Sökning i databaser för vetenskaplig evidens: Intraoperativ strålbehandling (IORT) vid bröstkirurgi

Frågeställning

Vilken dagsaktuell vetenskaplig evidens finns för rutinmässig användning av intraoperativ strålbehandling vid kirurgisk behandling av bröstcancer?

Bakgrund

Behandlingen av bröstcancer har förändras och förbättrats dramatiskt under senare år. William Halstead hävdade redan 1894 att hela bröstkörteln inklusive närliggande lymfkörtlar (och muskler) borde tas bort vid kirurgi av bröstcancer, vilket kom att bli rutinbehandling under nästan 100 år. Studier under de senaste 2-3 årtiodena har etablerat mycket stark evidens för att kirurgiskt avlägsna själva tumören i bröstkörteln med en viss marginal i stället för att avlägsna hela bröstkörteln (1995; 2000). Det är också väletablerat att konventionell extern strålbehandling 5 dagar i veckan under 5-6 veckor av hela bröstkörteln i samband med vävnadsbesparande kirurgisk behandling av bröstcancer minskar lokala återfallförekomsten från 28,3 % till 10,4 % (Clarke, Collins et al. 2005). Med förbättrad teknik leder denna typ av strålbehandling sällan (< 2 %) till suboptimala kosmetiska resultat (Donovan, Bleakley et al. 2007; Pignol, Olivotto et al. 2008) eller skadliga effekter på lungor och hjärta (Giordano, Kuo et al. 2005). Intraoperativ strålbehandling har främst introducerats i syfte att förenkla och minska kostnaderna i samband med strålbehandlingsproceduren och för att att förkorta behandlingstiden. Vid intraoperativ strålbehandling riktas hög stråldos i såret direkt mot den tumörnära delen av bröstet efter att tumören avlägsnats.

Lokal intraoperativ strålbehandling har prövats i mer än 100 år mot cancerformer med hög risk för lokala recidiv, men tyvärr med nedslående resultat utom de allra senaste åren. Studier av intraoperativ strålbehandling vid bröstcancer i början av 1990-talet blev en besvikelse eftersom återfallsförekomsten var densamma som hos patienter utan strålbehandling (Fentiman, Poole et al. 1996; Magee, Young et al. 1998). Orsakerna till detta var bl a oselekterade patientmaterial, att behandlingsteknikerna inte var tillräckligt utvecklade och kvalitetssäkrade avseende reproducerbarhet eller strålfält. Ett brett spektrum av välutvecklade tekniker för lokal strålbehandling av bröstkörteln finns nu för använding under operationen och/eller i efterförloppet (Orecchia and Leonardo 2011). Ett vanligt övergripande begrepp är ”accelerated partial breast irradiation” (APBI) med underbegreppen intraoperativ radioterapi (IORT) där en lokal standardiserad strålkälla används under operationen samt brachyterapi där olika typer av lokala strålkällor lämnas i bröstet även i efterförloppet av operationen (Wazer, Arthur et al. 2009).

Utvecklingsarbete inom lokal radioterapi vid bröstcancer har under senare år fokuserats på utveckling och standardisering av tekniker, urval av patienter för olika terapier, av kirurgisk teknik och val av lokal strålteknik. Detta har medfört att tillräckligt stora randomiserade och välkontrollerade studier är en bristvara. Den serie studier av intraoperativ strålbehandling som

kommit längst är den sk ”Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer” TARGIT (Vaidya, Joseph et al. 2010; Neumaier, Blank et al. 2012). Resultaten efter 4 års uppföljningstid hos noga utvalda patientkategorier var jämförbara med konventionell extern strålbehandling.

Metodrådets sammanfattande bedömning

Standardiserad intraoperativ strålbehandling vid bröstcancer är ett lovande alternativ för selekterade patienter (kvinnor äldre än 60 år och med tumör utan spridning) där traditionell konventionell extern strålbehandling 5 dagar i veckan under 5-6 veckor av hela bröstkörteln inte är tillämplig. Sammanfattningsvis tyder denna översiktliga litteraturgranskning på att randomiserade och kontrollerade prospektiva studier av behandlingsresultat med lång uppföljningstid saknas, och metoden därför tills vidare enbart bör tillämpas som en del i behandlingsstudier.

Sökning i HTA (Health Technology Assessment) databaser (2012-05-22)

SBU http://www.sbu.se/sv/: Ingen träff på ”intraoperativ strålning”

Socialstyrelsen – nationella riktlinjer
http://www.socialstyrelsen.se/riktlinjer/nationellariktlinjer: Ingen träff på ”intraoperativ strålning”

TRIP http://www.tripdatabase.com/search/advanced: “intraoperative radiation breast cancer” – 12 systematiska översikter varav de följande är mest relevanta.

År 2000: Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects of long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Sammanställning av resultaten an EXTERN/konventionell strålningsbehandling från 40 randomiserade och kontrollerade studier av totalt 19 582 kvinnor behandlade för bröstcancer. Resultaten visar minskad förekomst av lokal återkomst av tumörerna med två tredjedelar.

