mastectomy+AS, then RT versus no RT	4	360	647	0	0
Mastectomy alone, then RT versus no RT	7	3890	5597	0	0
More surgery versus less surgery, but the same (or no) RT					
IMC removal versus not, both with mastectomy and no RT	2	793	1082	0	0
Pectoral muscle removal versus not, both with mastectomy (mainly CAMS China trial)	4	1347	4925	2	~200
AC versus not in node-positive disease, both with mastectomy and some RT	2	240	266	5	~552
AC versus not in node-negative disease, both with mastectomy and no axillary RT	4	757	1154	0	0
Mastectomy+AC versus BCS+AC, neither with RT (part of NSABP B-06 trial)	1	660	1432	0	0
Mastectomy+AC versus BCS+AC, both with RT	2	185	428	0	0
BCS with more versus less breast surgery, neither with AC	0	0	0	3	~216
More surgery (active) versus less surgery plus RT (control)					
Nodal surgery versus RT	9	2910	4550	1	~100
Mastectomy+AC versus BCS+RT (Guy's Hospital trial)	1	509	630	0	0
Mastectomy versus BCS+RT, both with AC	7	1675	4125	3	~540
Total*	**78**	**21 531**	**42 080**	**19**	**~2923 (6%)**

RT=radiotherapy. AC=axillary clearance. AS=axillary sampling. IMC=internal mammary chain of lymph nodes. *Some trials (eg, NSABP B-06: about 700 mastectomy+AC+RT *vs* about 700 mastectomy+AC *vs* about 700 BCS+AC) contribute to more than one type of treatment comparison, so their control group might be counted more than once in the total. Without such double counting, the total would be 70 trials available, with 19 291 deaths among 38 047 women (93% of total). †Numbers of trials known to be unavailable: in such studies, numbers randomised are by year 2000, and might be uncertain (or wholly unavailable, in which case they are taken as 100, since such studies might well be small). ‡In eight trials of post-BCS RT all women were to have AC, but in two (85B Scottish and 85D West Midlands) only some were to do so. In most trials of post-BCS RT, irradiation was generally just to the breast, but in some the irradiated sites included axilla, supraclavicular fossa, and internal mammary chain (AF+IMC).

Table 1: **Availability of data from unconfounded randomised trials of local therapy that began by 1995**

difference between the treatment groups in the use of systemic therapy). No specific studies of the relevance of newer diagnostic techniques, such as sentinel lymph node biopsy,[21] were available. Webtables 1–3 give brief design details of each of the available treatment comparisons in the three main parts of table 1.

For all unconfounded randomised trials that began recruitment by 1995, information was sought for every patient on her initial characteristics, allocated treatment, and time to various outcomes. These outcomes were: breast cancer recurrence; whether the first such recurrence was a distant or an isolated local recurrence (ie, an ipsilateral locoregional recurrence occurring before any contralateral or other distant recurrence); cause-specific and overall mortality; and the incidence of second primary cancers before breast cancer recurrence.

Data management procedures

Trial identification and data handling procedures were as in the EBCTCG report on systemic therapies,[20] except that: (i) more detail was sought of the surgical procedures, radiotherapy regimens, and definitions of local recurrence (from protocols, publications, or correspondence; see webtables 1–3); (ii) breast cancer in the contralateral breast was not counted as local recurrence; (iii) more detail was sought (by correspondence) about the underlying causes of many of the deaths, particularly from circulatory disease, lung cancer, or uncertain causes, before any recurrence of breast cancer; and (iv) more definite information was sought (by correspondence) if it was unclear whether the first recurrence was just an isolated local recurrence.

In treatment comparisons where the extent of axillary surgery was identical in both groups, classification of axillary nodal status as positive or negative was based on pathological information where available, and on clinical information where not. The few women with unknown nodal status were combined with those with clinically node-positive disease. In treatment comparisons where the extent of axillary surgery differed between the groups (eg, axillary surgery *vs* axillary radiotherapy), classification of nodal status was based only on clinical information, to avoid bias.

For every randomised treatment comparison, local recurrence was defined in the same way for both groups. In the trials of radiotherapy versus not, this generally included recurrence (or a new breast cancer) in the residual breast tissue, scar area, chest wall, or ipsilateral regional lymph nodes, and in the trials involving surgery, trial-specific local recurrence definitions are given in webtables 2 and 3. Where recurrences just in a conserved breast or axilla had not originally been reported to the collaboration, information on them was sought, and they are now included as local recurrences.

Statistical analysis

All analyses were stratified by trial, by time since randomisation in single years, and by nodal status (negative or positive). The main analyses of local recurrence, breast cancer mortality, and overall mortality were also stratified by age in 5 groups (<40, 40–49, 50–59,

Panel: Webtables 1–4 and webfigures 1–10 on the *Lancet* website

Webtables 1–3 provide brief details of every available trial (including the anatomic sites treated surgically and the radiotherapy doses and sites irradiated), and webtable 4 shows how the statistics for breast cancer mortality are derived by logrank subtraction (ie, subtraction of the logrank statistics for mortality from causes other than breast cancer from the logrank statistics for any death). The 15-year time-to-event graphs in webfigures 1–3 provide more detail for some of the main meta-analyses (including the logrank statistics for local recurrence, breast cancer mortality, and any death during years 0–4, 5–9, 10–14, and ≥15), webfigures 4 and 5 relate the effect on local recurrence to the proportional effect on breast cancer mortality, and webfigure 6 gives various subgroup analyses. Webfigure 7 (radiotherapy side-effects) gives 15-year time-to-event graphs for the incidence of contralateral breast cancer and for mortality from causes other than breast cancer. Finally, the forest plots in webfigures 8–10 give summary results for every separate trial (separating women with node-negative and node-positive disease) for local recurrence, breast cancer mortality, and any death. This report and the webtables and webfigures are also available on the EBCTCG website (www.ctsu.ox.ac.uk/projects/ebctcg), along with Powerpoint images of some of them.

60–69, ≥70 years at randomisation). Only two groups (<50 and ≥50 years) were used, however, for analyses that were further subdivided by tumour characteristics (grade, size, oestrogen-receptor [ER] status, or actual number of involved nodes). Other aspects of the statistical methods and the formats of the figures are as before,[20] unless otherwise indicated, and are described on the EBCTCG website (see panel).

In early breast cancer, most local recurrences become apparent within the first few years, but much of the distant recurrence and breast cancer mortality occurs later.[4] The main analyses involve 5-year local recurrence risks and 15-year breast cancer mortality risks. Both are generally illustrated by 15-year graphs (for comparability with the EBCTCG report[20] on systemic therapies), but the logrank observed minus expected (O–E) values that yield the significance tests associated with such graphs are based on events throughout the entire period of follow-up, both during and after the first 15 years, unless otherwise indicated. For the major treatment comparisons, results for overall mortality ("any death") are also given, mainly on the website.

Collaborative review

Preliminary meta-analyses of the trials of local treatments had been presented and discussed at a meeting of collaborators in September, 2000, after which much additional detail was sought about methods and outcomes in these trials, and restructured, corrected meta-analyses emerged in 2004. A draft of the present report was circulated for comment by the collaborating trialists in June, 2005, was presented and discussed at a further meeting of collaborators in September, 2005, and was available for further comment in October, 2005. It was revised substantially in the light of these comments and recirculated when submitted for publication in November, 2005 (and, during the editorial process page proofs were posted on the password-protected EBCTCG website).

Role of the funding sources

This collaboration is funded from the general long-term financial support of the CTSU by organisations that had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The EBCTCG secretariat had full access to all the data and analyses and, after consultation with the collaborators, had final responsibility for the decision to submit for publication.

Results

Table 1 shows the numbers of trials and the numbers of randomised women who contributed to various local treatment comparisons. The two most extensively studied aspects of local treatment are radiotherapy after BCS (7311 women in 10 trials) and radiotherapy after mastectomy and axillary clearance (9933 women in 25 trials). The results (subdivided by nodal status, thereby making four separate treatment comparisons) for these two particular sets of trials are presented first. Then information from all the treatment comparisons in table 1 (again subdivided by nodal status, making a total of 24 comparisons) is used to relate the magnitude of the effect on local recurrence to that on breast cancer mortality. Finally, the effects of the radiotherapy regimens in these trials on the incidence of second cancers and on mortality from diseases other than breast cancer are presented.

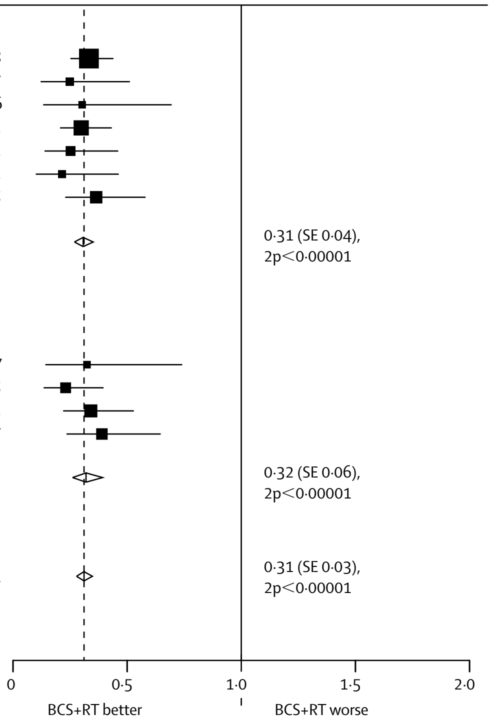
Radiotherapy after BCS

Figure 1 gives, for the ten trials of post-BCS radiotherapy, logrank analyses of the effects on local recurrence (upper part of figure) and on breast cancer mortality (lower part). Separate subtotals are given (a) for trials in which the conserved breast was the only site irradiated (sometimes with an additional boost to the scar) and (b) for those where other sites were also irradiated, such as the axilla and supraclavicular fossa. One of the ten trials contributed to both subtotals, so there are 11 strata in figure 1. The reduction in local recurrence (mainly in the conserved breast) produced by allocation to radiotherapy is substantial and highly significant ($p<0 \cdot 00001$) in every separate trial. There is no significant heterogeneity between the proportional reductions in local recurrence in the 11 different strata in figure 1, or in the two subtotals. The recurrence rate ratio, comparing those allocated radiotherapy with those not, is about 0·3 in every trial, corresponding to a proportional reduction of 70%. Considering all ten trials together, the 5-year risk of local

Isolated local recurrence (events/woman-years)

Year started and study name		RT sites	Events/woman-years: Allocated BCS+RT	Events/woman-years: Allocated BCS	BCS+RT events: Logrank O–E	BCS+RT events: Variance of O–E	Ratio of annual event rates BCS+RT : BCS
(a) Radiotherapy only to conserved breast: 14% node positive							
1976	NSABP B-06	BW*	125/6862	285/4991	−93·3	84·8	
1981	Uppsala-Örebro	BW	10/1636	43/1511	−17·7	12·7	
1982	St George's London	BW*	12/1202	31/1047	−11·5	9·6	
1984	Ontario COG	BW+S	53/3543	155/2754	−58·2	48·2	
1987	INT Milan 3	BW+S*	19/2478	60/2005	−25·1	18·2	
1989	NSABP B-21	BW+S*	6/1810	40/1729	−17·3	11·2	
1991	Swedish BCCG	BW	33/3718	92/3429	−30·8	30·5	
(a) Subtotal			258/ 21249	706/ 17466	−254·0	215·3	0·31 (SE 0·04), 2p<0·00001
5-year risk			7·2%	25·6%			
(b) Radiotherapy to conserved breast and other sites: 24% node positive							
1982	St George's London	BW+AF*	14/620	30/380	−10·9	9·7	
1985	Scottish	BW+S+(AF)+IMC	16/2598	83/2260	−33·0	22·5	
1985	West Midlands, UK	BW+S+AF+IMC	42/2398	104/1929	−36·8	34·2	
1986	CRC, UK	Various	33/1604	77/1454	−24·3	25·7	
(b) Subtotal			105/ 7220	294/ 6023	−105·0	92·1	0·32 (SE 0·06), 2p<0·00001
5-year risk			7·7%	26·7%			
Total (a+b)			363/ 28469	1000/ 23489	−359·0	307·4	0·31 (SE 0·03), 2p<0·00001
5-year risk			7·3%	25·9%			

Heterogeneity between 11 strata: χ^2_{10}=7·8; p=0·6



Breast cancer mortality (deaths/women)

Year started and study name		RT sites	Deaths/women: Allocated BCS+RT	Deaths/women: Allocated BCS	BCS+RT deaths: Logrank O–E	BCS+RT deaths: Variance of O–E	Ratio of annual death rates BCS+RT : BCS
(a) Radiotherapy only to conserved breast: 14% node positive							
1976	NSABP B-06	BW*	267/731	305/719	−19·7	135·0	
1981	Uppsala-Örebro	BW	37/184	34/197	2·3	16·8	
1982	St George's London	BW*	24/128	25/122	−2·5	10·9	
1984	Ontario COG	BW+S	91/416	123/421	−16·4	51·5	
1987	INT Milan 3	BW+S*	40/294	51/273	−6·2	21·3	
1989	NSABP B-21	BW+S*	8/337	8/336	0·5	3·9	
1991	Swedish BCCG	BW	32/593	41/594	−3·9	18·0	
(a) Subtotal			499/ 2683	587/ 2662	−45·8	257·4	0·84 (SE 0·06), 2p=0·004
15-year risk			28·0%	33·2%			
(b) Radiotherapy to conserved breast and other sites: 24% node positive							
1982	St George's London	BW+AF*	31/80	28/70	−2·1	12·2	
1985	Scottish	BW+S+(AF)+IMC	59/293	78/296	−5·0	30·2	
1985	West Midlands, UK	BW+S+AF+IMC	88/358	107/349	−11·4	45·3	
1986	CRC, UK	Various	76/259	89/261	−8·3	37·6	
(b) Subtotal			254/ 990	302/ 976	−26·9	125·3	0·81 (SE 0·08), 2p=0·02
10-year risk			28·2%	35·1%			
Total (a+b)			753/ 3673	889/ 3638	−72·7	382·7	0·83 (SE 0·05), 2p=0·0002
15-year risk			30·5%	35·9%			

Heterogeneity between 11 strata: χ^2_{10}=3·8; p=0·96

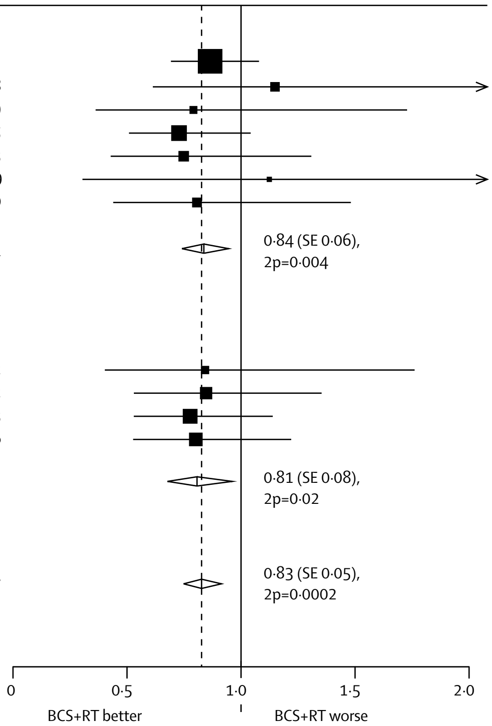


***Figure 1:* Effect of radiotherapy (RT) after BCS (ten trials) on local recurrence and on breast cancer mortality—event rate ratios**

O–E=observed–expected. BW=breast/chest wall. S=scar (as site of RT boost). AF=axilla/fossa. IMC=internal mammary chain. Sites in parentheses not always treated.

*Some systemic adjuvant therapy (same polychemotherapy and/or tamoxifen) in both groups.

99% CIs are given for trial-specific results (black squares) and 95% CIs are given for subtotals and totals (white diamonds).

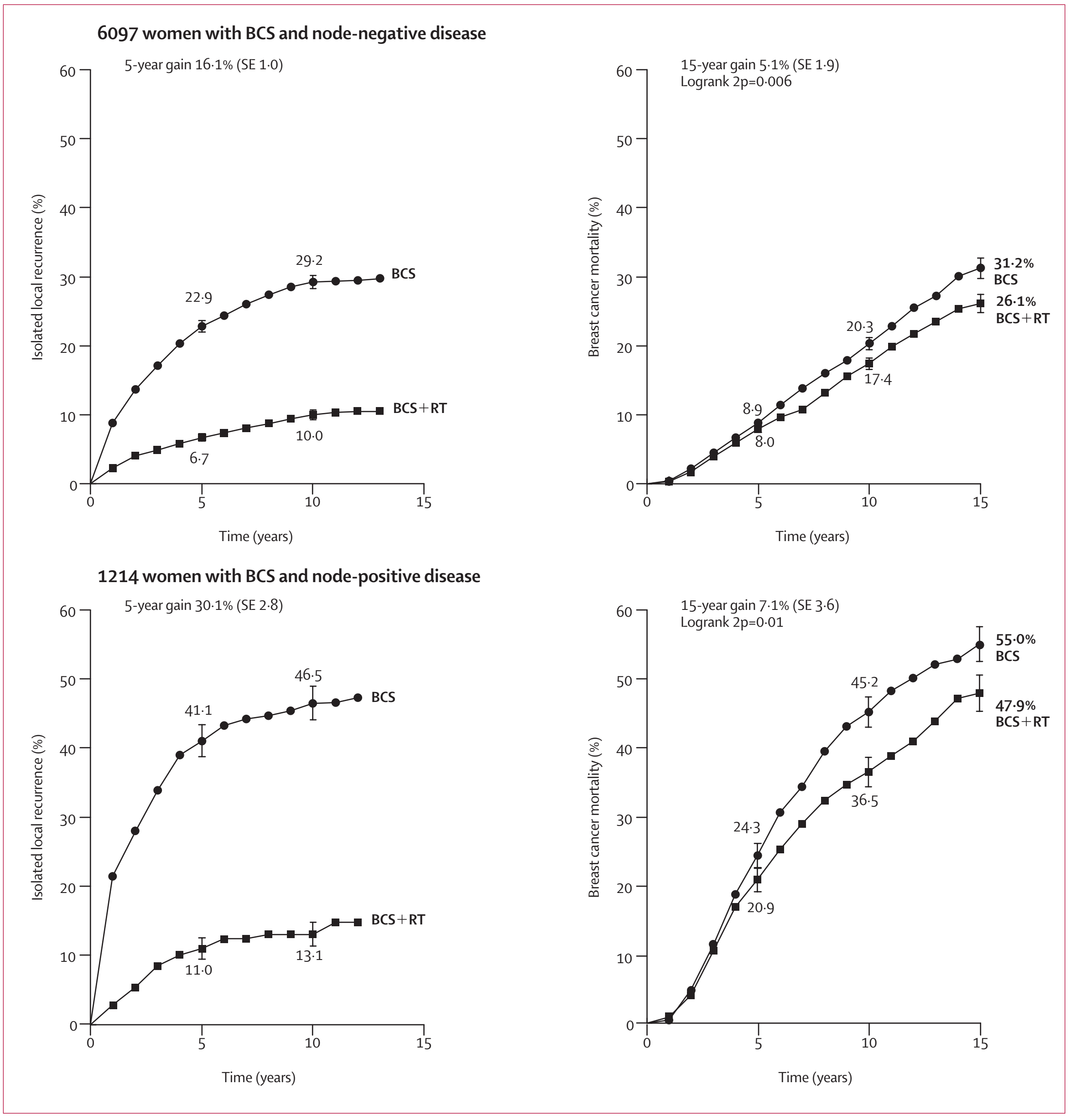


Figure 2: **Effect of radiotherapy (RT) after BCS on local recurrence and on breast cancer mortality—15-year probabilities**
Data from 10 trials. Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

recurrence is 7% among those allocated radiotherapy and 26% among those not, corresponding to an absolute reduction of 19% in this 5-year risk.

The proportional risk reduction for breast cancer mortality is much less extreme than that for local recurrence, and none of the trial-specific breast cancer mortality results is clearly significant on its own (as each of the 99% CIs overlaps unity). The total result at the bottom of figure 1 is, however, highly significant (breast cancer death rate ratio 0·83, SE 0·05, 95% CI 0·75–0·91, 2p=0·0002), indicating a reduction of about one-sixth in the annual breast cancer mortality rate. The 15-year risk of death from breast cancer (in the hypothetical absence of other causes) is 30·5% among those allocated post-BCS radiotherapy and 35·9% among those not (corresponding to an absolute reduction of 5·4%, SE 1·7). The similarity of the subtotals (a) and (b) in the upper part of figure 1 is because all of the effect in (a), and much of that in (b), is from irradiating the conserved breast, and the clear reduction in breast cancer mortality given in the total (a+b) at the foot of figure 1 shows the effectiveness of breast irradiation in these patients.

The total results in figure 1 for local recurrence and for breast cancer mortality are plotted in figure 2 by year since randomisation, separating node-negative and node-positive disease. The 5-year risk of local recurrence is substantially bigger in node-positive disease, as is the absolute reduction in this recurrence risk (ie, the 5-year gain: figure 2). The absolute reduction in breast cancer mortality also appears somewhat larger for women with node-positive disease, but the numbers are too small for this finding to be statistically reliable.

Radiotherapy after mastectomy and axillary clearance

Figure 3 gives the corresponding results for women with axillary clearance in the trials of post-mastectomy radiotherapy. In the majority of these trials radiotherapy was given to the chest wall and to the lymph nodes in the axilla, supraclavicular fossa, and internal mammary chain (webtable 1, webfigure 8).

For women with node-negative disease, the 5-year local recurrence risk after mastectomy and axillary clearance was only 6% even in the absence of radiotherapy. Although radiotherapy reduces it to 2% (2p=0·0002), the absolute 5-year gain is only 4% and there is no significant reduction in 15-year breast cancer mortality (indeed, there appears if anything to be a slight increase, but the numbers of events are small).

By contrast, for women with node-positive disease the 5-year local recurrence risk after mastectomy and axillary

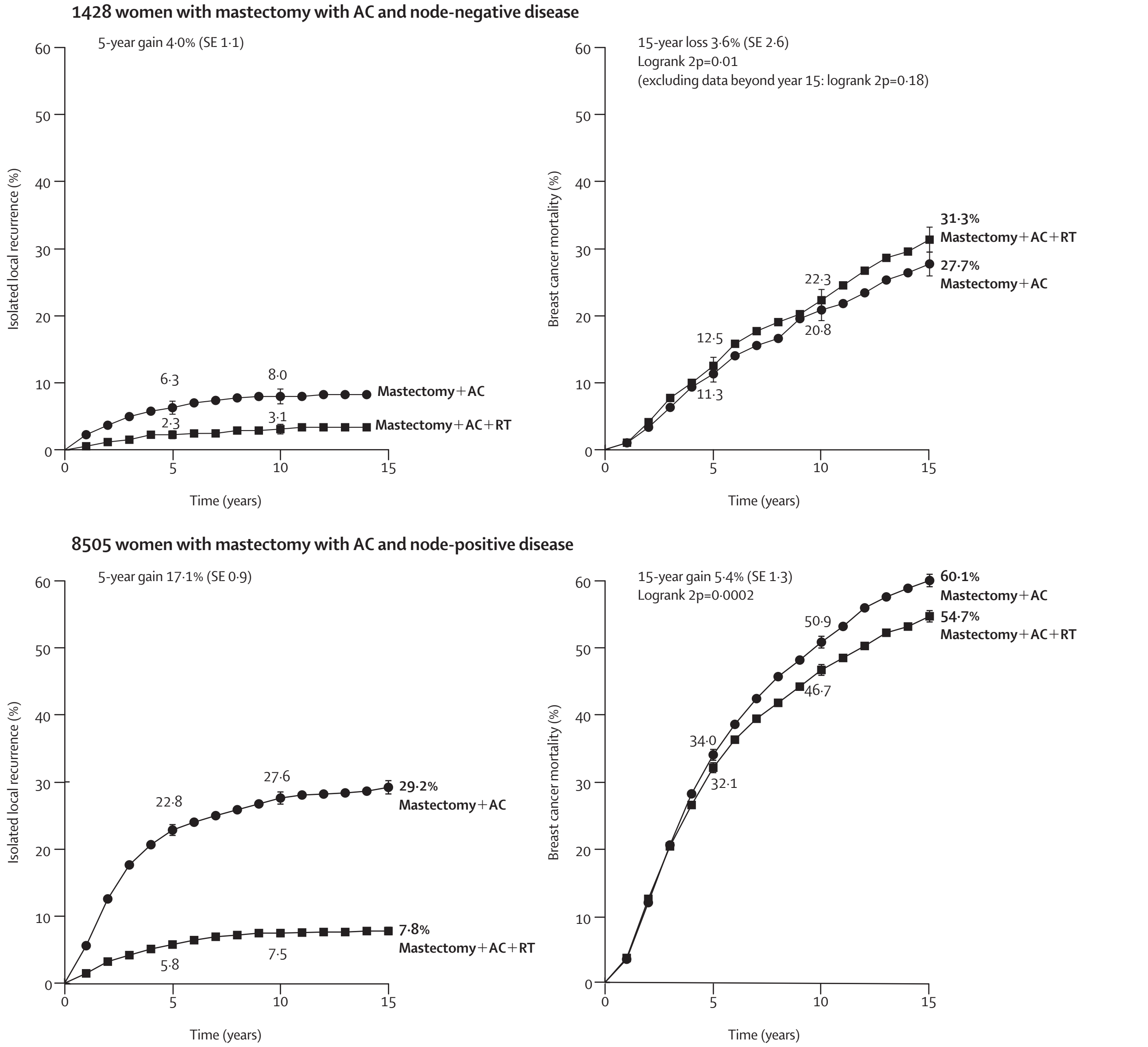


Figure 3: **Effect of radiotherapy (RT) after mastectomy and axillary clearance (AC) on local recurrence and on breast cancer mortality—15-year probabilities**
Data from 25 trials. Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

Type of local treatment comparison	Isolated local recurrences (events): cumulative risk by year 5 after randomisation				
	Events by year 5/ women randomised*		5-year risk (actuarial %)		Absolute reduction in 5-year risk (%), control–active
	Active	Control	Active	Control	Reduction (SE)
RT versus no RT, but same surgery					
BCS then RT versus no RT (10 trials)					
Node-negative	216/3071	637/3026	6·7	22·9	16·1% (1·0)
Node-positive	66/602	221/612	11·0	41·1	30·1% (2·8)
Mastectomy+AC then RT versus no RT (25 trials)					
Node-negative	13/662	41/691	2·3	6·3	4·0% (1·1)
Node-positive	214/4170	778/4170	5·8	22·8	17·1% (0·9)
Mastectomy+AS then RT versus no RT (4 trials)					
Node-negative	13/225	52/224	6·1	24·5	18·5% (3·5)
Node-positive	11/95	43/103	13·8	50·1	36·3% (7·5)
Mastectomy alone then RT versus no RT (7 trials)					
Node-negative	70/1427	307/1477	5·6	23·3	17·6% (1·4)
Node-positive	88/837	243/836	11·6	33·5	21·9% (2·3)
More surgery versus less surgery, but the same (or no) RT					
IMC removal versus not, neither with RT (2 trials)					
Node-negative	11/243	9/251	4·7	4·0	−0·7% (1·9)
Node-positive	42/286	50/302	19·1	21·3	2·2% (4·0)
Pectoral muscle removal versus not, both with same RT or no RT (4 trials)					
Node-negative	1/49	2/56	2·2	4·1	1·8% (3·5)
Node-positive	59/330	60/309	22·2	22·9	0·8% (3·8)
AC versus not, in node-positive disease, both with some RT (2 trials)					
Node-positive	7/129	13/137	7·5	13·5	6·1% (4·6)
AC versus not, in node-negative disease, neither with axillary RT (4 trials)					
Node-negative	51/572	119/582	11·9	23·0	11·1% (2·5)
Mastectomy+AC versus BCS+AC, neither with RT (part of NSABP B-06)					
Node-negative	46/432	149/432	10·9	36·5	25·6% (3·3)
Node-positive	46/281	128/287	18·9	52·1	33·1% (5·0)
Mastectomy+AC versus BCS+AC, both with RT (2 trials)					
Node-negative	2/59	4/60	5·7	5·2	−0·5% (4·6)
Node-positive	5/153	10/156	4·2	8·0	3·9% (3·1)
More surgery (active) versus less surgery plus RT (control)					
Nodal surgery versus RT (9 trials)					
Node-negative	123/1343	113/1329	10·8	9·6	−1·2% (1·3)
Node-positive	221/943	170/935	27·6	21·8	−5·8% (2·3)
Mastectomy+AC versus BCS alone+RT (Guy's Hospital)					
Node-negative	15/241	52/233	6·4	25·3	18·9% (3·7)
Node-positive	11/85	22/71	15·8	35·5	19·6% (8·8)
Mastectomy versus BCS+RT, both with AC (7 trials)					
Node-negative	71/1432	115/1438	5·3	8·6	3·3% (1·0)
Node-positive	40/610	26/645	7·9	4·7	−3·1% (1·5)

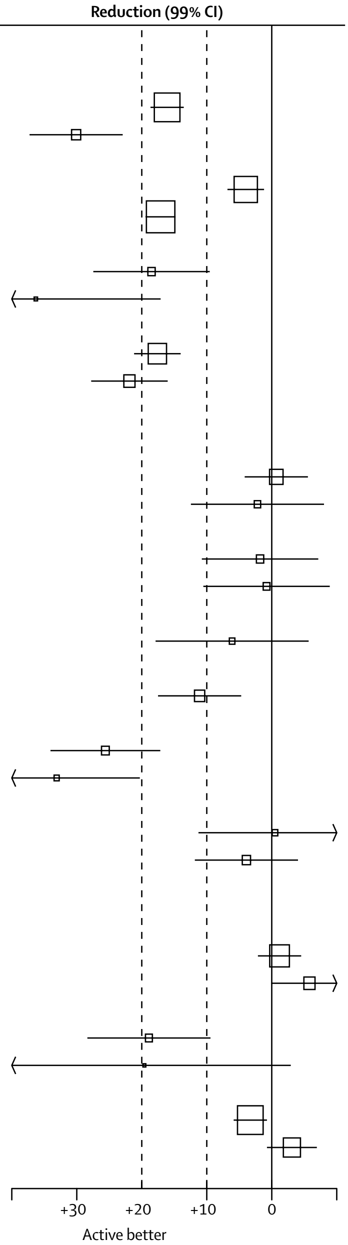


Figure 4: **Absolute reduction in 5-year local recurrence risk—78 randomised comparisons grouped into 24 types of local treatment comparison, based on treatments compared and nodal status**
RT=radiotherapy. AC=axillary clearance. AS=axillary sampling. IMC=internal mammary chain of lymph nodes.
*A few trials did not provide data on local recurrence, so in some comparisons numbers differ from table 1.

clearance is 23% in the absence of radiotherapy, which is substantial, and radiotherapy reduces it to 6%. Therefore, although the proportional reduction in the local recurrence rate produced by radiotherapy is similar in node-positive disease and in node-negative disease, the absolute 5-year gain is much larger (17%). In node-positive disease the 15-year breast cancer mortality with and without post-mastectomy radiotherapy is 54·7% versus 60·1%, an absolute reduction of 5·4% (SE 1·3, 2p=0·0002).

This analysis of the effects of post-mastectomy radiotherapy in node-positive disease is limited to the

8500 women who had had axillary clearance. Its findings for local recurrence and for breast cancer mortality would not have been materially altered, however, by inclusion of the additional 2500 women who had had only axillary sampling, or no axillary surgery (webfigure 8b). In every large trial of post-mastectomy radiotherapy in women with node-positive disease there was a similar proportional reduction in local recurrence, showing that the radiotherapy regimens used in all the main trials, recent or older, were of comparable efficacy in achieving local control (webfigure 8b). Hence, when assessing the relevance of local control to long-term breast cancer mortality, it is appropriate to consider the evidence from both recent and older trials.

Comparison of post-BCS and post-mastectomy radiotherapy trials

In the post-BCS radiotherapy trials, the site of local recurrence was generally available. When it was, over 90% (578 of 636) of the local recurrences among controls involved the conserved breast, as did over 90% of the effect of radiotherapy on local recurrence. In the post-mastectomy radiotherapy trials, the site of local recurrence was not generally available. However, little breast tissue remains after mastectomy, so the main effect of radiotherapy on local recurrence in these post-mastectomy trials must involve other sites, such as the chest wall or regional lymph nodes.

Coincidentally, the 5-year risks of local recurrence without radiotherapy, and the reduction in those risks produced by radiotherapy, were similar among women with node-negative disease in the post-BCS trials and among women with node-positive disease in the post-mastectomy trials (figure 2, upper panels, and figure 3, lower panels). The control 15-year breast cancer mortality was, of course, lower among women in the post-BCS trials (about 80% of whom had small tumours [greatest dimension ⩽20 mm] and node-negative disease) than among women in the post-mastectomy trials with node-positive disease. For both, however, it was substantial, and for both the absolute reduction in breast cancer mortality with radiotherapy was about 5%. The apparent similarity of the absolute reductions in 15-year breast cancer mortality in these two types of radiotherapy trial after similar absolute reductions in 5-year local recurrence risk suggests that the effect on long-term survival of avoiding a recurrence in a conserved breast is approximately comparable with that of avoiding a recurrence at other locoregional sites.

Three categories of local treatment comparison

To examine the general relationship between the effects of local treatment differences on local recurrence and their effects on breast cancer mortality, all the treatment comparisons listed in table 1 were subdivided by nodal status, making a total of 24 such comparisons. These were then grouped arbitrarily into three categories according to the absolute reduction (<10%, 10–20%, or >20%) in the 5-year local recurrence risk. The 24 white squares and their 99% CIs in figure 4 display these absolute reductions in risk. (The length of the side of each white square is inversely proportional to the standard error of the absolute reduction.) The vertical broken lines correspond to absolute reductions of 10% and 20% in risk, and have been used as arbitrary cut-points to group these 24 types of comparison into three categories, according to the absolute reduction in this risk. These categories involve, respectively, 17 000, 20 000, and 5000 women, with mean absolute reductions of 1%, 17%, and 26% in the 5-year local recurrence risk.

Most of the substantial absolute reductions in local recurrence risk involved the addition of radiotherapy. (The others involved conservation of the breast or axilla [or both] without effective radiotherapy to the conserved tissue.) Furthermore, almost all the comparisons of radiotherapy versus no radiotherapy involved substantial absolute reductions in local recurrence; the one exception was that after mastectomy and axillary clearance in women with pathologically node-negative disease, the risk of local recurrence without radiotherapy was so low that no large absolute reduction was possible (figures 3 and 4). In the lower part of figure 4 the four earliest trials (those starting during 1951–1970: webfigure 10) had high local recurrence risks despite radiotherapy. Omission of these early trials from subsequent analyses would make no material difference to the main conclusions.

Local control and long-term breast cancer mortality

The absolute reductions in breast cancer mortality that correspond to the three categories of local treatment comparison are shown in table 2. The differences in breast cancer mortality are greater at 15 years than at 5 years, and the 15-year differences in breast cancer mortality in the three categories are approximately proportional to the differences in 5-year local recurrence risk. The regression line through zero, relating the absolute effects on local recurrence to those on breast cancer mortality, suggests that a local treatment difference that reduces the 5-year local recurrence risk by 20% would reduce the 15-year breast cancer mortality by 5·2% (SE 0·8, 2p<0·00001).

	Breast cancer mortality (%)			
	5-year risk (active *vs* control)	5-year absolute reduction (SE)	15-year risk (active *vs* control)	15-year absolute reduction (SE)
(a) <10% (mean 1%)	18·8 *vs* 19·5	0·6 (0·6)	41·3 *vs* 42·3	1·0 (0·9)
(b) 10–20% (mean 17%)	21·8 *vs* 23·3	1·5 (0·6)	44·0 *vs* 48·5	4·5 (0·8)
(c) >20% (mean 26%)	24·9 *vs* 26·7	1·8 (1·3)	47·4 *vs* 53·4	6·0 (1·6)
Subtotal (b+c) (mean 19%)	**22·4 *vs* 24·0**	**1·6 (0·6)**	**44·6 *vs* 49·5**	**5·0 (0·8)**

Weighted regression line through zero, relating mortality reduction to recurrence reduction: 5·2%, SE 0·8, absolute reduction in 15-year breast cancer mortality for 20% absolute reduction in 5-year local recurrence risk.

Table 2: **Breast cancer mortality risks by time since randomisation and by category of absolute reduction in 5-year local recurrence risk (from figure 4)**

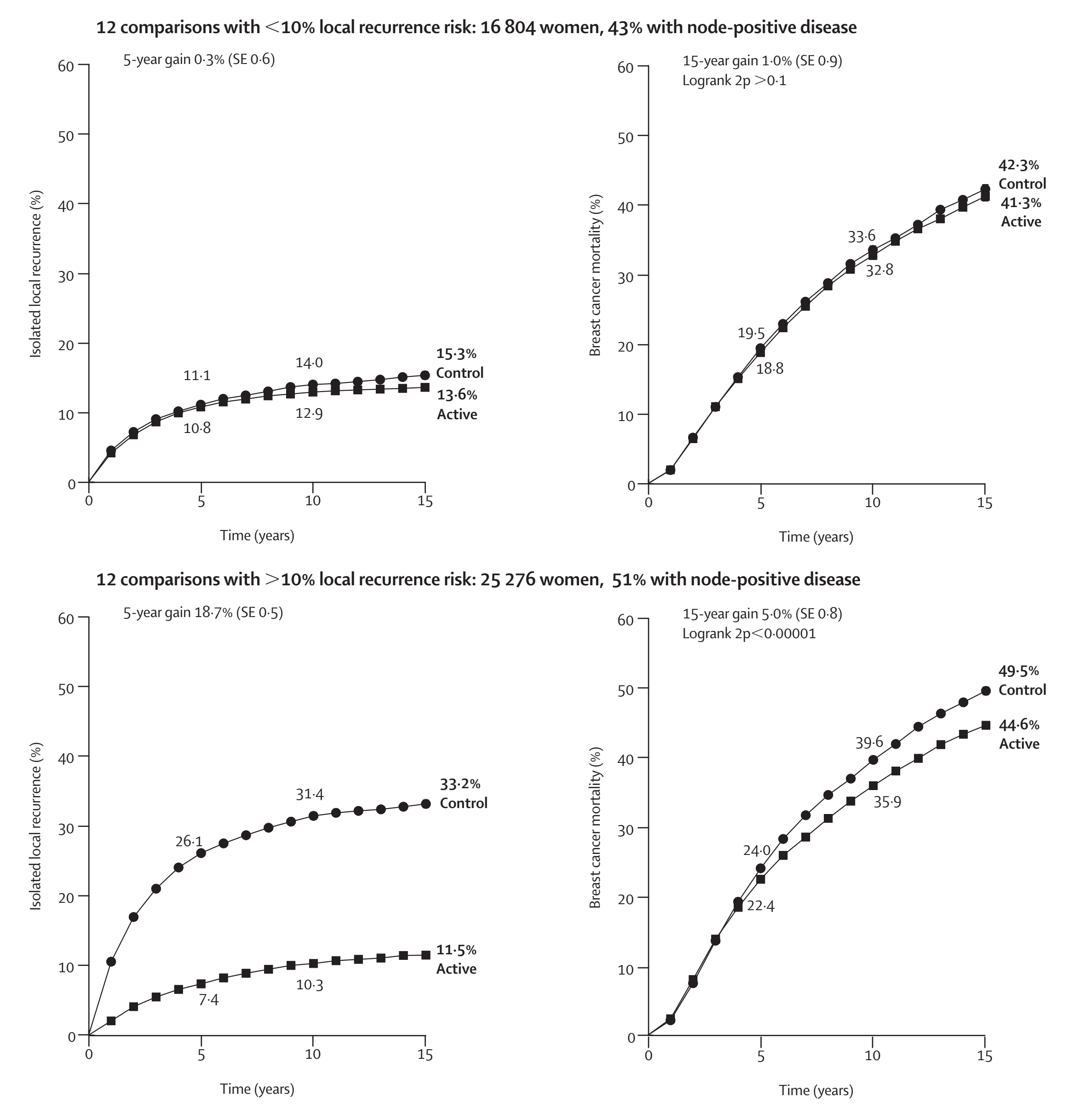


***Figure 5:* Local recurrence and breast cancer mortality for treatment comparisons that produce a less than 10% (upper panels) or more than 10% (lower panels) absolute reduction in 5-year local recurrence risk—15-year probabilities**
Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

A quantitatively similar conclusion can be obtained by combining the second and third categories (b and c in table 2), and analysing the resulting total of 25 000 women. Among them, treatment reduced the 5-year local recurrence risk by a mean of 19% and reduced the 15-year breast cancer mortality by 5·0% (SE 0·8, 2p<0·00001). The findings for these 25 000 women are plotted against time since randomisation in figure 5 (lower panels). The effect on local recurrence is substantial, and is seen rapidly; indeed, much of it is apparent within the first two or three years. In contrast, there is no apparent effect on breast cancer mortality within the first two or three years, although there is a moderate but definite effect on 15-year breast cancer mortality. Most of these 25 000 women were in trials of radiotherapy and half had node-negative disease, so the results for them are intermediate between those for post-BCS radiotherapy in node-negative disease (figure 2, upper panels) and post-mastectomy radiotherapy in node-positive disease (figure 3, lower panels).