År 2002 - Cuncins-Hearn A, Saunders C, Walsh D, Borg M, Buckingham J, Frizelle F, Maddern G. A systematic review of intraoperative radiotherapy in early stage breast cancer. North Adelaide, S. Australia, Australia: Royal Australasian College of Surgeons, Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP) - Surgical. ASERNIP-S Report; 27. 2002 A systematic review of intraoperative radiotherapy in early stage breast cancer– inte tillräcklig evidens.

År 2002 ASERNIP-S rapport No. 27 från Australien. A Systematic Review of Intraoperative Radiotherapy in Early Stage Breast Cancer.
http://www.surgeons.org/media/291393/IORTreview1002.pdf sammanfattad för sjukvårdspersonal http://www.surgeons.org/media/291377/IORTexecsum1002.pdf och sammanfattad för allmänheten
http://www.surgeons.org/media/291361/IORTconsum0802.pdf. Slutsatsen är att evidensen för användning av intraoperativ strålbehandling för tidig bröstcancer är svag.

År 2003 Adelaide Health technology Assessment Intra-operative radiation therapy: Applied to women undergoing breast cancer surgery aimed at reducing tumour recurrence. http://www.google.se/url?sa=t&rct=j&q=adelaide%20health%20technology%20assessment%20intra-operative%20radiation%20therapy%3A%20applied%20to%20women%20undergoing%20breast%20cancer%20surgery%20aimed%20at%20reducing%20tumour%20recurrence&source=web&cd=1&ved=0CFAQFjAA&url=http%3A%2F%2Fwww.horizonscanning.gov.au%2Finternet%2Fhorizon%2Fpublishing.nsf%2FContent%2FA06892DEAF6EEA3ACA2575AD0080F323%2F%24File%2Fv2_6.pdf&ei=wE-7T82xBpOL4gTcucDNCQ&usg=AFQjCNFVBs2FgG78wsze9lZWJndv6gU58Q. Intraoperativ strålbehandling vid bröstcancer reducerar lokala recidiv jämförbart med konventionell strålbehandling och ger färre biverkningar.

År 2004: National Institute for Health Research. A systematic review of intraoperative radiotherapy in early stage breast cancer. http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=12003008159. Originalrapporten återtagen från nätpublicering. Slutsatsen är att det inte finns evidens för att intraoperative radioterapi är överlägsen konventionell extern radioterapi vid bröstcancer.

År 2009: Schiller-Fruhwirth I, Wild C, Geiger-Gritsch S, Mittermayr T. Intraoperative radiotherapy for primary breast cancer. Systematic Review Vienna: Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA). Decision Support Document 23. 2009 http://eprints.hta.lbg.ac.at/832/1/DSD_23.pdf . Evidensgrad 3 – den näst lägsta.

År 2010: En spanskspråkig HTA – rapport som sträcker sig till och med år 2009 “Cantero-Munoz P, Ruano-Ravina A. Radioterapia intraoperatoria en cancer de mama y cancer colorrectal. [Intraoperative radiotherapy in breast and colorectal cancer] Santiago de Compostela: Galician Agency for Health Technology Assessment (AVALIA-T). IA2010/01. 2010” http://www.sergas.es/MostrarContidos_N3_T02.aspx?IdPaxina=60063&uri=/docs/Avalia-t/IA2010-01-RIO-mama-recto.pdf&hifr=1250&seccion=0 sammanfattad på http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=32009100403&UserID=0 med slutsatsen att största delen av befintliga studier är av låg kvalitet. Patienter med bröstcancer som har fått intraoperativ strålbehandling har en aning bättre överlevnad än de som fått extern strålbehandling och förekomsten av komplikationer är jämförbar.

År 2011: Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy British Journal of Surgery 2011;98:326-333, kommenterat i National Institute for Health Research http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12011001501. Konventionell extern strålbehandling minskar risken för lokal återkomst av tumörer.

Sökning på ”IORT”

År 2009: The Breast 18;327-334:2009 Long-term follow-up-findings in mammography and ultrasound after intraoperative radiotherapy (IORT) for breast cancer. Högre förekomst av lokala “dystropiska kalcifikationer” och “oljecystor” vid röntgen- och ultraljudsundersökningar vid intraoperative radioterapi än vid konventionell radioterapi.

Clinical Evidence http://www.clinicalevidence.com/x/index.html

Inga träffar på “intraoperative radiation breast cancer” eller ”IORT”

International Network of Agencies for Health Technology Assessment http://www.inahta.net/

Inga träffar på “intraoperative radiation breast cancer” eller ”IORT” utöver de som rapporterats ovan

Nasjonalt kunnskapssenter for helsetjenesten, Norge http://www.kunnskapssenteret.no/

Inga relevanta träffar på ”Brystkreft” eller ”strålebehandling”

För metodrådet i Sydöstra sjukvårdsregionen den 30 maj 2012

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Litteraturreferenser

(1995). "Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group." The New England journal of medicine **333**(22): 1444-1455.