Further details of these comparisons are given on the website (webtable 4, webfigures 3–6). For the treatment comparisons involving more than a 10% reduction in local recurrence risk, logrank analyses by period of follow-up provide formal confirmation that the main reduction in local recurrence occurs during just the first few years. By contrast, for breast cancer mortality there is no material effect during years 0–2. Subsequently, however, there are highly significant reductions in breast cancer mortality: $2p<0\cdot00001$ during each of the time periods 3–4 years and 5–9 years, and $2p=0\cdot0003$ during the time period 10–14 years after randomisation. After year 15, however, there is no evidence of any further gain (or loss of the earlier gain) in breast cancer mortality (webfigure 6c). Among those of the 25 000 women who survived to year 15, the ratio, treatment versus control, of the annual breast cancer mortality rates in subsequent years was 1·03, SE 0·08.

Tests of heterogeneity

For each of the three categories of treatment comparison in table 2, webfigure 4 shows the breast cancer mortality ratios (treatment versus control) separately during the first 5 years after randomisation and in later years, giving a total of six mortality ratios. For none of these six mortality ratios is there any significant heterogeneity between the contributions to it from different types of treatment comparison (webfigure 5). Moreover, the sum of the six heterogeneity test statistics ($\chi^2_{42}=41\cdot2$, $p=0\cdot5$) provides no significant evidence of heterogeneity between the proportional effects on breast cancer mortality of local treatments that have similar absolute effects on local recurrence risks. Such overall tests of heterogeneity with many degrees of freedom are, however, not very sensitive to any real heterogeneity that might exist. A more relevant observation is that in 3 quite different circumstances the avoidance of local recurrence (mainly during the first 5 years) appeared to be of comparable relevance to breast cancer mortality (mainly after the first 5 years): (i) in the trials of post-BCS radiotherapy; (ii) in those of post-mastectomy radiotherapy; and (iii) in the aggregated results from the trials of breast conservation or axillary conservation without effective radiotherapy to the conserved tissue (total logrank O–E –28·9 [15·7+5·1+8·1] with variance 145·2, breast cancer mortality ratio 0·82, SE 0·08, $2p=0\cdot02$; webfigure 5).

Subgroup analyses

Analyses of selected treatment comparisons in subgroups of age and of tumour characteristics (grade, size, ER status, and amount of nodal involvement, where available) are given in webfigure 6. Any apparent differences or similarities between the subgroup-specific treatment effects are likely to be much more trustworthy for local recurrence than for breast cancer mortality, because differences in local treatment can have such large effects on local recurrence rates. For women with node-negative disease in the trials of radiotherapy after BCS (webfigure 6a), and for women with node-positive disease in the trials of radiotherapy after mastectomy and axillary clearance (webfigure 6b), radiotherapy produced similar *proportional* reductions in local recurrence risk, irrespective of age, tumour grade, tumour size, ER status, or amount of nodal involvement. Consequently, within each subgroup the *absolute* benefit produced by radiotherapy was determined principally by the magnitude of the local recurrence risk in unirradiated women.

	5-year local recurrence risk (%) in trials of:			
	(a) RT after BCS (node-negative)		(b) RT after mastectomy and AC (node-positive)	
	RT versus control	Absolute reduction (SE)	RT versus control	Absolute reduction (SE)
Age (years)				
<50	11 *vs* 33	22 (2)	6 *vs* 23	17 (1)
50–59	7 *vs* 23	16 (2)	6 *vs* 24	18 (2)
60–69	4 *vs* 16	12 (1)	5 *vs* 23	18 (2)
≥70	3 *vs* 13	11 (2)	..	..
Tumour grade				
Well differentiated	4 *vs* 14	10 (2)	4 *vs* 22	18 (3)
Moderately differentiated	9 *vs* 26	17 (2)	4 *vs* 30	26 (2)
Poorly differentiated	12 *vs* 34	22 (3)	6 *vs* 40	34 (4)
Tumour size (T category)				
1–20 mm (T1)	5 *vs* 20	15 (1)	5 *vs* 22	17 (2)
21–50 mm (T2)	14 *vs* 35	21 (3)	6 *vs* 30	24 (2)
>50 mm (T3 or T4*)	..	..	8 *vs* 36	28 (4)
ER status				
ER-poor	12 *vs* 30	18 (3)	8 *vs* 28	20 (2)
ER-positive	6 *vs* 25	19 (2)	6 *vs* 24	18 (2)
Number of involved nodes				
1–3	..	..	4 *vs* 16	12 (2)
≥4	..	..	12 *vs* 26	14 (2)
All women	**7 *vs* 23**	**16 (1)**	**6 *vs* 23**	**17 (1)**

See webfigures 6a and 6b for more details on characteristics, including separate results for those in whom the relevant characteristic is not known. *T4=tumour of any size with direct extension to skin or chest wall.

***Table 3:* Effects of age and tumour characteristics on 5-year risks of local recurrence in trials of radiotherapy (RT) (a) after BCS in women with node-negative disease and (b) after mastectomy and axillary clearance (AC) in women with node-positive disease**

Age

Table 3 gives 5-year local recurrence risks for various subgroups in the trials of radiotherapy after BCS (generally with axillary clearance) in node-negative disease and in the trials of radiotherapy after mastectomy and axillary clearance in node-positive disease. In the former, most local recurrences are in the conserved breast, and the 5-year risk of such recurrence in the breast is known to be about twice as great in younger as in older women.[22–25] Hence, the absolute effects of post-BCS radiotherapy on local recurrence (mainly in the conserved breast) were greater in younger than in older women (5-year risk reductions of 22%, 16%, 12%, and 11% for those aged <50, 50–59, 60–69, and ≥70 years respectively; test for trend in absolute benefits $2p=0\cdot00002$). By contrast, there was no trend with age in the 5-year risks of local recurrence (mainly in the chest wall or lymph nodes) among women with mastectomy, axillary clearance, and

Site of cancer or cause of death, and 3-digit ICD-9 code(s)	Events	Logrank O–E*	Variance of (O–E)	Ratio of rates†	2p
Incidence of contralateral breast cancer					
By years since randomisation (and, for cases, mean year of randomisation)					
0–4 (1980)	673	1·3	161·1	1·01 (0·08)	0·9
5–14 (1980)	627	53·5	150·2	1·43 (0·10)	0·00001
≥15 (1975)	151	2·1	33·4	1·06 (0·18)	0·7
By age at randomisation					
<50 years	600	11·7	143·0	1·09 (0·09)	0·3
≥50 years	851	45·1	201·3	1·25 (0·08)	0·002
By use of systemic therapy					
With chemotherapy or tamoxifen	649	21·7	158·0	1·15 (0·09)	0·08
Without chemotherapy or tamoxifen	802	35·1	186·4	1·21 (0·08)	0·01
Total contralateral breast cancer	1451	56·9	344·4	1·18 (0·06)	0·002
Incidence of other specified cancers‡					
Lung cancer (162)	215	24·3	51·1	1·61 (0·18)	0·0007
Oesophagus cancer (150)	31	5·4	7·5	2·06 (0·53)	0·05
Leukaemia (204–208)	59	7·5	13·9	1·71 (0·36)	0·04
Soft-tissue sarcoma (158, 171)	26	5·4	6·4	2·34 (0·62)	0·03
Thyroid cancer	26	−2·3	6·2	0·69 (0·34)	0·4
Bone cancer	28	1·7	6·9	1·28 (0·43)	0·5
Other specified malignant disease	966	16·4	220·7	1·08 (0·07)	0·3
Total other specified cancers	1351	58·4	312·7	1·20 (0·06)	0·001
Mortality before recurrence, from causes other than breast cancer					
By cause					
Circulatory disease	1510	77·6	345·4	1·25 (0·06)	0·00003
Heart disease, etc§	1106	60·7	252·7	1·27 (0·07)	0·0001
Stroke	345	9·1	80·9	1·12 (0·12)	0·3
Pulmonary embolism	59	7·8	11·8	1·94 (0·41)	0·02
Other specified cause	1455	6·4	335·8	1·02 (0·06)	0·7
Lung cancer	156	21·7	37·5	1·78 (0·22)	0·0004
Oesophagus cancer	23	4·9	5·6	2·40 (0·68)	0·04
Leukaemia	31	2·4	7·0	1·40 (0·45)	0·4
Soft-tissue sarcoma	7	1·3	1·7	2·13 (1·14)	0·3
Respiratory disease (460–519, 786)	241	−1·0	55·5	0·98 (0·13)	0·9
Other known cause	997	−22·9	228·5	0·90 (0·06)	0·1
Unspecified cause, not breast cancer	701	7·8	159·4	1·05 (0·08)	0·5
By years since randomisation (and, for deaths, mean year of randomisation)					
0–4 (1976)	756	7·4	176·4	1·04 (0·08)	0·6
5–14 (1975)	1513	37·7	348·4	1·11 (0·06)	0·05
≥15 (1970)	1397	46·9	304·8	1·17 (0·06)	0·01
By age at randomisation					
<50 years	554	27·4	129·6	1·24 (0·10)	0·02
≥50 years	3112	64·4	699·8	1·10 (0·04)	0·02
Total non-breast-cancer deaths¶	3666	91·8	829·4	1·12 (0·04)	0·001

O–E=observed–expected. *Approximate excess number of events in radiotherapy group is 2(O–E). †Ratio of annual event rates (SE), irradiated versus unirradiated, estimated from O–E, and its variance V as exp([O–E]/V).[20] ‡Primary cancers of all specified sites (140–194, 200–208) except non-melanoma skin (173) and breast. Includes radiotherapy versus not: 3 versus 2 thyroid cancer (193), 1 versus 0 bone cancer (170). §All circulatory (390–459, 785, 798) except stroke (430–438) and pulmonary embolism (415, 451, 453, 673). ¶Analyses in table (and in corresponding webfigure 7) stratified by only two groups of age; had they been stratified by five age groups, as in main analyses, and the node-negative patients in the 80Y Edinburgh trial appropriately removed (see footnotes added in proof to webtables 2 and 3), the mortality results would have changed only very slightly (eg, for total non-breast-cancer deaths the logrank O–E would have been 93·4 with variance 789·2, rate ratio 1·126, SE 0·04, 2p=0·0009).

Table 4: **Effect of radiotherapy on incidence of second cancers before recurrence of breast cancer, and on mortality from causes other than breast cancer (23 500 women in 46 trials of adding radiotherapy, and 9300 in 17 trials of radiotherapy *vs* more surgery)**

node-positive disease. Hence, the absolute effects of post-mastectomy radiotherapy on the risk of such local recurrence were also approximately independent of age (local recurrence reductions of 17%, 18%, and 18% for women aged <50, 50–59, and 60–69 years respectively; there were few older women in these trials).

Tumour characteristics

In both types of trial, the 5-year local recurrence risk without radiotherapy was higher, and the absolute reduction in this risk from radiotherapy was correspondingly greater, in women with tumours that were large or with direct extension to the skin or chest wall (T2/T3/T4 tumours) or poorly differentiated, but there was little relevance of ER status to these risks. For women with mastectomy, axillary clearance, and node-positive disease, the number of involved nodes (1–3 or ≥4) was unavailable for more than half the women (webfigure 6b). Where it was available, the 5-year local recurrence risks, irradiated versus control, were 4% versus 16% for women with one to three involved nodes (reduction 12%, SE 2) and 12% versus 26% for women with four or more involved nodes (reduction 14%, SE 2; table 3). The 15-year local recurrence reductions differed more substantially, however, and were 14% and 20% for women with one to three and for those with four or more involved nodes, respectively (webfigures 2d and 2e).

Systemic therapy

In trials of systemic therapy,[20] 5 years of tamoxifen reduced the local recurrence rate by about one half in women with ER-positive disease (local recurrence rate ratio 0·47, SE 0·08) and, irrespective of ER status, polychemotherapy reduced it by about one third (ratios 0·63, SE 0·08, and 0·70, SE 0·05, for women aged <50 and 50–69 years, respectively); webfigures 9R, 4aR, 4bR in the recent EBCTCG report[20] on systemic therapy.

The local treatment comparisons that produced more than a 10% absolute reduction in 5-year local recurrence risk were, however, effective in the presence or in the absence of systemic therapy (ie, of chemotherapy or tamoxifen [or both] to both trial groups, or to neither). Among the women who received systemic therapy, the mean absolute reduction in 5-year local recurrence risk was 20% (8% *vs* 28%, webfigure 6c), and the 15-year reduction in breast cancer mortality was 5·9% (SE 1·2; 49·1% *vs* 55·1%: 2p<0·00001). Thus, better local treatment adds to the effects of systemic therapy on local recurrence and on breast cancer mortality.

Four-to-one ratio of absolute effects

Although in the present analyses subgroup-specific results derived for local recurrence might well be fairly reliable (as the effects of local treatment on local recurrence can be so extreme), subgroup-specific results for breast cancer mortality might well not be. Hence, unduly selective emphasis on particularly favourable or unfavourable *mortality* results from particular subgroups or particular trials, or even from particular types of treatment comparison, could give rise to misleading over-estimation or under-estimation of the real relevance of local disease control to long-term breast cancer mortality. Instead, the most reliable estimate of the effect on breast cancer mortality of a particular local treatment comparison in particular subgroups of women might come not from the apparent results for breast cancer mortality in those subgroups, but from estimating the effect of that treatment comparison on local recurrence risk in those subgroups, and then applying the general finding that a 20% absolute reduction in 5-year local recurrence risk leads to about a 5% absolute reduction in 15-year breast cancer mortality (ie, a four-to-one ratio of absolute effects).

Diseases other than the original breast cancer

Table 4 shows the incidence of second cancers and of mortality from causes other than breast cancer in all the trials in table 1 that tested radiotherapy (ie, all trials of radiotherapy *vs* not [with the same surgery] and all trials of more surgery *vs* radiotherapy [with active and control reversed]). There was an excess cancer incidence among women allocated radiotherapy that mainly involved contralateral breast cancer (2p=0·002) and lung cancer (2p=0·0007), and there was an excess mortality from causes other than breast cancer that mainly involved heart disease (2p=0·0001) and lung cancer (2p=0·0004). Based on much smaller numbers, there was also a moderately significant excess mortality from pulmonary embolism and excess incidence of oesophagus cancer, leukaemia and soft tissue sarcoma.

The effects of these radiotherapy regimens on contralateral breast cancer and on mortality from causes other than breast cancer are plotted against time since randomisation in webfigure 7. The averaged effects on 15-year outcome are not large (9·3% *vs* 7·5% for contralateral breast cancer, 15·9% *vs* 14·6% for non-breast-cancer mortality), but they may well vary substantially from one regimen to another, and the absolute 15-year mortality differences could also depend strongly on tumour laterality (which can affect cardiac radiation dose), smoking habits (which affect both vascular and lung cancer risks), other vascular risk factors, and, particularly, on age.

The excess of contralateral breast cancer with radiotherapy appears mainly during the period 5–14 years after randomisation (table 4, webfigure 7) and is significant even among women aged 50 years or older when randomised (table 4). When the excess mortality from causes other than breast cancer is subdivided by time since randomisation, the proportional excess again appears to be less during the first 5 years than in subsequent years, but it is separately significant for the periods 5–14 years and 15 years or more after randomisation. The mean dates of randomisation for those who died 5–14 years and 15 years or more after randomisation were, however, 1975 and 1970, respectively, and the radiotherapy regimens of the early 1970s may well have involved greater hazards than many current regimens. The excess mortality from causes other than breast cancer is significant both for women younger than 50 years of age and for women older than 50 years of age when randomised (2p=0·02 for both), but the CIs for the age-specific risks are wide. The numbers are not sufficient for the main hazards (contralateral breast cancer, lung cancer, or heart disease) to be reliably subdivided by both follow-up duration and age.

Results of similar analyses of the trials of more versus less surgery indicate no significant effect of more surgery on non-breast-cancer mortality (mortality ratio 1·11, SE 0·09).

Overall mortality in radiotherapy trials

Figure 6 compares, for the two main radiotherapy analyses, the effects on breast cancer mortality with the effects on overall mortality. In the post-BCS radiotherapy trials the absolute reduction in 15-year overall mortality is about as large as that in 15-year breast cancer mortality. For these post-BCS trials there is as yet,

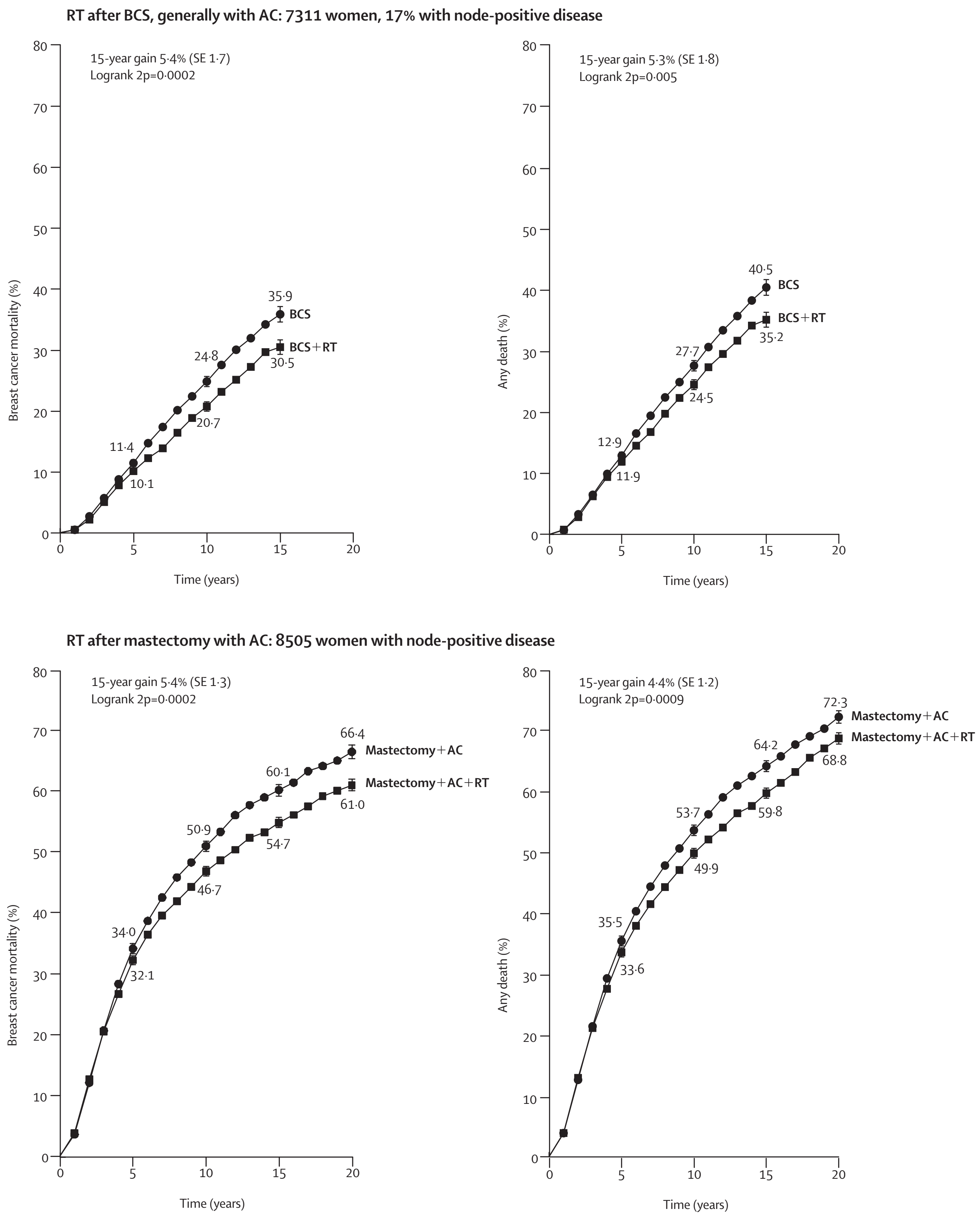


Figure 6: **Effect of radiotherapy (RT) on breast cancer mortality and on all-cause mortality after BCS or after mastectomy with axillary clearance (AC)—15-year or 20-year probabilities**
Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

however, little follow-up beyond year 15—indeed, many women have not yet been followed to year 15. In the trials of radiotherapy after mastectomy and axillary clearance in node-positive disease, the reduction in 15-year all-cause mortality is 4·4% (SE 1·2, 64·2% *vs* 59·8%, 2p=0·0009). This is less than the 5·4% reduction in 15-year breast cancer mortality. At 20 years, the reduction in breast cancer mortality remains unchanged at 5·4% (66·4% *vs* 61·0%), while that for all-cause mortality, although still significant, is only 3·5% (72·3% *vs* 68·8%), indicating a continuing excess of non-breast-cancer mortality long after treatment with the older radiotherapy regimens.

Discussion

Main findings

About three-quarters of the local recurrence risk (and more than three-quarters of any treatment effects on local recurrence) occurred during the first 5 years after randomisation. By contrast, more than half the 15-year breast cancer mortality (and much more than half of any such treatment effects on breast cancer mortality) occurred after the first 5 years. Some local treatment comparisons (eg, axillary clearance *vs* effective axillary radiotherapy; mastectomy *vs* BCS plus effective radiotherapy; post-mastectomy radiotherapy in node-negative disease) involved little (<10%) absolute difference in the 5-year risk of local recurrence and, in aggregate, these comparisons also involved little difference in 15-year breast cancer mortality (figure 5, upper panel).

Local recurrence and breast cancer mortality

The other local treatment comparisons are those that involved absolute differences of more than 10% in the 5-year risk of local recurrence (eg, post-BCS radiotherapy, mainly to the conserved breast; post-mastectomy radiotherapy in node-positive disease; conservation of the breast or axilla without effective radiotherapy to the conserved tissue). In the aggregate of all such comparisons, involving a total of 25 000 women, the 5-year local recurrence risks were 7% active versus 26% control (reduction 19%) and the 15-year breast cancer mortality risks were 44·6% versus 49·5% (reduction 5·0% SE 0·8, 2p<0·00001). Treatment comparisons that produced similar-sized effects on local recurrence tended to produce similar-sized effects on breast cancer mortality (webfigure 5). In particular, both for the 7300 women in trials of post-BCS radiotherapy (mostly with axillary clearance and pathologically node-negative disease) and for the 8500 women in trials of post-mastectomy radiotherapy after axillary clearance in node-positive disease, the absolute reductions in 5-year local recurrence and in 15-year breast cancer mortality were similar in magnitude to those in the aggregated results in all 25 000 women, and were highly significant. This finding indicates that the avoidance of recurrence in a conserved breast and the avoidance of other local recurrence (eg, in the chest wall or regional lymph nodes) are of comparable relevance to 15-year breast cancer mortality. In these two particular radiotherapy comparisons, as in the aggregated results, differences in local treatment that substantially affect locoregional recurrence would, in the hypothetical absence of other causes of death, avoid about one breast cancer death over the next 15 years for every four such recurrences avoided. Moreover, even when it does not affect survival, avoiding a local recurrence can be of substantial benefit.

Non-breast-cancer mortality and overall mortality

The absence of other causes of death is, of course, not a realistic assumption, particularly for older patients. Even the general mortality that is not caused by breast cancer or its treatment makes the 15-year survival gain somewhat smaller for overall mortality than for breast cancer mortality (as it reduces, by a similar factor, the proportion of 15-year survivors in both the treatment group and the control group). Moreover, most of the substantial differences in local recurrence in these trials were produced by radiotherapy, and some of the radiotherapy regimens, at least in the older trials of post-mastectomy radiotherapy, appreciably increased mortality more than 5 years later from diseases other than breast cancer, with most of this excess mortality involving heart disease and lung cancer. In addition, this overview confirms the previous evidence[26,27] that radiotherapy can increase the incidence of contralateral breast cancer more than 5 years later, which would slightly reduce its net beneficial effect on 15-year breast cancer mortality. (We cannot ascertain from the present data whether therapeutic doses of radiation affect the incidence of new ipsilateral breast cancer in a conserved breast, as new and recurrent tumours are not separated.) Nevertheless, at least in the post-BCS radiotherapy trials, and among women with axillary clearance and node-positive disease in the post-mastectomy radiotherapy trials, the radiotherapy regimens that were tested produced moderate but definite reductions not only in 15-year breast cancer mortality but also in 15-year overall mortality (figure 6).

Further effects after year 15

The evidence as to what will happen after year 15 is still limited. Thus far, these trials have shown that the treatments that substantially reduced the 5-year local recurrence risk moderately reduced 15-year breast cancer mortality and 15-year overall mortality. They also suggest that there will be little additional gain or loss after year 15 in breast cancer mortality (ratio, treatment *vs* control, of annual breast cancer death rates during the period after year 15=1·03, SE 0·08: webfigure 3b). There is, however, evidence from the aggregate of all radiotherapy trials of a somewhat higher death rate during the period after year 15 from causes other than breast cancer (ratio, radiotherapy *vs* not, of annual non-breast-cancer death rates after year 15=1·17, SE 0·06), but the mean date of randomisation for those dying in this late period was 1970, and the late hazards could well be substantially lower for modern radiotherapy regimens than for those of the 1960s and 1970s.

Breast cancer mortality rates remain substantial throughout at least the second decade after diagnosis (and perhaps beyond) as does the incidence of contralateral breast cancer, while lung cancer and heart disease rates increase with advancing age. If long-term follow-up of many of these trials is continued to 20 or more years, or even to 30 or more years, distinguishing between different causes of death (and, to the extent possible, between new and recurrent tumours in a conserved breast), the ensuing data will clarify substantially the long-term risks and benefits of the post-BCS radiotherapy regimens in these trials, as three-quarters of the women were still alive in the present analyses (table 1). It will also help clarify substantially the benefits and risks of both the older and the more recent post-mastectomy radiotherapy regimens in these trials.

Low and high local recurrence risks

Radiotherapy produces its greatest absolute effects on local recurrence in women who are at greatest risk of local recurrence (table 3, figures 2 and 3). For, whether the underlying risk is low or high, about 70% of it can be avoided by radiotherapy. In the trials of post-BCS radiotherapy, the risk of local recurrence among controls depended strongly on nodal status (5-year risks: 23% node-negative, 41% node-positive) and, among those with node-negative disease, young age, poor tumour differentiation, and large tumour size all indicated a high local recurrence risk (table 3). The large majority (78%) of the node-negative tumours in the post-BCS radiotherapy trials were small (1–20 mm in their longest diameter), but, even with such small tumours, without radiotherapy the 5-year risk of local recurrence was 20% (table 3).

In the trials of radiotherapy after mastectomy and axillary clearance, the 5-year risk of local recurrence among the controls depended strongly on the number of involved nodes, where this information was available (risks 6%, 16%, and 26% respectively for 0, 1–3, and ⩾4 involved nodes). Among women with mastectomy, axillary clearance, and node-negative disease the absolute reduction in 5-year local recurrence risk after radiotherapy was only 4% (2% *vs* 6%), so if one death from the original breast cancer is avoided for every four local recurrences avoided, then the expected reduction in 15-year breast cancer mortality after radiotherapy would be only 1% (less the adverse effects of any increase in contralateral disease). Relatively few such women were randomised, however, and among them the apparent effect of radiotherapy on breast cancer mortality happened to be slightly unfavourable.

Only where the absolute effects of radiotherapy on local recurrence are substantial can they be used to help quantify any proportional relationship between effects on local control and on breast cancer mortality. Among all women with mastectomy, axillary clearance, and node-positive disease, the absolute effects of radiotherapy on the 5-year local recurrence risk were substantial (6% *vs* 23%), particularly if the tumour was poorly differentiated or large, and breast cancer mortality was correspondingly reduced. In these post-mastectomy trials, however, age was of little or no relevance to local recurrence (mainly in the nodes or chest wall), even though in the post-BCS trials age was of substantial relevance to local recurrence (mainly in the conserved breast): table 3.

Generalisability of findings

Changes in practice

There have been, and will continue to be, substantial changes in the use, or methods, of screening, surgery, pathology, radiotherapy, and systemic adjuvant therapy since many of these trials began.[28–30] In particular, tumour sizes are generally smaller, systemic therapy is more effective, radiotherapy is less likely to be given to the internal mammary chain of lymph nodes or to a surgically-cleared axilla, and there has been increasing recognition of the late side-effects of radiotherapy and of the need when treating early breast cancer to limit doses to the heart and lungs. Hence, depending mainly on the doses to the heart, lungs, and contralateral breast, the late hazards of current and future radiotherapy regimens might well be much lower than those of the regimens studied in the older trials. Moreover, advances in early diagnosis, surgery, and systemic therapy mean that the 5-year risks of local recurrence might well be much less than in these trials. Nevertheless, some risk is likely to remain, since the desire to control local recurrence (after either BCS or mastectomy) has to be balanced not only against the late adverse effects but also against the cosmetic and functional effects of excessive local treatment.

Prediction of absolute risks and benefits

Prediction from these trials of the long-term risks of current radiotherapy regimens will depend on approximate comparison of current and previous radiation doses to the heart, lungs, etc, while prediction of the eventual effects on breast cancer mortality will depend on what the local recurrence risks would currently be without radiotherapy.

The absolute risks of local recurrence in these trials and the absolute benefits and hazards of radiotherapy in these trials cannot be generalised because of the continuing changes in practice since the trials began. Nevertheless, the quantitative relationship in these trials between local disease control and 15-year breast cancer mortality should still be relevant to current and future treatment decisions. Where it is possible to estimate the absolute risk of a particular type of local recurrence after a particular type of surgery, it is also possible to estimate the absolute reduction in this risk that effective radiotherapy would achieve (as radiotherapy avoids about 70% of the risk of recurrence in the irradiated sites) or that would have been avoided by more extensive surgery (as surgery eliminates the possibility of recurrence in the excised tissue). From the absolute reduction in local recurrence the absolute reduction in breast cancer mortality can be inferred.

For example, if additional local treatment led to an estimated reduction in the 5-year local recurrence risk of, say, about 12% then, from the general four-to-one relationship between effects on local recurrence and on breast cancer mortality, it could reasonably reliably be inferred that the 15-year reduction in breast cancer mortality would be about 3%, even though directly randomised proof of such a small mortality difference would be difficult to obtain.

Combination of effects of local and systemic therapy

Likewise, as the risk of recurrence in a conserved breast is about twice as great in younger as in older women, it could reasonably reliably be inferred that radiotherapy to a conserved breast (or, in the absence of radiotherapy, mastectomy rather than BCS) would have a correspondingly greater effect on breast cancer mortality in younger than in older women, even though the age-specific subgroup analyses of mortality have wide confidence intervals (webfigure 6a). Furthermore, avoidance of death from breast cancer gains more additional years of life expectancy for younger than for older women.

Systemic therapy can approximately halve the 5-year risks of both local and distant recurrence.[20] In the absence of radiotherapy, the risk of local recurrence, although reduced by surgery and systemic therapy, may still be substantial. If it is, then addition of radiotherapy (or in some cases more extensive surgery) would further reduce it by a substantial amount and thereby further reduce 15-year breast cancer mortality by a moderate amount.[10–12,31,32] Indeed, webfigure 6c suggests that the relationship between local control and breast cancer mortality is much the same with or without systemic therapy. This conclusion may be of general validity, even though it is based on the methods of local control and types of systemic therapy studied in these particular trials. If so, the moderate differences in 15-year breast cancer mortality produced by better local control can be combined with the moderate differences produced by chemotherapy and hormonal therapy (and, probably, by newer systemic therapies), yielding in total quite substantial effects on 15-year breast cancer mortality. Hence, although for the addition of radiotherapy (or for other ways of improving local control) the effects on breast cancer mortality are only moderate, several such moderate reductions in mortality (from earlier diagnosis, from improvements in local control, from the introduction of systemic therapy, and from progressive changes in its efficacy) may, in combination, approximately halve a middle-aged patient's 15-year risk of death from breast cancer. In some countries the introduction of several such improvements in diagnosis or treatment has, in aggregate, already led to substantial reductions since 1990 in the national breast cancer mortality rates in middle age.[20]

Conclusion

The main purpose of the present overview is to help predict the effects of different treatment strategies on long-term survival. It makes no treatment recommendations, nor does it assess the costs or the functional, cosmetic, or psychological effects of different treatments. In early breast cancer, local treatments that substantially improve local control have little effect on breast cancer mortality during the first few years, but have definite, although moderate, effects by 15 years, and avoidance of local recurrence in a conserved breast and elsewhere are of comparable relevance to 15-year breast cancer mortality. These trials of radiotherapy and of the extent of surgery show that, in the hypothetical absence of other causes of death, about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided. Although the management of early breast cancer continues to change, it is reasonable to assume that this approximate four-to-one relationship will continue to apply and will still be of relevance to future treatment choices.

Contributors

The main contributors are the individuals or collaborative groups who undertook, or are now continuing follow-up of, the trials that are reviewed, and who provided trial data or other relevant information (including comments on previous versions of the manuscript). Acting on their behalf, the EBCTCG secretariat (M Clarke, R Collins, S Darby, C Davies, P Elphinstone, V Evans, J Godwin, R Gray, C Hicks, S James, E MacKinnon, P McGale, T McHugh, R Peto, C Taylor, Y Wang) accept full responsibility for the overall content of this report on the data provided and on the other relevant information received. S Darby, P McGale, R Peto, and C Taylor also accept responsibility for the data and information provided on the trials of local treatments being accurately reported on the study website.

Conflict of interest statement

The secretariat declare that they all have no conflict of interest.

Acknowledgments

The main acknowledgment is to the tens of thousands of women who took part in the trials reviewed here. Funding for the EBCTCG secretariat is by direct support from the UK Medical Research Council, and a special grant from Cancer Research UK, to the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) in the Nuffield Department of Clinical Medicine, University of Oxford. This paper is dedicated to Richard Doll (1912-2005), epidemiologist extraordinary.[33]

EBCTCG collaborators, listed by institution or trial organisation

ACETBC, Tokyo, Japan—O Abe, R Abe, K Enomoto, K Kikuchi, H Koyama, H Masuda, Y Nomura, K Sakai, K Sugimachi, T Tominaga, J Uchino, M Yoshida.

Addenbrooke's Hospital, Cambridge, UK—J L Haybittle.

ATLAS Trial Collaborative Study Group, Oxford, UK—C Davies.

Auckland Breast Cancer Study Group, New Zealand—V J Harvey, T M Holdaway, R G Kay, B H Mason.

Australian-New Zealand Breast Cancer Trials Group, Sydney, Australia—J F Forbes, N Wilcken.

Austrian Breast Cancer Study Group, Vienna, Austria—M Gnant, R Jakesz, M Ploner.
Beatson Oncology Centre, Glasgow, UK—H M A Yosef.
Belgian Adjuvant Breast Cancer Project, Liège, Belgium—C Focan, J P Lobelle.
Berlin-Buch Akademie der Wissenschaften, Germany—U Peek.
Birmingham General Hospital, UK—G D Oates, J Powell.
Bordeaux Institut Bergonié, France—M Durand, L Mauriac.
Bordet Institute, Brussels, Belgium—A Di Leo, S Dolci, M J Piccart.
Bradford Royal Infirmary, UK—M B Masood, D Parker, J J Price.
Breast Cancer Study Group of the Comprehensive Cancer Centre, Limburg, Netherlands—P S G J Hupperets.
British Columbia Cancer Agency, Vancouver, Canada—S Jackson, J Ragaz.
Cancer and Leukemia Group B, Washington, DC, USA—D Berry, G Broadwater, C Cirrincione, H Muss, L Norton, R B Weiss.
Cancer Care Ontario, Canada—H T Abu-Zahra.
Cancer Research Centre of the Russian Academy of Medical Sciences, Moscow, Russia—S M Portnoj.
Cancer Research UK, London, UK—M Baum, J Cuzick, J Houghton, D Riley.
Cardiff Trialists Group, UK—R E Mansel.
Case Western Reserve University, Cleveland, OH, USA—N H Gordon.
Central Oncology Group, Milwaukee, WI, USA—H L Davis.
Centre Claudius Regaud, Toulouse, France—A Beatrice, J Mihura, A Naja.
Centre Léon-Bérard, Lyon, France—Y Lehingue, P Romestaing.
Centre Paul Lamarque, Montpellier, France—J B Dubois.
Centre Regional François Baclesse, Caen, France—T Delozier, J Mace Lesec'h.
Centre René Huguenin, Paris, St Cloud, France—P Rambert.
Charles University, Prague, Czech Republic—L Petruzelka, O Pribylova.
Cheltenham General Hospital, UK—J R Owen.
Chemo N0 Trial Group, Germany —N Harbeck, F Jänicke, C Meisner.
Chicago University, IL, USA—P Meier.
Christie Hospital and Holt Radium Institute, Manchester, UK—A Howell, G C Ribeiro (deceased), R Swindell.
Clinical Trial Service Unit, Oxford, UK—J Burrett, M Clarke, R Collins, S Darby, C Davies, P Elphinstone, V Evans, J Godwin, R Gray, C Harwood, C Hicks, D Jackson, S James, E MacKinnon, P McGale, T McHugh, G Mead (deceased), P Morris, J Oulds, R Peto, C Taylor, Y Wang.
Coimbra Instituto de Oncologia, Portugal—J Albano, C F de Oliveira, H Gervásio, J Gordilho.
Copenhagen Radium Centre, Denmark—H Johansen, H T Mouridsen.
Dana-Farber Cancer Institute, Boston, MA, USA—R S Gelman, J R Harris, I C Henderson, C L Shapiro.
Danish Breast Cancer Cooperative Group, Copenhagen, Denmark—P Christiansen, B Ejlertsen, H T Mouridsen, S Møller, M Overgaard.
Danish Cancer Registry, Copenhagen, Denmark—B Carstensen, T Palshof.
Düsseldorf University, Germany—H J Trampisch.
Dutch Working Party for Autologous Bone Marrow Transplant in Solid Tumours, Groningen, Netherlands—O Dalesio, E G E de Vries, S Rodenhuis, H van Tinteren.
Eastern Cooperative Oncology Group, Boston, MA, USA—R L Comis, N E Davidson, R Gray, N Robert, G Sledge, D C Tormey, W Wood.
Edinburgh Breast Unit, UK—D Cameron, U Chetty, P Forrest, W Jack.
Elim Hospital, Hamburg, Germany—J Rossbach.
Erasmus MC/Daniel den Hoed Cancer Center, Rotterdam, Netherlands—J G M Klijn, A D Treurniet-Donker, W L J van Putten.
European Institute of Oncology, Milan, Italy—A Costa, U Veronesi.
European Organization for Research and Treatment of Cancer, Brussels, Belgium—H Bartelink, L Duchateau, C Legrand, R Sylvester, J A van der Hage, C J H van de Velde.
Evanston Hospital, IL, USA—M P Cunningham.
Fox Chase Cancer Centre, Philadelphia, PA, USA—R Catalano, R H Creech.
French Adjuvant Study Group (GFEA), Guyancourt, France—J Bonneterre, P Fargeot, P Fumoleau, P Kerbrat, M Namer.
German Adjuvant Breast Group (GABG), Frankfurt, Germany—W Jonat, M Kaufmann, M Schumacher, G von Minckwitz.
German Breast Cancer Study Group (BMFT), Freiburg, Germany—G Bastert, H Rauschecker, R Sauer, W Sauerbrei, A Schauer, M Schumacher.
Ghent University Hospital, Belgium—A de Schryver, L Vakaet.
GIVIO Interdisciplinary Group for Cancer Care Evaluation, Chieti, Italy—M Belfiglio, A Nicolucci, F Pellegrini, M Sacco, M Valentini.
Glasgow Victoria Infirmary, UK—C S McArdle, D C Smith.
Gruppo Oncologico Clinico Cooperativo del Nord Est, Aviano, Italy—E Galligioni.
Gruppo Ricerca Ormono Chemio Terapia Adiuvante (GROCTA), Genova, Italy—F Boccardo, A Rubagotti.
Groote Schuur Hospital, Cape Town, South Africa—D M Dent, C A Gudgeon, A Hacking.
Guadalajara Hospital de 20 Noviembre, Mexico—A Erazo, J Y Medina.
Gunma University, Japan—M Izuo, Y Morishita, H Takei.
Guy's Hospital, London, UK—I S Fentiman, J L Hayward, R D Rubens, D Skilton.
Heidelberg University I, Germany—H Scheurlen.
Heidelberg University II, Germany—M Kaufmann, D von Fournier.
Hellenic Cooperative Oncology Group, Athens, Greece—U Dafni, G Fountzilas.
Helsinki Deaconess Medical Centre, Finland—P Klefstrom.
Helsinki University, Finland—C Blomqvist, T Saarto.
Innsbruck University, Austria—R Margreiter.
Institut Curie, Paris, France—B Asselain, R J Salmon, J R Vilcoq.
Institut Gustave-Roussy, Paris, France—R Arriagada, C Hill, A Laplanche, M G Lê, M Spielmann.
Instituto Nazionale per la Ricerca sul Cancro, Genova, Italy—P Bruzzi, E Montanaro, R Rosso, M R Sertoli, M Venturini.
Instituto Oncologico Romagnolo, Forli, Italy—D Amadori.
Integraal Kankercentrum, Amsterdam, Netherlands—J Benraadt, M Kooi, A O van de Velde, J A van Dongen, J B Vermorken.
International Breast Cancer Study Group (Ludwig), Bern, Switzerland—M Castiglione, F Cavalli, A Coates, J Collins, J Forbes, R D Gelber, A Goldhirsch, J Lindtner, K N Price, C M Rudenstam, H J Senn.
International Collaborative Cancer Group, Charing Cross Hospital, London, UK—J M Bliss, C E D Chilvers, R C Coombes, E Hall, M Marty.
Israel NSABC, Tel Aviv, Israel—R Borovik, G Brufman, H Hayat, E Robinson, N Wigler.
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy—G Bonadonna, T Camerini, G De Palo, M Del Vecchio, F Formelli, P Valagussa.
Italian Cooperative Chemo-Radio-Surgical Group, Bologna, Italy—A Martoni, F Pannuti.
Italian Oncology Group for Clinical Research, Parma, Italy—G Cocconi, A Colozza, R Camisa.
Japan Clinical Oncology Group–Breast Cancer Study Group, Matsuyama, Japan—K Aogi, S Takashima.
Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan—O Abe, T Ikeda, K Inokuchi, K Kikuchi, K Sawa.
Kawasaki Medical School, Japan—H Sonoo.
Krakow Institute of Oncology, Poland—S Korzeniowski, J Skolyszewski.
Kumamoto University Group, Japan—M Ogawa, J Yamashita.
Leuven Akademisch Ziekenhuis, Gasthuisberg, Belgium—J Bonte, R Christiaens, R Paridaens, W Van den Bogaert.
Marseille Laboratoire de Cancérologie Biologique APM, France—P Martin, S Romain.
Memorial Sloan-Kettering Cancer Center, New York, NY, USA—T Hakes, C A Hudis, L Norton, R Wittes.
Metaxas Memorial Cancer Hospital, Athens, Greece—G Giokas, D Kondylis, B Lissaios.
Mexican National Medical Centre, Mexico City, Mexico—R de la Huerta, M G Sainz.
National Cancer Institute, Bethesda, MD, USA—R Altemus, K Cowan, D Danforth, A Lichter, M Lippman, J O'Shaughnessy, L J Pierce, S Steinberg, D Venzon, J A Zujewski.
National Cancer Institute, Bari, Italy—A Paradiso, M De Lena, F Schittulli.
National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada—J D Myles, J L Pater, K I Pritchard, T Whelan.
National Kyushu Cancer Center, Japan—Y Nomura.

National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, PA, USA—S Anderson, G Bass, A Brown, J Bryant, J Costantino, J Dignam, B Fisher, C Redmond, S Wieand, N Wolmark.
Nolvadex Adjuvant Trial Organisation, London, UK—M Baum, I M Jackson (deceased), M K Palmer.
North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN, USA—J N Ingle, V J Suman.
North Sweden Breast Cancer Group, Umea, Sweden—N O Bengtsson, H Jonsson, L G Larsson.
North-Western British Surgeons, Manchester, UK—J P Lythgoe, R Swindell.
Northwick Park Hospital, London, UK—M Kissin.
Norwegian Breast Cancer Group, Oslo, Norway—B Erikstein, E Hannisdal, A B Jacobsen, J E Varhaug.
Norwegian Radium Hospital, Oslo, Norway—B Erikstein, S Gundersen, M Hauer-Jensen, H Høst, A B Jacobsen, R Nissen-Meyer.
Nottingham City Hospital, UK—R W Blamey, A K Mitchell, D A L Morgan, J F R Robertson.
Oncofrance, Paris, France—M Di Palma, G Mathé, J L Misset.
Ontario Clinical Oncology Group, Hamilton, Canada—R M Clark, M Levine, K I Pritchard, T Whelan.
Osaka City University, Japan—K Morimoto.
Osaka National Hospital, Japan—K Sawa, Y Takatsuka.
Churchill Hospital, Oxford, UK—E Crossley, A Harris, D Talbot, M Taylor.
Parma Hospital, Italy—G Cocconi, B di Blasio.
Petrov Research Institute of Oncology, St Petersburg, Russia—V Ivanov, V Semiglazov.
Piedmont Oncology Association, Winston-Salem, NC, USA—J Brockschmidt, M R Cooper.
Prefectural Hospital, Oita, Japan—H Ueo.
Pretoria University, South Africa—C I Falkson.
Royal Marsden Hospital, Institute of Cancer Research, London, UK—R A'Hern, S Ashley, T J Powles, I E Smith, J R Yarnold.
St George's Hospital, London, UK—J C Gazet.
St Luke's Hospital, Dublin, Ireland—N Corcoran.
Sardinia Oncology Hospital A Businico, Cagliari, Sardinia—N Deshpande, L di Martino.
SASIB International Trialists, Cape Town, South Africa—P Douglas, A Hacking, H Høst, A Lindtner, G Notter.
Saskatchewan Cancer Foundation, Regina, Canada—A J S Bryant, G H Ewing, L A Firth, J L Krushen-Kosloski.
Scandinavian Adjuvant Chemotherapy Study Group, Oslo, Norway—R Nissen-Meyer.
Scottish Cancer Therapy Network, Edinburgh, UK—L Foster, W D George, H J Stewart, P Stroner.
South Sweden Breast Cancer Group, Lund, Sweden—P Malmström, T R Möller, S Rydén, I Tengrup, L Tennvall-Nittby.
South-East Sweden Breast Cancer Group, Linköping, Sweden—J Carstenssen, M Dufmats, T Hatschek, B Nordenskjöld, M Söderberg.
South-Eastern Cancer Study Group and Alabama Breast Cancer Project, Birmingham, AL, USA—J T Carpenter.
South-West Oncology Group, San Antonio, TX, USA—K Albain, J Crowley, S Green, S Martino, C K Osborne, P M Ravdin.
Stockholm Breast Cancer Study Group, Sweden—U Glas, U Johansson, L E Rutqvist, T Singnomklao, A Wallgren.
Swiss Group for Clinical Cancer Research (SAKK), Bern, and OSAKO, St Gallen, Switzerland—M Castiglione, A Goldhirsch, R Maibach, H J Senn, B Thürlimann.
Tel Aviv University, Israel—H Brenner, A Hercbergs.
Tokyo Cancer Institute Hospital, Japan—M Yoshimoto.
Toronto-Edmonton Breast Cancer Study Group, Canada—G DeBoer, A H G Paterson, K I Pritchard.
Toronto Princess Margaret Hospital, Canada—J W Meakin, T Panzarella, K I Pritchard.
Tumour Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China (in collaboration with the Oxford CTSU)—Y Shan, Y F Shao, X Wang, D B Zhao (CTSU: ZM Chen, HC Pan).
Tunis Institut Salah Azaiz, Tunisia—J Bahi.
UK Multicentre Cancer Chemotherapy Study Group, London, UK—M Reid, M Spittle.
UK/Asia Collaborative Breast Cancer Group, London, UK—G P Deutsch, F Senanayake, D L W Kwong.
University Federico II, Naples, Italy—A R Bianco, C Carlomagno, M De Laurentiis, S De Placido.
University of Texas MD Anderson Cancer Center, Houston, TX, USA—A U Buzdar, T Smith.
Uppsala-Örebro Breast Cancer Study Group, Sweden—J Bergh, L Holmberg, G Liljegren, J Nilsson.
Vienna University Hospital 1st Department of Gynaecology, Austria—M Seifert, P Sevelda, C C Zielinsky.
Wessex Radiotherapy Centre, Southampton, UK—R B Buchanan, M Cross, G T Royle.
West Midlands Oncology Association, Birmingham, UK—J A Dunn, R K Hills, M Lee, J M Morrison, D Spooner.
West of Scotland Breast Trial Group, Glasgow, UK—A Litton.
Western Cancer Study Group, Torrance, CA, USA—R T Chlebowski.
Würzburg University, Germany—H Caffier.

References

1 Cuzick J, Stewart H, Peto R, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. *Cancer Treat Rep* 1987; **71:** 15–29.

2 Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 1994; **12:** 447–53.

3 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. *N Engl J Med* 1995; **333:** 1444–55.

4 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; **355:** 1757–70.

5 Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347:** 1233–41.

6 National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. *J Natl Cancer Inst* 2001; **93:** 979–89.

7 Ceilley E, Jagsi R, Goldberg S, et al. Radiotherapy for invasive breast cancer in North America and Europe: results of a survey. *Int J Radiat Oncol Biol Phys* 2005; **61:** 365–73.

8 Nattinger AB, Hoffman RG, Kneusel RT, Schapira MM. Relation between appropriateness of primary therapy for early-stage breast carcinoma and increased use of breast-conserving surgery. *Lancet* 2000; **356:** 1148–53.

9 Arriagada R, Rutqvist LE, Mattsson A, Kramar A, Ratstein S. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. *J Clin Oncol* 1995; **13:** 2869–78.

10 Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997; **337:** 949–55.

11 Overgaard M, Jensen M-B, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999; **353:** 1641–48.

12 Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005; **97:** 116–26.

13 Vinh-Hung V, Verschraegen C, for the Breast Conserving Surgery Project. Breast-conserving surgery with or without radiotherapy: pooled analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst* 2004; **96:** 115–21.

14 Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300 000 women in US SEER cancer registries. *Lancet Oncol* 2005; **6:** 557–65.

15 Carr ZA, Land CE, Kleinerman RA, et al. Coronary heart disease after radiotherapy for peptic ulcer disease. *Int J Radiat Oncol Biol Phys* 2005; **61:** 842–50.

16 Deutsch M, Land SR, Begovic M, et al. The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy. Results of National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials B-04 and B-06. *Cancer* 2003; **98:** 1362–68.

17 Solin LJ, Fowble BL, Martz KL, Goodman RL, Hanks GE. Results of the 1983 patterns of care process survey for definitive breast irradiation. *Int J Radiat Oncol Biol Phys* 1991; **20**: 105–11.

18 Shank B, Moughan J, Owen J, Wilson F, Hanks GE. The 1993–94 patterns of care process survey for breast irradiation after breast-conserving surgery: comparison with the 1992 standard for breast conservation treatment. *Int J Radiat Oncol Biol Phys* 2000; **48:** 1291–99.

19 Taghian A, Jagsi R, Makris A, et al. Results of a survey regarding irradiation of internal mammary chain in patients with breast cancer: practice is culture driven rather than evidence based. *Int J Radiat Oncol Biol Phys* 2004; **60**: 706–14.

20 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365:** 1687–717.

21 Krag D, Ashikaga T. The design of trials comparing sentinel-node surgery and axillary resection. *N Engl J Med* 2003; **349:** 603–05.

22 Arriagada R, Lê MG, Guinebretiere J-M, Dunant A, Rochard F, Tursz T. Late local recurrences in a randomised trial comparing conservative treatment with total mastectomy in early breast cancer patients. *Ann Oncol* 2003; **14**: 1617–22.

23 Bartelink H, Horiot J-C, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001; **345:** 1378–87.

24 Fisher ER, Anderson S, Tan-Chui E, Fisher B, Eaton L, Wolmark N. Fifteen-year prognostic discriminants for invasive breast carcinoma. National Surgical Adjuvant Breast and Bowel Project Protocol B-06. *Cancer* 2001; **91 (suppl 8):** 1679–87.

25 Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001; **19:** 1688–97.

26 Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med* 1992; **326:** 781–85.

27 Storm HH, Andersson M, Boice JD Jr, et al. Adjuvant radiotherapy and risk of contralateral breast cancer. *J Natl Cancer Inst* 1992; **84:** 1245–50.

28 Kini VR, Vicini FA, Victor SJ, Dmuchowski CF, Rebner M, Martinez AA. Impact of the mode of detection on outcome in breast cancer patients treated with breast-conserving therapy. *Am J Clin Oncol* 1999; **22:** 429–35.

29 Pierce LJ, Moughan J, White J, Winchester DP, Owen J, Wilson JF. 1998–1999 patterns of care study process survey of national practice patterns using breast-conserving surgery and radiotherapy in the management of stage I-II breast cancer. *Int J Radiat Oncol Biol Phys* 2005; **62**: 183–92.

30 Fuller SA, Haybittle JL, Smith REA, Dobbs HJ. Cardiac doses in post-operative breast irradiation. *Radiother Oncol* 1992; **25:** 19–24.

31 Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; **337:** 956–62.

32 Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000; **18:** 1220–29

33 Kinlen LJ. Richard Doll, epidemiologist extraordinary. *Nature* 2005; **438**: 41.

Consensus Conference on Breast Conservation

Gordon F Schwartz, MD, MBA, FACS, Umberto Veronesi, MD, FACS(Hon), Krishna B Clough, MD, J Michael Dixon, MB, ChB, FRCS(Eng), FRCS(Edin), Ian S Fentiman, MD, DSc, Sylvia H Heywang-Köbrunner, MD, Roland Holland, MD, PhD, Kevin S Hughes, MD, FACS, Robert E Mansel, MB, MS, FRCS, Richard Margolese, MD, Ellen B Mendelson, MD, Ivo A Olivotto, MD, FRCPC, Juan P Palazzo, MD, Lawrence J Solin, MD, the Consensus Conference Committee*

In a single generation, treatment of most women with early-stage breast cancer has changed dramatically. Clinical trials with more than 20 years followup have documented that, for appropriately selected patients, breast-conserving operations followed by whole-breast irradiation have outcomes equivalent to mastectomy. The appropriate selection of patients remains controversial. Questions remain about the role of new diagnostic imaging modalities, radiation therapy techniques, achieving optimal cosmesis, and the choice and timing of adjuvant chemotherapy.

To address these issues, the Fifth International Consensus Conference of the Breast Health Institute, cosponsored by the European Institute of Oncology, was convened in Milan, Italy, April 29 through May 1, 2005, inviting a group of experts in breast cancer and breast conservation, representing each of the disciplines involved in the care of these patients. From recorded transcripts of the discussion, these proceedings were written to summarize the opinions and conclusions of the entire group. The conference dealt only with invasive cancer; ductal carcinoma in situ was intentionally not discussed.

DEFINITION

Breast-conserving therapy (BCT) implies complete removal of the breast tumor with a concentric margin of surrounding healthy tissue performed in a cosmetically acceptable manner (lumpectomy) usually followed by radiation therapy. Surgical evaluation of the axillary lymph nodes is customarily part of breast conservation; the panelists agreed that treatment of the breast and axilla should be considered separately; presence of pathologically positive axillary lymph nodes is not a contraindication to breast conservation.

OUTCOMES AFTER BREAST CONSERVATION

BCT and mastectomy offer equivalent longterm survival for appropriately selected patients. Breast conservation does imply risk for "in-breast" recurrence or a new primary cancer in the same breast. Unlike local recurrence after mastectomy, usually a forerunner of systemic disease, most panelists agreed that in-breast recurrence after BCT can be an isolated event treated successfully by additional operation, usually mastectomy. Nevertheless, there was unanimous support for every effort being made to achieve optimal local control.

The goal of BCT should be a 10-year local recurrence rate between 5% and 10%; <1% per year. Demographics of the treated population might produce variations in these observations, but the group unanimously supported these 10-year benchmarks.

Treatment of in-breast recurrence is traditionally by mastectomy, with or without reconstruction. Several panelists championed local excision alone for recurrence as ductal carcinoma in situ or for small invasive tumors, but acknowledged that a second attempt at breast conservation is associated with increased risk of additional recurrence. Use of accelerated partial breast irradiation (APBI; discussed later) to treat an in-breast recurrence was discussed; there was no agreement on appropriate indications for such an approach. All agreed that a short interval between initial treatment and recurrence (<2 years) implies radioresistance, and APBI would be inappropriate in those patients. All concurred that a second course of whole-breast irradiation is not appropriate, irrespective of the time between events.

Occurrence and treatment of axillary recurrence was

*See Appendix for full list of committee members and their affiliations.

Sponsored by the Breast Health Institute, Philadelphia, PA, and the European School of Oncology, Milan, Italy, April 28 to May 1, 2005.

Correspondence address: Gordon F Schwartz, MBA, MD, FACS, 1015 Chestnut St, Ste 510, Philadelphia, PA 19107-4305. email: gordon.schwartz@yahoo.com

ISSN 1072-7515/06/$32.00
doi:10.1016/j.jamcollsurg.2006.04.009

Abbreviations and Acronyms

APBI = accelerated partial breast irradiation
BCT = breast-conserving therapy
IMN = internal mammary lymph node
MG = mammography
SN = sentinel nodes
US = ultrasonography
XRT = radiation treatment

addressed, although this event after a well-performed axillary dissection is negligible. With respect to SLNB, available data fail to document a greater frequency of axillary recurrence after SLNB performed by experienced surgical teams. Treatment of axillary recurrence must be individualized to the patient circumstances; if axillary recurrence were to follow SLNB, completion axillary dissection was advocated along with any other treatment recommendations.

Can a second SLNB be performed for in-breast recurrence? The surgeons on the panel, all experienced in SLNB, agreed that a second SLNB is possible and, when successful, could be considered accurate. There is little evidence-based data to support this conclusion. All agreed that if the axilla had not been completely dissected at the time of initial diagnosis, an axillary staging procedure was indicated.

SURGICAL TECHNIQUES

Primary lesion

Wide local excision of the primary lesion is crucial. There was no controversy about the need to achieve clear microscopic margins around the boundaries of the tumor, even if it means an additional procedure to do so. There was considerable debate about the width of the clear margin required.

Initial diagnosis of breast cancer is optimally confirmed by "minimally invasive" core biopsy. Fine-needle aspiration biopsy can be used, but only in close liaison with an experienced cytopathologist. After the diagnosis is established, therapeutic options should be discussed. Currently, the majority of women with T1 and small T2 (<3 cm) cancers are suitable candidates for breast conservation. Selected larger tumors can be treated by BCT if the primary tumor can be excised adequately with clear margins and acceptable cosmesis. Oncoplastic techniques might be warranted to allow wide excision with clear margins without compromising cosmesis. Oncoplastic surgery, combining sound principles of surgical oncology with those of plastic surgery, can extend breast-conservation possibilities. When used, breast-reshaping techniques should be performed at the time of initial surgical excision. It is difficult to correct a poor cosmetic result secondarily, after radiation therapy.

The first invasive surgical step after diagnosis of invasive cancer by the initial core biopsy should be the attempt at complete excision (usually including whatever axillary procedure has been recommended). Some women remain in favor of mastectomy; their wishes should be respected. When there is a relative contraindication to radiation therapy (discussed here later), mastectomy remains appropriate.

Tumor margins

The panelists agreed to disagree about the width of the margins required to justify BCT after local excision of the primary tumor; all concurred that there should be no evidence of tumor at the transected edge of the excision, as per National Surgical Adjuvant Breast and Bowel Project guidelines. Most panelists agreed that a wider margin implies lower likelihood of recurrence, despite the lack of evidence-based data supporting any specific margin width. Most radiation oncologists were comfortable with a margin of at least 1 to 2 mm. The panelists favoring wide margins all insisted that this could be achieved in most patients with a minimally negative effect on cosmesis. The technique of shaved margins after wide excision of the lesion was also considered acceptable, because this technique implies at least a 10-mm free margin.

The group recognized the dichotomy between extent of local excision and cosmetic result. The surgeons skilled in oncoplastic techniques championed this approach to extend the scope of breast conservation to include patients with tumors 3 to 5 cm in diameter. The panelists endorsed the teaching of oncoplastic techniques as part of surgical training for specialists in breast cancer care.

Other previously controversial issues about BCT include what has been called an extensive in situ ductal component within the excised tumor, and the presence of lobular carcinoma in situ at the margins. There was agreement that there was no volume of ductal carcinoma in situ within the primary lesion that would preclude BCT. Likewise, presence of lobular carcinoma in situ or atypical ductal or atypical lobular hyperplasia at the margins was not a factor that would either require reexcision or interdict BCT. Marking the boundaries of the tumor site with radiopaque clips was encouraged by surgeons and radiation oncologists.

An additional question involved treatment of central lesions. If the nipple-areolar complex is directly involved by tumor, then it must be removed with the local excision, and the patient must decide if the sacrifice of this tissue is enough to tip the scales for her toward mastectomy, although the center of the breast can be subsequently reconstructed, if desired. The wide excision of central lesions is often an indication for oncoplastic techniques to avoid flattening of the breast and to allow optimal reshaping of the breast contour. In patients with lesions close to, but not involving, the nipple-areolar complex, breast conservation without removing the nipple and areola is an option, as long as a clear plane can be developed between the base of the nipple and the lesion.

Nonpalpable cancers

Localization of nonpalpable lesions after initial core biopsy by the traditional procedure of needle-guided localization most commonly used in North America has been, in part, replaced by the radioguided occult lesion-localization technique in some centers, using a radioactive tracer injected under radiographic control to localize both the lesion and the sentinel nodes (SN). Whatever the technique, satisfactory identification of the lesion, proof of its excision, and clear margins are the criteria of appropriate operation.

The axilla

The contemporary treatment of carcinoma of the breast includes the axillary lymph nodes. In elderly patients, those with intercurrent disease or small, especially favorable cancers, such treatment might be debatable, but the group unanimously endorsed axillary staging if axillary node status would influence a therapeutic decision.

Axillary SLNB has replaced traditional axillary dissection in women with clinically negative axillary findings and was unanimously endorsed. Whether internal mammary nodes were to be considered part of the SN discussion was controversial. The majority of the panelists do not currently try to identify or dissect internal mammary nodes. Which technique of SLNB was best was not stressed, as long as the SN could be identified and were accurate predictors in >90% of patients. Most clinical trials support use of both radiocolloid and blue dye to achieve the highest rates of SN identification. (Radiocolloid is the only technique possible for identification of internal mammary nodes.)

When SN are positive for metastatic disease, whether the remainder of the axilla should be dissected was a minor point of contention. If the SN demonstrate macrometastasis on frozen section, a majority agreed that completion dissection of the axilla was appropriate. Several panelists thought that radiation to the axilla was a suitable substitute for additional operation. Traditional breast radiation fields do not completely encompass the axillary node sites, and special attention to the anatomy of the fields would be necessary to ensure that levels I and II would be included with whole-breast radiation. There is a current European Organization for Research and Treatment of Cancer clinical trial comparing completion axillary dissection and radiation therapy with the axilla for confirmed positive SN that can help answer this question. A small minority of the panel questioned whether either additional operation or radiation was required, because these patients would be undergoing adjuvant chemotherapy.

When a single SN shows micrometastasis, the panel was evenly divided about the need for completion axillary dissections or axillary radiation, because the majority of patients with micrometastasis do not have additional node metastasis. Immunohistochemical markers are being used commonly to identify submicroscopic metastasis, single cells or small groups of cells. Because their clinical importance is uncertain, presence of immunohistochemically positive cells is not a current criterion for completion of axillary dissection or for adjuvant therapy.

Extent of axillary dissection when indicated by the presence of positive SN was debated. North American surgeons favored levels I and II axillary dissection. A few European surgeons favored including level III. Most panelists felt that the additional dissection of level III did not improve survival and increases the risk of lymphedema. All agreed that a precise anatomic dissection removing at least 10 nodes was essential.

SELECTION OF PATIENTS FOR BREAST CONSERVATION

Tumor size

Nonpalpable tumors detected by initial imaging are usually suitable for BCT, but there is, theoretically, no size limitation for breast conservation so long as local excision with clear margins can be achieved with an acceptable cosmetic result. Tumors up to 5.0 cm in diameter have been successfully treated by BCT, in both randomized trials and retrospective studies. There might be a role for oncoplastic techniques in such situations.

Detailed imaging should be performed before definitive operation, to exclude presence of multiple primary cancers, an occult contralateral breast cancer, and diffuse calcifications that can indicate widespread additional ductal carcinoma in situ.

Multicentric carcinoma

Multicentricity is the occurrence of two separate cancers in different quadrants of the same breast, far enough apart that they cannot be excised through a single incision. The panelists agreed that if two separate cancers were close enough to be excised as a single specimen, with clear margins and acceptable cosmesis, BCT could still be used. An additional concern with multicentric tumors is the complexity of adding a radiation boost to more than one site in the same breast, which is not currently recommended.

Age

The panelists agreed that the younger the patient, the more likely there is to be a local recurrence after breast conservation. Nevertheless, all concurred that this does not preclude use of breast conservation in these patients, as long as physicians and patients accept this increased risk. After controlling for other factors, there is no worse longterm survival after breast conservation compared with mastectomy in young patients. Most women younger than 50 years of age should have a boost dose of radiation to improve local control.

Whether radiation therapy could be avoided in older women who would be undergoing adjuvant hormonal therapy after local excision was debated. All concurred that all groups of patients benefit by addition of radiation therapy to local excision, but the gain in older women can be small, and routine use of radiation treatment (XRT) in this group was not resolved. Individualizing the decision about XRT in older women based on tumor characteristics and physiologic rather than chronologic age was encouraged. The role of accelerated partial-breast radiation was discussed for this group of patients (and will be discussed here later).

Ultrasonography and MRI

Evidence for use of ultrasonography (US) as a supplement to mammography for screening does not exist, but US can help characterize masses, architectural distortions, or areas of asymmetry. It is not usually helpful in the differentiation of calcifications. US can aid in evaluating the mammographically dense breast to avoid overlooking additional suspicious lesions and can help guide the percutaneous biopsy of palpable or image-detected lesions.

Because the sensitivity and specificity of US are so operator- and technique-dependent, the practice guidelines for breast US promoted by the American College of Radiology should be observed.[1] Mammography (MG) and US are complementary, so the group emphasized a preference for MG and US (and MRI, if used), to be correlated and interpreted together by the same radiologist(s). Whether US of the axilla is valuable to identify metastatic nodes was controversial; US was considered helpful if it might identify and prove a positive node by percutaneous fine-needle biopsy or core biopsy before treatment planning.

The addition of MRI to MG and US has increased the diagnostic accuracy of these modalities when used together. MRI is highly sensitive but less specific; its use in staging breast cancer patients is probably helpful but still debatable. There is a need for agreement on which enhancing lesions require biopsy and how far to pursue so-called suspicious lesions before considering breast conservation safe. Routine use of MRI has not yet been shown to be valuable in a randomized trial, but advocates of MRI argued that MRI might affect treatment recommendations in up to 20% of patients.

MRI can be useful in patients with large lesions, to aid in planning surgical excision or for patients with suspected second lesions on MG or US. In patients with dense breasts or with lesions difficult to evaluate by MG, such as invasive lobular carcinomas, MRI might help guide the extent of operation required. US might be an easier and less costly technique to use in these situations. The panelists agreed that MRI requires considerable technical and interpretation skills; all agreed that MRI facilities should have dedicated breast coils with a minimum field strength of 1.5 Tesla.

The panelists agreed that breast MRI is a promising tool; its potential has not yet been realized, and its use remains controversial. Probably its best use is in patients who present with axillary metastasis and negative MG and US, and for screening women who are positive for breast cancer genes 1 and 2 or those under 40 years of age. The group agreed that MRI in premenopausal women should be performed between days 7 and 17 of the menstrual cycle because of parenchymal enhancement seen at other times of the cycle. There was agreement that all imaging procedures should be completed before any surgical procedure (other than biopsy) is performed, and that MRI should be performed by facilities that have the capability of working up the findings to completion, ie, MRI-guided biopsy. MRI is helpful in establishing the precise size of the cancer, the presence of multifocality, or the presence of an additional cancer in the same breast (multicentricity). MRI, when used, should be performed before or as soon as possible after a core biopsy. A core biopsy can obscure neighboring findings or precise size measurements if accompanied by a substantial hematoma, but the ability of MRI to exclude a second lesion will usually not be impaired.

Another situation in which MRI might be helpful is for cancers that present with nipple discharge. These cancers are often widespread within the ductal system and difficult to excise. MRI can define the tumor boundaries more clearly and make the margins easier to clear widely if the MRI findings guide the dissection.

The group endorsed clinical trials that use MRI findings to modify treatment but agreed that routine use of MRI before breast conservation was not yet confirmed. Its role in selected subgroups of patients as described here is promising. An MRI diagnosis of a second lesion should never influence a treatment decision without histologic proof (biopsy). Mastectomy should not be performed on the basis of MRI findings only.

Pathology

The panelists agreed that the handling and interpretation of breast biopsies and other breast specimens should follow standardized protocols that are regularly updated to incorporate modifications necessitated by advances in new immunohistochemical and subcellular techniques and surgical innovations. The College of American Pathologists provides a set of guidelines specifying the current basic information required in pathology reports.[2] This protocol should be followed. Each pathology laboratory can make minor adjustments to these guidelines to fit its own needs and requirements.

The accuracy of margin assessment and overall pathologic interpretation of the surgical specimen is dependent on the cooperation of the surgeon, the radiologist, and the pathologist. The surgeon should appropriately mark and orient the specimen. The margins of the specimen should be inked if submitted as a single tissue excision, or shaved and submitted in separately marked containers if that technique is used. Submitting an x-ray of the specimen for comparison with earlier imaging studies is helpful in locating the lesion within the specimen and assessing its extent. In patients undergoing BCT, it is preferable to submit the entire specimen after sectioning at 3- to 5-mm intervals. If the specimen is too large to submit in its entirety, then all the grossly and radiologically suspicious areas should be submitted. A specimen x-ray can also aid identification of the closest margins to the tumor. In all cases in which specimen radiography is obtained, the x-rays should be available to the pathologist for radiographic–pathologic correlation.

To assess margin status, pathologists usually evaluate two types of specimens. Either multiple shaved margins are submitted as separate specimens by the surgeon, or the tumor is excised and submitted as one single specimen with specific markings about its orientation provided by the surgeon. Both of these techniques were considered appropriate.

Emerging technologies in evaluation of tumor characteristics can impact outcomes and therapeutic recommendations and should be adopted as available. Analysis of gene profiles in breast tumors can be a valuable tool with considerable potential impact, but issues that should be resolved before gene profiling is routinely applied to patient care include quality control, statistical analysis of the data, and establishment of expression thresholds. All of these subjects were deemed suitable for research trials, but are not ready for use in current clinical practice.

WHO TREATS BREAST CANCER?

The skill of the treatment team is crucial to successful outcomes. A dedicated, interdisciplinary breast center as a care model for breast cancer diagnosis and treatment is optimal. In Europe, such centers are common, and it has been generally accepted that an institution must treat at least 150 patients with breast cancer per year to be considered a breast cancer specialty center.

Because breast cancer patients are usually referred to a surgeon first, European guidelines recommend that breast surgeons work in close collaboration with radiologists, pathologists, and medical and radiation oncologists. The European panelists also agreed that breast surgeons should treat a minimum number of breast cancer patients annually. The current European minimum requirement for a specialized center is 50 patients per surgeon per year. Favoring establishment of such quotas and building specialized centers are the observations that use of BCT is more common, the rate of post-BCT recurrence is lower, and survival of women with breast cancer is higher when they are treated in specialized breast centers. In North America, where patterns of referral are not mandated, and geographical distances can preclude patients from traveling far from home, such guidelines might prove difficult to adopt.

Radiation therapy

The consensus panel discussion included technical aspects of XRT. The goal of XRT is to treat the target volume and minimize dose to surrounding normal tissues. The conventional target volume initially includes the whole ipsilateral breast. The whole breast dose is generally 45 to 50.4 Gy delivered over 4.5 to 5 weeks. Typical daily fraction size is 1.8 or 2.0 Gy delivered 5 days per week. Megavoltage photons, most commonly 6 MV, treat the breast through tangent fields. There were no specific guidelines about the acceptable volume of lung and heart (for left-sided breast cancers) that could be treated, except that treatment of these organs should be minimized while still treating the target volume adequately.

Historically, radiation treatment planning was simple and used fluoroscopic simulation, single-plane dosimetry, simple wedges, no lung correction, and no three-dimensional treatment planning. Longterm outcomes data for breast-conservation treatment have been obtained from patients treated using these techniques.

More recently, CT-based simulation and treatment planning have become widely available and are now preferred by many radiation oncologists. Intensity-modulated radiation treatment is an even more sophisticated method of dose delivery; treatment planning studies have shown that intensity-modulated radiation treatment can improve dose homogeneity within the target volume and reduce the dose to normal tissues, including ipsilateral lung and heart (for left-sided lesions). The panelists endorsed the potential value of more sophisticated radiation treatment planning and dose delivery, but await longterm outcomes data to support this practice change.

Randomized trials have shown an improvement in local control when a boost dose of radiation treatment is delivered to the primary tumor site after the initial whole-breast radiation, including the tumor site plus a 1-cm to 2-cm margin of normal tissue. The absolute benefit from the boost is proportional to the baseline risk, and younger patients have the greatest absolute benefit from adding the boost. The tumor bed dose from combined whole-breast plus boost XRT is typically 60 to 66 Gy. Boost XRT most commonly uses electrons, but various methods have been described, including three-dimensional photon beams and brachytherapy. Some radiation oncologists use a boost dose for all patients; others selectively add a boost dose for higher-risk patients or when the margins of resections are not confirmed as pathologically negative. The majority of North American radiation oncologists use a boost for virtually all patients with invasive cancers.

When to radiate regional lymph nodes (axilla, supraclavicular fossa, and internal mammary lymph nodes) remains controversial. No consensus could be reached about the indications for adding or modifying nodal radiation in the presence of extracapsular extension or involved lymph nodes, and this was an area of accepted lack of agreement among the panelists. The lower axilla is typically included within standard tangential fields, but risk of arm lymphedema increases with the addition of direct nodal fields to the supraclavicular fossa and axilla. A randomized clinical trial (National Cancer Institute of Canada-Clinical Trials Group study MA20) is accruing patients in North America and Australia, comparing whole-breast XRT with whole-breast plus nodal XRT.

Another area of disagreement was management of the internal mammary lymph nodes (IMNs), especially when this area is the site of drainage on sentinel lymph node mapping. A minority of the panelists recommended biopsy of the specific IMN, restricting IMN radiation to those with positive biopsies. A large European Organization for Research and Treatment of Cancer trial comparing IMN radiation with no IMN radiation has completed accrual, but results from this trial await analysis.

In selecting patients for treatment, advanced age and substantial intercurrent disease were discussed as relative contraindications to XRT (discussed here later). It was accepted that there is no group of patients for whom XRT does not additionally decrease in-breast recurrence compared with local excision alone. The panelists agreed that individual patient circumstances might dictate substitution of hormonal therapy for XRT in some elderly, informed patients with completely removed, estrogen-receptor–positive disease. In patients with estrogen-receptor–negative disease, hormonal therapy is not an option, so the panelists recommended XRT for all but the weakest patients.

XRT might also be avoided in those with especially favorable tumors, eg, small tubular or mucinous/colloid carcinomas. Again, the same caveats apply. The panelists agreed that there might be patients with such favorable tumors that XRT is not needed, but a precise algorithm to identify them does not exist.

CONTRAINDICATIONS TO WHOLE-BREAST XRT

Pregnancy is currently an absolute contraindication to XRT. Breast cancer occurring in pregnancy need not imply mastectomy. It is possible to perform the operation and then wait until after delivery to start radiation therapy. The breast cancer care should be coordinated with a high-risk obstetrics specialist, because delivery might be induced or accomplished by cesarean section at an earlier than usual gestational age. A delay of up to 3 months between operation and XRT was not considered harmful.

A relative contraindication to XRT is a history of mantle radiation for Hodgkin disease because the mantle technique partially radiates both breasts. Whether there is a certain time from treatment for Hodgkin disease and diagnosis of breast cancer beyond which the tissues will tolerate whole-breast XRT is controversial, and there are little data extant to make such a recommendation. A small number of patients have been treated with BCT plus whole-breast XRT with acceptable outcomes. A history of mantle XRT for Hodgkin disease is one possible indication for APBI (discussed later in this article) if the earlier treatment fields do not overlap the excision site. There are no data to support or refute this suggestion.

A personal history of scleroderma, systemic or discoid lupus, or dermatomyositis was considered a relative contraindication to XRT; none of the radiation oncologists on the panel was eager to treat these patients. Rheumatoid arthritis was not considered a contraindication.

Another special circumstance was the presentation of breast cancer as axillary node metastases without a demonstrable primary lesion in the breast by clinical examination or by breast imaging with MG and US. In such situations, breast MRI should be performed, because MRI will detect the primary tumor in 80% to 90% of patients with negative MG and US and negative physical examination. Presuming that diagnosis of breast cancer is a reasonable certainty based on microscopic and immunohistochemical characteristics of the axillary node(s) and appropriate workup to rule out another primary site, many of these patients will be treated with neoadjuvant chemotherapy. Even if not, the group felt that axillary operation followed by XRT to the breast was an alternative to mastectomy, even if the primary site could not be found. The need for postoperative radiation to the node-bearing areas after axillary dissection remained a controversial topic, with most panelists reserving judgment based on the microscopic findings in the axilla.

A corollary of the treatment of the "occult" cancer is the fortuitous finding of cancer in a breast specimen removed during the course of a breast reduction or mastopexy. In such situations, if margin assessment is considered accurate, ie, the tumor has not been transected, and there is no tumor thought to be within the remaining breast, BCT is reasonable. Surgical attention to the axilla followed by XRT to the breast is acceptable treatment. If there is a suspicion of macroscopic residual cancer in the breast, mastectomy might be the only tenable option.

Earlier breast augmentation

The group felt strongly that a comment was necessary about the occurrence of carcinoma in patients who have previously undergone augmentation mammoplasty. The presence of an implant, silicone or saline, does not influence the decision for BCT and does not interfere with the technical delivery of radiation treatment. There is no reason to remove the implant, assuming that the tumor can be successfully excised. Radiation therapy to that breast will produce some fibrosis and increase the risk of capsular contraction. As long as the patient understands that her breast might not be the same as it was before treatment, breast conservation can proceed.

APBI

Recent interest has focused on APBI, which is the delivery of radiation to a limited target volume—the surgical cavity plus a 1-cm to 2-cm margin—generally in a single treatment or over 1 week. This contrasts with conventional whole-breast XRT, which generally takes 5 to 7 weeks. APBI has been designed for patient convenience; it is not expected to improve local control or survival. Since its introduction in the 1990s, APBI has been used in multiple phase I and II clinical trials with short-term (5 years) local failure rates that are similar to those for whole-breast radiation. Support for APBI has been based on observations of in-breast failures after traditional radiation therapy, because recurrence is seen most frequently (70% to 80%) at or near the site of the original tumor.

The optimal APBI technique has not been determined. At least four methods of APBI have been described: brachytherapy implant; balloon brachytherapy (MammoSite); external-beam radiation treatment, with or without intensity-modulated radiation treatment; intraoperative radiation treatment, using electrons (electron intraoperative treatment) or an orthovoltage source (targeted intraoperative radiotherapy). Each of these APBI methods has potential advantages and disadvantages, and none has been proved superior to another.

Several phase III randomized trials comparing APBI with conventional whole-breast radiation are accruing patients. Each trial is evaluating a different APBI technique, but each trial uses whole-breast photon XRT as the control arm. The panelists overwhelmingly endorsed entering patients into these randomized trials so that the relative worth of APBI in comparison with standard, whole-breast radiation treatment can be established. Longterm outcomes for these randomized trials will be necessary to judge the differences between these two forms of radiation treatments for the multiple end points of survival, local control, cosmesis, and complications.

Because there are now multiple open randomized trials, the panelists agreed that APBI should not be used outside of a protocol study except in exceptional circumstances, which might include women who live at a considerable distance from an XRT facility and who cannot undertake a lengthy period of treatment, or elderly patients with intercurrent diseases that might already limit longterm survival. When APBI is used, the criteria for surgical procedures and techniques and the pathologist's handling of the specimens are the same as when conventional whole-breast radiation therapy is used.

Adjuvant chemotherapy

As the indications for adjuvant chemotherapy have expanded, more patients must plan to undergo both radiation and chemotherapy. The correct sequence of these treatments has been questioned, and many institutions have adopted one approach or another. The panelists agreed that there are no current data to support which should be undertaken first, radiation or chemotherapy. All agreed that radiation and chemotherapy should not routinely be given concurrently. A majority felt that there was no advantage to XRT or chemotherapy given first for node-negative patients; patient choice and local traditions could influence this decision. For patients with node-positive disease, a majority agreed that chemotherapy should be given before XRT. There was consensus that hormonal agents should not be given concurrently with chemotherapy, but there was no contraindication to their use during XRT. The optimal choice and duration of chemotherapy and hormonal therapy were not part of the discussion.

Initial patient workup and followup

For those patients with stage I cancers, pretreatment evaluation includes appropriate evaluation of the breast alone. There is no advantage in performing additional blood tests, bone scans, or chest x-rays either before or after treatment, except in the presence of symptoms. For patients with stage II or III cancer, a pretreatment metastatic evaluation with liver enzymes, a bone scan, and chest x-ray is appropriate. The addition of chest, abdominal, and pelvic CT or MRI and PET scans should be individualized and depends on the presenting situation. Whether these studies are repeated serially after treatment should be an individual rather than a universal decision.

The timing of the first mammogram after treatment is controversial. The panel unanimously agreed that it should not be performed before 6 months have elapsed after completion of radiation therapy, and many thought a year would be preferable. The tradition of 6-month mammograms of the treated breast for 2 years after treatment has become popular, but has not been shown to be superior to annual mammography. Both breasts must be imaged at least annually, with other imaging studies, eg, breast US and MRI, added as indicated by individual circumstances. Whether serial (annual) MRI examinations might add to the accuracy of following the treated breast was debated; no data exist to support or challenge this suggestion. The cost can be prohibitive. The value of following the treated breast by MRI was considered a suitable subject for a clinical trial.

FUTURE DIRECTIONS

The panelists were aware and supportive of the increasingly valuable information from molecular and genomic profiling of breast malignancies and their enormous potential. Such information is already having a major impact on reclassifying and managing breast malignancies, particularly for using systemic therapies. There is an increasing number of newer chemotherapeutic and biologic agents, some of which have already demonstrated substantial impact in reducing the number of breast cancer deaths in subsets of patients and possibly even reducing the rate of local recurrence. Although recognizing each of these issues, their direct impact on BCT remains to be established by future investigations. Newer imaging techniques, including functional imaging, are rapidly undergoing development. These newer imaging techniques hold great promise relative to BCT. Such imaging advances will likely impact on many diverse aspects of BCT, although this impact remains to be demonstrated in clinical practice.

As the conference concluded, the panelists largely concurred on standards for the selection of patients for BCT, agreeing that tumor characteristics, such as histology, multifocality, presence of extensive in situ (ductal) component, do not affect suitability for treatment by BCT as long as the tumor can be completely excised with clear margins. The major disagreement was the width of the clear margin required around the tumor, ranging from no tumor at the transected edge of the excision to free margins of 10 mm circumferentially around the tumor.

The emerging role of MRI in the selection of patients for breast conservation was appreciated by all of the participants. Lack of specificity of MRI requires continuing clinical trials to unravel this problem before MRI can be used to define patient selection more precisely.

The faculty of this conference unanimously agreed with the concept of multidisciplinary treatment centers as the most efficient and effective manner in which breast cancer patients should be treated. As the science of breast cancer expands exponentially, patient benefits depend on the continuing collaboration and cooperation of multiple disciplines. All panelists agreed that the major issues in BCT had been addressed in enough detail to permit development of these formalized guidelines for patient care. The group recognized that these published proceedings are editorial opinions of the group and not strictly evidence-based. They must not be construed as establishing a standard of care to which all treating physicians should adhere. Individual patient management must be determined by unique patient circumstances and health providers' capabilities. Treatment recommendations are the responsibility of individual physician(s) with the full participation of the patient.

Appendix

Participants, 2005 Breast Consensus Conference

Chairman: Gordon F Schwartz, MD, MBA, FACS, Department of Surgery, Jefferson Medical College, Philadelphia, PA

Co-Chairman: Umberto Veronesi, MD, FACS(Hon), Director, European School of Oncology, Milan, Italy

Consensus Committee

Harry Bartelink, MD, PhD, Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Luigi Cataliotti, MD, Department of Surgery, University of Florence, Florence, Italy

Krishna B Clough, MD, Director, Paris Breast Center, Paris, France

J Michael Dixon, MB, ChB, FRCS(Eng), FRCS(Edin), Edinburgh Breast Unit, Western General Hospital, Edinburgh, Scotland, UK

Domenico M D'Ugo, MD, Department of Surgery, Universita Cattolica del Sacro Cuore, Rome, Italy

Ian S Fentiman, MD, DSc, Department of Surgical Oncology, Guy's Hospital, London, England, UK

Monica Fornier, MD, Breast Cancer Medical Service, Memorial Sloan-Kettering Cancer Center, New York, NY

Alain Fourquet, MD, Département de Radiothérapie Oncologique, Institut Curie, Paris, France

Oreste Gentilini, MD, Department of Surgery, European School of Oncology, Milan, Italy

Sylvia H Heywang-Köbrunner, MD, Department of Breast Imaging and Intervention, Klinikum Rechts der Isar, Technical University Munich, Munich, Germany

Roland Holland, MD, PhD, National Expert and Training Center for Breast Cancer Screening, University Medical Center Nijmegen, Nijmegen, The Netherlands

Kevin S Hughes, MD, FACS, Avon Comprehensive Breast Evaluation Center, Massachusetts General Hospital, Boston, MA

Vincenzo Lattanzio, MD, Servizio di Radiologia Senologica SARIS, Centro Riferimento Regionale, Azienda Ospedaliera Policlinico, Bari, Italy

Robert E Mansel, MB, MS, FRCS, Division of Hospital Specialties, Wales College of Medicine, Cardiff University, Cardiff, Wales, UK

Richard Margolese, MD, Department of Surgery, Jewish General Hospital, Montreal, Quebec, Canada

Shahla Masood, MD, Department of Pathology, University of Florida, Jacksonville, FL

Beryl McCormick, MD, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

Ellen B Mendelson, MD, Department of Radiology, Northwestern University, Chicago, IL

Ivo A Olivotto, MD, FRCPC, Division of Radiation Oncology, University of British Columbia and British Columbia Cancer Agency, Victoria, British Columbia, Canada

Juan P Palazzo, MD, Department of Pathology, Jefferson Medical College, Philadelphia, PA

Lori J Pierce, MD, Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor, MI

Christopher J Poole, MD, Division of Cancer Studies, University of Birmingham, Birmingham, UK

Emiel J Th Rutgers, MD, PhD, Department of Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Lawrence J Solin, MD, Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, PA

Fattaneh Tavassoli, MD, Department of Pathology, Yale University School of Medicine, New Haven, CT

Daniela A Terribile, MD, Department of Surgery, Università Cattolica del Sacro Cuore, Rome, Italy

Michael Untch, MD, Department of Gynecology & Breast Cancer Center, Academic Hospital of the University Charité Berlin, Berlin, Germany

Umberto Veronesi, MD, FACS(Hon), Director, European Institute of Oncology, Milan, Italy

REFERENCES

1. American College of Radiology. ACR practice guideline for the performance of a breast ultrasound examination. 2002 Rev. Reston, VA: American College of Radiology; 2002:763–765.
2. Fitzgibbons PL, Connolly JL, Page DL. Breast protocol: applies to all invasive carcinomas of the breast. 2005 Rev. Northfield, IL: College of American Pathologists; 2005:1–26.

ASBD Breast Healthcare Update

A highlights newsletter discussing current and future issues in breast disease for members of multidisciplinary breast cancer teams

ACCELERATED PARTIAL BREAST IRRADIATION: MOVING FORWARD

Author
Robert R. Kuske, MD, FAACE
Arizona Oncology Services, Scottsdale, Arizona
Clinical Professor, The University of Arizona Health Sciences Center

Commentaries
Susan J. Hoover, MD
Director, Diagnostic Breast Center, Lifetime Cancer Screening and Prevention Center, Medical Director of Diversity Affairs, Assistant Professor of Surgery, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida
Jay L. Bosworth, MD
Long Island Radiation Therapy Manhasset, New York

Breast Healthcare Update

The American Society of Breast Disease (ASBD) is the only clinically based professional society that advocates an interdisciplinary team approach to breast health management. The ASBD promotes breast disease prevention, early detection, diagnosis, treatment, rehabilitation, and research.

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Breast Healthcare Update provides new and useful information to the Society's diverse community of healthcare professionals. We welcome suggestions for topics for future issues. Please send your comments to «membership@asbd.org».

ACCELERATED PARTIAL BREAST IRRADIATION: MOVING FORWARD

ROBERT R. KUSKE, MD, FAACE
Arizona Oncology Services, Scottsdale, Arizona
Clinical Professor, University of Arizona Health Sciences Center

IN THIS ISSUE

Radiation therapy plays a strong role in breast cancer — from the earliest stage to the latest stage of the disease. Most patients with breast cancer will benefit from radiation therapy, either as a curative or an adjuvant therapy or in a palliative setting.

Radiation therapy is a component of breast-conserving therapy for most patients with ductal carcinoma in situ. Women with early-stage invasive cancers undergo lumpectomy and radiation therapy, usually with sentinel node mapping. Those with more diffuse or advanced breast cancers receive mastectomy, with many benefiting from consolidative chest wall and nodal irradiation to reduce the risk for local/regional recurrence while improving the chance for cure. In patients who experience a chest wall recurrence, radiation therapy serves as a mainstay of treatment. Radiation therapy also plays a role in almost all patients with locally advanced or inflammatory breast cancer. In terms of patients with bone metastases or spread to other organs, radiation therapy plays a vital role in improving the quality of life (QoL) of breast cancer patients who can no longer be cured by significantly relieving their pain, bleeding, or suffering.

Radiation therapy after breast-conserving surgery is delivered to the whole breast over a period of 5 to 6 weeks. Recently, however, technological advances in radiation delivery have allowed the concept of accelerated partial breast irradiation (APBI) to rapidly emerge as a potential alternative. APBI refers to radiation therapy that is delivered over a much shorter period of time than the standard 5 to 6 weeks, and is delivered to only a portion of the breast. Thus, APBI may allow some patients with barriers to standard radiation therapy, such as extreme age, difficulty in finding transportation to and from a facility, or a physical handicap, to receive appropriate adjuvant radiation therapy. In the past, some women with small breast cancers required mastectomy because 30 to 35 trips to the radiation department were impractical or impossible. APBI, potentially, allows these women to keep their breasts and have effective treatment.

APBI investigations and clinical trials

Interest in APBI has grown dramatically and has yet to crest. We have gone from a patient insisting on a 4- to 5-day alternative to 6 weeks of conventional radiotherapy (inspiring the concept at the Ochsner Clinic in 1991), to single-institution trials at two hospitals, to a national phase 2 cooperative group trial and, finally, to multiple, ongoing international phase 3 trials.

The oldest and most studied method of APBI is brachytherapy — literally, "treatment from a short distance." Radioactive seeds are positioned within plastic catheters inserted in and around the lumpectomy cavity, with the goal being to sterilize the 1–2 cm of breast tissue surrounding the surgical site. In this way, the tissue at greatest risk for residual cancer cells after breast-conserving surgery receives dose-intense radiation therapy.

The first modern brachytherapy trial took place at the Ochsner Clinic in New Orleans. Between 1992 and 2000, 162 women with in situ or invasive breast cancers ≤3 cm in size, node-negative or from 1 to 3 positive nodes, and with negative surgical margins were treated by interstitial multiplanar brachytherapy. The breast recurrence rate at 7 years on this prospective IRB-approved clinical trial was only 3 percent. Outcomes were mirrored by William Beaumont Hospital, in Michigan, providing impetus for the Radiation Therapy Oncology Group (RTOG) Trial 95-17. The RTOG 95-17 was the first cooperative group phase 2 trial of partial breast irradiation, and 2-plane interstitial brachytherapy was implemented. One hundred patients, with similar selection criteria to the single-institution trials noted above, were enrolled from 10 institutions between 1997 and 2000, with 99 deemed eligible. Results at 4 years demonstrate an ipsilateral breast cancer recurrence rate of 3 percent — the same as the contralateral new primary cancer rate. It was very important to demonstrate in this trial that brachytherapy was feasible in diverse practice settings and could be administered with measurable quality assurance and low toxicity rates, and the published outcomes documented these expectations.

The five international trials should answer the question of whether we need to treat the entire breast every time.

Next step: phase 3 trials

The pinnacle of clinical research, especially with a new treatment that potentially represents a paradigm shift, is the phase 3 randomized controlled trial. The sequence of investigations into APBI represents a model for the way medicine should evolve. Over the last 15 years, science has progressed from a hypothesis that the entire breast may not need to be treated in cancer that is detected early. It was further hypothesized that therapy would be much more accessible and convenient for women, and that brachytherapy would be highly effective in terms of local control with excellent cosmetic outcomes and low toxicity. Pilot trials at two large institutions demonstrated that the treatment could be delivered safely with comparable outcomes to historical controls of the standard therapy. Initial success led to innovative technologies such as the MammoSite balloon catheter and three-dimensional conformal external beam APBI, which could be incorporated into future trials. Multiple international phase 3 randomized trials comparing 5-day APBI of one form or another with 6-week whole-breast irradiation are now ongoing.

NSABP B-39/RTOG 0413 trial

In North America, the National Surgical Adjuvant Breast Project (NSABP) B-39 trial opened in 2005. The trial is a cooperative effort with the Radiation Therapy Oncology Group (RTOG 0413) and is open to all cooperative groups through the intergroup Cancer Trials Support Unit mechanism. This prospective randomized cooperative group trial seeks to enroll 3,000 women: 1,500 will receive partial breast irradiation; 1,500, whole-breast irradiation. If selected for APBI, a woman may be treated by any of three techniques: interstitial multicatheter brachytherapy, MammoSite, or three-dimensional conformal external beam APBI. Choice of APBI method is at the discretion of the patient and the investigator, but each investigator and institution must be credentialed to deliver the chosen method. The computer randomization process eliminates bias from patient selection. This trial was initiated about a year and a half ago, and is now one of the most successful breast cancer trials in history, accruing approximately 150 to 160 patients per month. It is extremely popular with patients, referring physicians, and radiation oncologists.

Entering a patient into the NSABP/RTOG trial. In the author's practice, every eligible woman is presented the opportunity to participate in the trial. Study candidates include patients with noninvasive ductal carcinoma of the breast (intraductal or in situ breast cancer), stage I breast cancers ≤2 cm in size that are node negative, and stage II breast cancers ≤3 cm in size that are either node negative or have minimal involvement of 1 to 3 positive axillary lymph nodes with negative surgical margins. When a patient expresses an interest in participating, a CT scan is obtained to make sure that the lumpectomy cavity does not exceed 30 percent of the breast volume. If the cavity is larger, then too much tissue has been removed for APBI, and the patient is not a candidate for the trial. After the patient signs an informed consent form, the research coordinator sends relevant information about the patient (e.g., age, disease stage, and intent to receive chemotherapy) to trial headquarters in Pittsburgh. Within 12 hours, the institution is notified via phone or e-mail as to whether the patient has been randomized to 6 weeks of whole breast irradiation or 5 days of APBI.

Women who sign up for this trial are heroic, because they are yielding their ability to choose their treatment on behalf of future generations of women. Hundreds of thousands of women will be grateful to these 3,000 who have put their treatment on the line, allowing a computer to choose for them and thereby determine the standard of care for local therapy of

continued on page 4

APBI DELIVERY METHODS

Partial breast irradiation can be delivered by several different methods, described below.

Interstitial brachytherapy. Widely used in the United States, interstitial brachytherapy, which means "radiation from the inside out," is the oldest radiation delivery method, introduced shortly after Madame Curie discovered radium and used 50 years before external beam radiotherapy. With this delivery method, radiation sources are inserted directly into the tissues that harbored the original cancer. Interstitial brachytherapy is state-of-the-art treatment for gynecologic, head and neck, and soft- tissue malignancies. In 1991, at the Ochsner Clinic in New Orleans, the regimen for treating soft-tissue sarcomas developed at Memorial Sloan-Kettering in New York was adapted for breast cancer, and the first modern-day partial breast irradiation technique using interstitial brachytherapy was initiated. To date, studies with the longest follow-up for APBI in breast cancer provide evidence-based medicine for this potential paradigm shift.

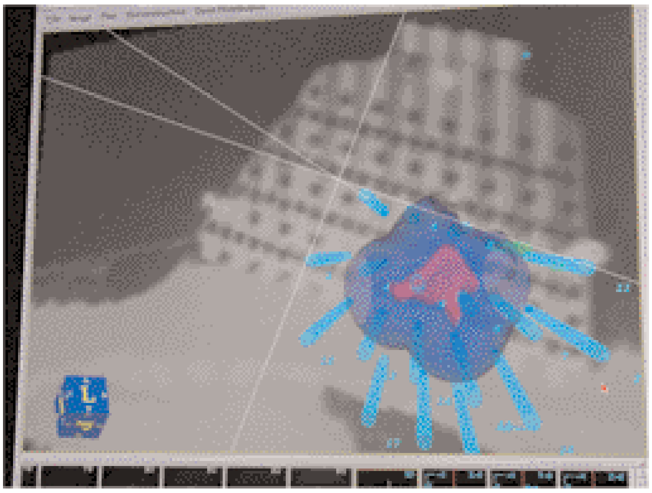


FIGURE 1 Interstitial multicatheter breast brachytherapy using CT-guidance and a special breast template

Interstitial brachytherapy can produce isodose curves covering any shape or size lumpectomy cavity, and offers a freely controllable radiation margin. It provides the ultimate conformal radiation delivery, with the least dose to surrounding normal tissues. The complexity of this treatment and the skill dependence of the procedure, however, have led to simpler methods of delivering partial breast irradiation such as the MammoSite catheter and intraoperative electron beam.

MammoSite. The first simplification of brachytherapy was balloon intracavitary brachytherapy, where a single catheter is centered inside a spherical or elliptical balloon. There is usually one dwell position or a limited number of linear dwell positions. Insertion and physics calculations are much easier than with interstitial brachytherapy, and like that method, the dose is 34 Gy in 10 fractions over 5 days, with each treatment fraction separated by at least 6 hours. We typically give two treatments per day — one each morning and afternoon — and the patient returns for these treatments for 5 days. Because of the physics limitations of a single dwell position, the dose can be prescribed only 1 cm beyond the surface of the balloon, and symmetrically around the central catheter. Even with tissue compres-

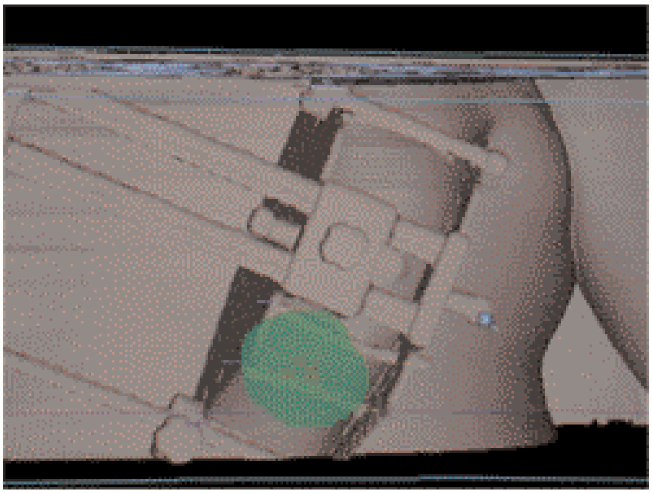


FIGURE 2 Top view of a brachytherapy catheter insertion using image guidance

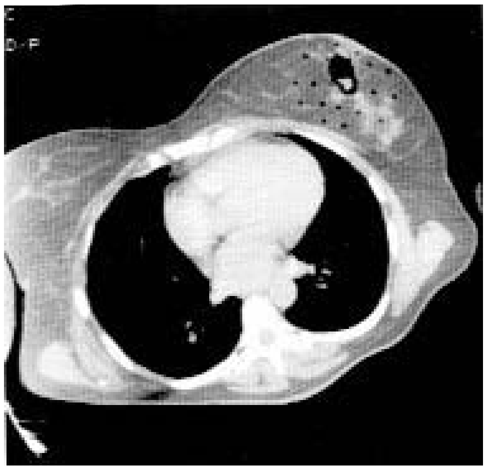
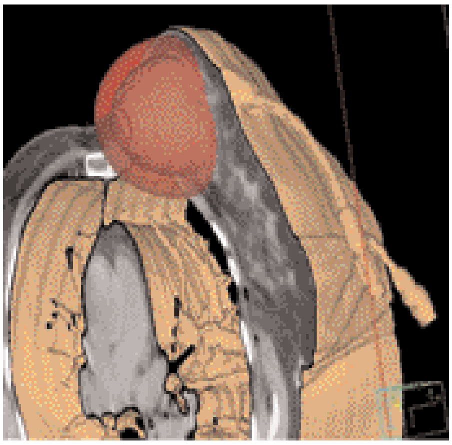


FIGURE 3 CT after brachytherapy is used to calculate the dose 1.5 to 2 cm beyond the cavity

APBI DELIVERY METHODS
continued

sion, the dose does not extend as far as with interstitial brachytherapy. Narrow skin separations (<7mm), irregular shaped cavities, or air/fluid loculations pose significant difficulties with this technique. This option is the most widely available method for carefully selected patients and cavities.

Three-dimensional conformal APBI. To simplify partial breast irradiation for non-procedural radiation oncologists, we now have the capability to deliver similar dosages and the same fractionation schemes as with conventional linear accelerators. With three-dimensional conformal APBI, we use CT scans to visualize the lumpectomy cavity, allowing us to contour the target volume, termed the *Planning Treatment Volume – Eval,* defined as a 2.5 cm margin around the surgical cavity. Physicists and dosimetrists typically plan 4 to 5 external radiation beams covering the target to a dose of 38.50 Gy in 10 fractions over 5 days. Breathing motion and set-up uncertainty pose technical challenges accounted for in the extra margin width. This method lacks the dose inhomogeneity inherent in brachytherapy, with a hotter central dose, so the prescribed dose must be greater with this technique (385 cGy per fraction). Exit dose to other parts of the body is possible. In our experience, symptomatic skin reactions are not unusual with this technique; however, it is a popular



- 34 Gy
- 10 fractions over 5 days
- Dose at balloon surface is higher

FIGURE 4 Three-dimensional rendering of applicator surface and prescription dose cloud in balloon intracavitary breast brachytherapy. Prescription dose in red is 1 cm beyond the balloon.

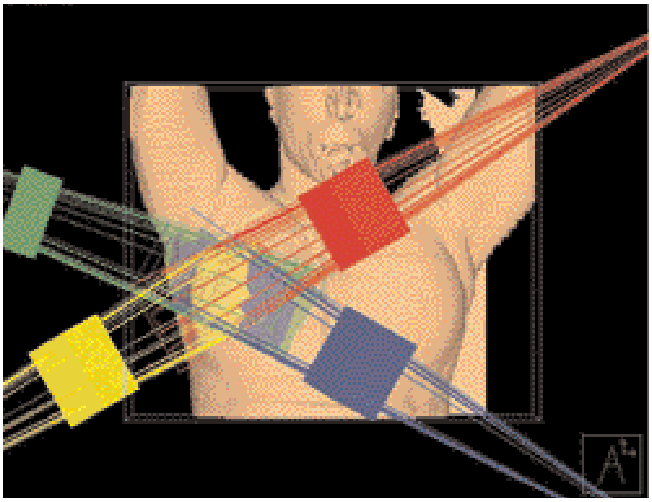


FIGURE 5 Three-dimensional conformal APBI

breast cancer in the future. Their lasting tribute will be the knowledge of whether APBI is equal to, less than, or better than conventional whole breast irradiation.

In mid-2006, the halfway mark in patient accrual for the NSABP/RTOG trial was reached. I am proud that one of my patients was the 1,500th patient to be entered in this trial. This landmark — the halfway point — has occurred in only 1 year, which is miraculous. As of September 2006, the Arizona Oncology Services Foundation has entered over 140 women in this important investigation. Amazingly, to the credit of Arizona women, approximately 80 percent of all eligible patients are signing up for the trial. Women in the United States and Canada, as well as their physicians, are to be commended for such enthusiastic participation. As a result, we now anticipate that the trial will end earlier than the 4 years' time that was originally planned, and its success so far has exceeded all expectations. Of course, the faster we complete the trial, the sooner we will have the answers we need.

In addition to survival, a primary endpoint obviously is the 5-year tumor recurrence rate in the treated breast. The cosmetic outcome will be rigorously evaluated by the treating physician and digital photos at regular intervals. The third outcome is QoL, where, in a subset of patients, we are using questionnaires to evaluate a woman's QoL with the different treatments. One of the expectations of the trial investigators is that the QoL of women who receive the 5-day treatment with only part of the breast being treated will be higher than those who are undergoing 6 weeks of whole-breast irradiation, but we need to document that hypothesis scientifically. There is also the question of whether radiation oncologists in North America will be able to achieve the results that have been reported by experienced brachytherapists. This is an aspect of the study that interests the National Cancer Institute (NCI) — the reproducibility of APBI. Can this technology be taken out of a few expert centers and applied across North America? Results from the phase 3 trial may help answer this question.

APBI method, because radiation oncologists and physicists are comfortable using linear accelerators. This technique requires a substantial investment in physics and dosimetry time to meet all the dose constraints and normal tissue limits. In spite of labor costs, three-dimensional conformal tends to be the least reimbursed form of APBI.

Soft x-rays (Intrabeam). This technique, pioneered in England by Michael Baum, MD, and Jayant Vaidya, MD, treats a tiny sliver of breast tissue beyond the lumpectomy cavity (approximately 2 mm) at a very low dose in a single intraoperative treatment.

Intra-operative electron beam. Umberto Veronesi, MD, and colleagues from Milan, Italy, have investigated this single-dose radiation treatment to the surgical bed at the time of surgery. Skin hooks separate the skin edges, the breast tissue is undermined and manipulated into the cavity, a posterior lead shield protects the underlying lung/heart, and a single, very high dose of electrons are delivered into an uncertain amount of breast tissue after quadrantectomy. Covering a defined target volume with quality assurance and documentation poses a significant challenge with this technique. A phase 3 trial in Italy is nearing completion, and various institutions in the United States. are evaluating this single-dose treatment.

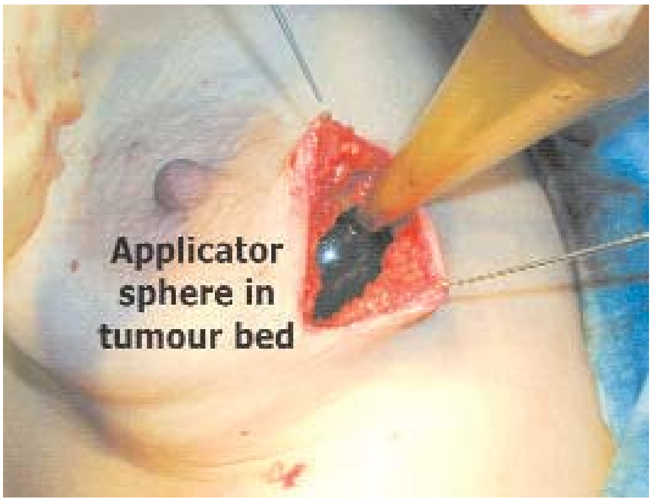


FIGURE 6 Intrabeam intraoperative soft X-rays

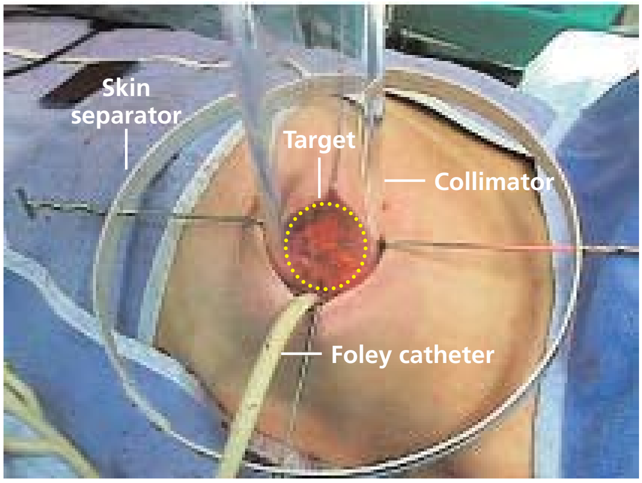


FIGURE 7 Intraoperative single fraction electron beam

Off-Trial APBI. Some centers around the country are allowing a “back door” into partial breast irradiation. Patients are being offered APBI if they want it, without the 50 percent risk of being randomized to 6 weeks of whole-breast irradiation. Although there are many strong factors influencing the way these centers present options to their patients, including the patients’ personal needs as well as their own priorities, I would urge these medical institutions to encourage participation in the clinical trial. We must stay committed to this research and document that partial breast irradiation is as good as or better than whole-breast irradiation. If there is a “back door” to receive the 5-day treatment, a high percentage of eligible women will take it, which will slow down accrual to the trial.

Results and follow-up. Once the trial accrues its 3,000th patient, now anticipated to be as early as March 2007, the study stops and new patients cannot enter the trial. Unless the NCI approves a larger sample size extending the study duration, we will then enter a follow-up period of data collection and analysis. During the follow-up period, patients will get mammograms every 6 months and physical examinations about every 3 months by their surgeons, radiation oncologists, and/or medical oncologists.

Some patients will receive chemotherapy (women who were randomized to whole breast irradiation receive chemotherapy before whole breast irradiation, whereas APBI is given prior to systemic therapy). During follow-up, in-breast recurrence is one of the primary endpoints, and digital photographs of both breasts will be taken for visual comparison and cosmetic evaluation at regular intervals. Cosmetic outcome will be judged by the patient, physician, and a separate panel reviewing the photos. As noted, we also will evaluate the QoL of patients with a validated instrument as well as survival.

Conclusion

Radiation therapy has been proven throughout every stage of breast cancer to reduce the risk of local and regional recurrence, and has an increasing role in the management of breast cancer. With external beam techniques, radiation must be given more slowly, over a period of 5 to 7 weeks. Because conventional therapy includes a large volume of normal tissue, including the entire breast, skin, chest wall, ribs, lung, and (for left-sided lesions) the heart, the dose per fraction is kept low to decrease the late effects (e.g., breast fibrosis, skin telangiectasia, pneumonitis, myocardial infarction). Brachytherapy and other APBI techniques deliver a highly conformal dose of radiation to only the volume of breast tissue at highest risk for relapse, 1–2 cm around the lumpectomy cavity. Exposure is tightly confined; therefore, the dose per fraction can be increased, allowing the same tumoricidal dose to be given in 1 week. Thus far, single-institution and national phase 2 trials have demonstrated impressive results with APBI in terms of tumor control and cosmetic outcome. NSABP B-39/RTOG 0413 and the international phase 3 trials are underway to address a key issue: Do we need to treat the whole breast in women with favorable breast cancers?

Future studies should define the optimal radiation margin after adequate breast-conserving surgery. Is 2 cm beyond the cavity necessary, or is $\leq$1.5 cm sufficient in specific cases? Despite the individual variation in selection criteria and treatment parameters, the five international prospective phase 3 trials should answer the basic question of whether we need to bow to Halsted[1] and treat the entire breast in every case. The best treatment technique, dose, and fractionation schemes will require ongoing future studies. Should the outcomes of APBI be within an acceptable range of whole breast irradiation, select women with early-stage breast cancer will have a much more convenient alternative to conventional whole breast irradiation with less exposure to the lungs, heart, and other normal tissues.

[1] In 1896, William S. Halsted, MD, a Johns Hopkins surgeon, performed the first radical mastectomy, which became the standard of care for women with breast cancer for the next 75 years.

Suggested Clinical Readings

Baglan KL, Martinez AA, Frazier RC, et al. The use of high-dose-rate brachytherapy alone after lumpectomy in patients with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys*. 2001;50:1003–1011.

Kuerer HM, Julian TB, Strom EA, et al. Accelerated partial breast irradiation after conservative surgery for breast cancer. *Ann Surg*. 2004;239:338–351.

Kuske RR, Boyer C, Bolton JS, et al. Long-term results of the Ochsner Clinic prospective phase II breast brachytherapy trial [abstract]. 27th Annual San Antonio Breast Cancer Symposium; December 8, 2004; San Antonio, Texas.

Kuske RR, Winter K, Arthur D, et al. A phase II trial of brachytherapy alone following lumpectomy for stage I or II breast cancer: initial outcomes of RTOG 95-17 [abstract]. *J Clin Oncol*. 2004 ASCO Annual Meeting Proceedings. 2004;22:565.

Kuske RR, Winter K, Arthur DW, et al. Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: toxicity analysis of RTOG 95-17. *Int J Radiat Oncol Biol Phys*. 2006; 65:45–51.

Vicini FA, Beitsch PD, Quiet CA, et al. First analysis of patient demographics, technical reproducibility, cosmesis, and early toxicity: results of the American Society of Breast Surgeons MammoSite breast brachytherapy trial. *Cancer*. 2005;104:1138–1148.

Wazer DE, Kaufman S, Cuttino L, et al. Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. *Int J Radiat Oncol Biol Phys*. 2006;64:489–495. Available at: «http://www.ncbi.nlm.nih.gov/entrez/utils/lofref.fcgi?itool=AbstractPlus-def&PrId=3048&uid=16246495&db=pubmed&url=http://linkinghub.elsevier.com/retrieve/pii/S0360-3016(05)01159-4». Accessed Oct. 10, 2006.

Commentaries

FROM SURGICAL ONCOLOGY

Susan J. Hoover, MD
Director, Diagnostic Breast Center, Lifetime Cancer Screening and Prevention Center, Medical Director of Diversity Affairs, Assistant Professor of Surgery, H. Lee Moffitt Cancer Center and Research Institute
Tampa, Florida

Dr. Kuske has written a concise yet comprehensive review of radiation therapy utilization in the treatment of breast cancer. The article eloquently reviews where we have been, where we are, and where we are going with this treatment modality.

Radiation therapy is an integral part of managing this disease, and as the article implies, accelerated partial breast irradiation (APBI) may have potential to revolutionize breast cancer therapy in much the same way as breast conservation therapy and sentinel lymph node biopsy have done. Application of APBI is another treatment method in the prevailing trend of "minimization" of local therapies for breast cancer.

Anecdotally, as a result of treating a relatively older population of breast cancer patients in Florida, I have found patient interest in APBI to be remarkable. Patients know about it, read about it, and want it, often mentioning their desire for APBI during the initial treatment consultation before surgery. Many of these women lead very active lifestyles, travel long distances to tertiary referral centers, have physical impairment, or provide care for loved ones — factors that make it more difficult for them to invest the time necessary for lengthy adjuvant radiation treatments. As well, minimization of toxicity and preservation of body image are important factors for many older women, which makes APBI even more enticing to them — especially when faced with some of the obstacles previously noted.

I am in agreement with Dr. Kuske that consideration of patients' needs is of course important, but what better way to honor this while providing top-notch medical science than with enrollment on a clinical trial? Enrollment allows for addressing patient circumstances in a controlled and regulated environment, which is safer for patients and allows for better understanding of this treatment's efficacy. I found this article to be particularly relevant and timely, and look forward to watching APBI develop as a possible permanent fixture in the treatment options for my patients.

FROM RADIATION ONCOLOGY

Jay L. Bosworth, MD
Long Island Radiation Therapy
Manhasset, New York

For over a decade, there has been increasing interest in treating patients with breast cancer with a technique known as accelerated partial breast irradiation (APBI), as discussed by Dr. Kuske. The current standard when using breast conservation surgery is external beam irradiation to the whole breast, once a day, 5 days a week, for 4 to 5 weeks. This is often followed by a boost dose to the tumor bed for another 5 to 7 days. Interstitial implants also have been used in the past to deliver this boost.

Because most recurrences occur in the region of the initial tumor, the question of treating the tumor bed arose and was addressed in some trials. Preliminary data have suggested that partial breast irradiation may yield the same low recurrence rate as whole breast irradiation. Accelerated treatments were introduced to reduce the time of radiation and inconvenience for many patients who had to receive treatment for 6 weeks, which requires a higher daily dose. The optimum daily dose (number of fractions per day or total dose) has not been established. Past RTOG studies have established that partial breast irradiation can be given with either external beam or an interstitial implant. A current trial, NSABP B-39/RTOG 0413, as reviewed by Dr. Kuske, is accruing patients to determine whether APBI will yield equivalent local tumor control in the breast as compared to whole breast irradiation. Quality-of-life issues as well as toxicity also will be compared. The trial is not designed to determine if any of the methods of APBI is better than another method.

There are some concerns and unanswered questions regarding APBI. Some of the excellent results reported may be due to the lack of long-term follow-up. In addition, as recently reported, there may be a subgroup of patients who do not need radiation following conservative surgery. A percentage of these patients could have been included in the prior studies. Toxicity after accelerated irradiation may take many years to manifest. There are also other methods of delivering partial breast radiation, which include intraoperative radiation and external beam radiation with a patient in the prone position. The NSABP B-39/RTOG 0413 trial is an important study that may influence the treatment of breast cancer in the future.

THE ASBD STATEMENT

Accelerated Partial Breast Irradiation

The Consensus Committee of the American Society of Breast Disease periodically authors statements on emerging areas of interest to breast specialists and their patients with the goal of clarifying issues particularly related to interdisciplinary breast healthcare.

Partial breast irradiation is defined as radiation therapy delivered to a small portion of the breast around a margin-negative excision of a breast cancer. As a limited amount of normal tissue is in the radiotherapy field, treatment is generally accelerated. Conventional breast irradiation is delivered daily in 5 to 7 weeks. Partial breast irradiation has been delivered from a single treatment to daily treatment over 4½ weeks. The most common treatment plan in the United States is twice-per-day treatment in 1 week.

The most common approaches to partial breast irradiation in the United States include:

1. Brachytherapy, using multiple parallel catheters or a single balloon catheter placed within or around the surgical cavity into which high-dose radioactive sources are placed.
2. Multiple small fields delivered with external beam radiation.

In some centers in Europe, a single fraction of intraoperative radiation is delivered. Each approach has its advantages and disadvantages in regard to coverage of the target volume, dose to normal tissue, ease of treatment, and acute and long-term toxicity. Each technique requires a skilled surgeon, radiation oncologist, and radiation physicist in placement of the treatment device, treatment planning, and treatment delivery.

The optimal patient for partial breast radiation has a breast tumor whose risk of recurrence is limited to the surgical bed after a margin-negative excision. The brachytherapy feasibility trials allowed only node-negative patients with tumors <3 cm and without negative prognostic features, such as young age, extensive intraductal component, lobular histology, extensive lymphovascular invasion, or multifocality. Physical and anatomic requirements for balloon catheter include adequate skin (soft tissue overlying the balloon) thickness and a surgical cavity conforming to the balloon catheter. Toxicity and poor cosmetic outcome from brachytherapy treatment is technique dependent.

Although several thousand women have been treated with partial breast irradiation, follow up is <10 years. The largest series reports its results at 7 years and includes only 199 highly selected patients. An ongoing U.S. trial is randomizing patients to conventional versus partial breast irradiation. Outside of clinical trials, caution should be used in patient selection and treatment. There is no test of equivalence for these different approaches.

Partial breast irradiation may cost more than conventional radiation and may not be covered by all insurance plans. The ASBD strongly encourages the participation of patients in the national study RTOG-412/NSABP B-39.

EDUCATIONAL GOAL

Although this newsletter does not provide continuing medical education credit, it is designed to meet the educational needs of the American Society of Breast Disease members, who include medical, surgical, and radiation oncologists, diagnostic radiologists, pathologists, allied health professionals, and other clinicians diagnosing and/or treating breast cancer.

Accelerated partial breast irradiation (APBI) is an emerging and rapidly developing technology, and its use in breast healthcare management is a topic of increasing discussion. This newsletter provides a history of the technology and describes current clinical trials to evaluate the efficacy of APBI. Multiple perspectives are provided through expert commentaries along with the ASBD Consensus Committee statement on the topic. This newsletter offers useful and timely information for breast specialists and other medical professionals.

EDUCATIONAL OBJECTIVES

After reading this newsletter, ASBD members should be able to:

- Describe the current role of radiation therapy in breast cancer treatment
- Explain the potential advantages of APBI in breast cancer treatment
- Discuss current clinical trials of APBI
- Compare methods of APBI in use and/or under investigation
- Comment on the differences between APBI and whole breast radiation

Author:
Robert R. Kuske, MD, FAACE
Arizona Oncology Services, Scottsdale, Arizona
Clinical Professor, The University of Arizona Health Sciences Center

Commentaries by:
Susan J. Hoover, MD
Director, Diagnostic Breast Center, Lifetime Cancer Screening and Prevention Center
Medical Director of Diversity Affairs
Assistant Professor of Surgery
H. Lee Moffitt Cancer Center and Research Institute
Tampa, Florida

Jay L. Bosworth, MD
Long Island Radiation Therapy
1129 Northern Blvd.
Manhasset, New York 11030

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Dr. Kuske has served as a consultant for Nucletron Corp. and BioLucent Inc.

The American Society of Breast Disease
P. O. Box 140186
Dallas, TX 75214
Visit us online at www.asbd.org

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