BACKGROUND: Randomized trials of radiotherapy and surgery for early breast cancer may have been too small to detect differences in long-term survival and recurrence reliably. We therefore performed a systematic overview (meta-analysis) of the results of such trials. METHODS: Information was sought on each subject from investigators who conducted trials that began before 1985 and that compared local therapies for early breast cancer. Data on mortality were available from 36 trials comparing radiotherapy plus surgery with the same type of surgery alone, 10 comparing more extensive surgery with less extensive surgery, and 18 comparing more extensive surgery with less extensive surgery plus radiotherapy. Information on mortality was available for 28,405 women (97.4 percent of the 29,175 women in the trials). RESULTS: The addition of radiotherapy to surgery resulted in a rate of local recurrence that was three times lower than the rate with surgery alone, but there was no significant difference in 10-year survival; among a total of 17,273 women enrolled in such trials, mortality was 40.3 percent with radiotherapy and 41.4 percent without radiotherapy (P = 0.3). Radiotherapy was associated with a reduced risk of death due to breast cancer (odds ratio, 0.94; 95 percent confidence interval, 0.88 to 1.00; P = 0.03), which indicates that, after 10 years, there would be about 0 to 5 fewer deaths due to breast cancer per 100 women. However, there was an increased risk of death from other causes (odds ratio, 1.24; 95 percent confidence interval, 1.09 to 1.42; P = 0.002). This, together with the age-specific death rates, implies, after 10 years, a few extra deaths not due to breast cancer per 100 older women or per 1000 younger women. During the first decade or two after diagnosis, the excess in the rate of such deaths that was associated with radiotherapy was much greater women who were over 60 years of age at randomization (15.3 percent vs. 11.1 percent [339 vs. 249 deaths]) than among those under 50 (2.5 percent vs. 2.0 percent [62 vs. 49 deaths]). Breast-

conserving surgery involved some risk of recurrence in the remaining tissue, but no significant differences in overall survival at 10 years were found in the studies of mastectomy versus breast-conserving surgery plus radiotherapy (4891 women), more extensive surgery versus less extensive surgery (4818 women), or axillary clearance versus radiotherapy as adjuncts to mastectomy (4370 women). CONCLUSIONS: Some of the local therapies for breast cancer had substantially different effects on the rates of local recurrence--such as the reduced recurrence with the addition of radiotherapy to surgery--but there were no definite differences in overall survival at 10 years.

(2000). "Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group." Lancet **355**(9217): 1757-1770.

BACKGROUND: The long-term effects of radiotherapy on mortality from breast cancer and other causes remain uncertain. METHODS: A meta-analysis was done of 10-year and 20-year results from 40 unconfounded randomised trials of radiotherapy for early breast cancer. It involved central review of individual patients' data on recurrence and cause-specific mortality from 20000 women, half with "node-positive" disease. Radiotherapy fields generally included not only chest wall (or breast) but also axillary, supraclavicular, and internal mammary nodes. FINDINGS: A reduction of approximately two-thirds in local recurrence was seen in all trials, largely independent of the type of patient or type of radiotherapy (8.8% vs 27.2% local recurrence by year 10). Hence, to assess effects on breast cancer mortality of substantially better local control, results from all trials were combined. Breast cancer mortality was reduced (2p=0.0001) but other, particularly vascular, mortality was increased (2p=0.0003), and overall 20-year survival was 37.1% with radiotherapy versus 35.9% control (2p=0.06). There was little effect on early deaths, but logrank analyses of later deaths indicate that, on average after year 2, radiotherapy reduced annual mortality rates from breast cancer by 13.2% (SE 2.5) but increased those from other causes by 21.2% (SE 5.4). Nodal status, age, and decade of follow-up strongly affected the ratio of breast cancer mortality to other mortality, and hence affected the ratio of absolute benefit to absolute hazard from these proportional changes in mortality. INTERPRETATION: Radiotherapy regimens able to produce the two-thirds reduction in local recurrence seen in these trials, but without long-term hazard, would be expected to produce an absolute increase in 20-year survival of about 2-4% (except for women at particularly low risk of local recurrence). The average hazard seen in these trials would, however, reduce this 20-year survival benefit in young women and reverse it in older women.

Clarke, M., R. Collins, et al. (2005). "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." Lancet **366**(9503): 2087-2106.

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.

Donovan, E., N. Bleakley, et al. (2007). "Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy." Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology **82**(3): 254-264.

BACKGROUND: Radiation dose distributions created by two dimensional (2D) treatment planning are responsible for partial volumes receiving >107% of the prescribed dose in a proportion of patients prescribed whole breast radiotherapy after tumour excision of early breast cancer. These may contribute to clinically significant late radiation adverse effects. AIM: To test three dimensional (3D) intensity modulated radiotherapy (IMRT) against 2D dosimetry using standard wedge compensators in terms of late adverse effects after whole breast radiotherapy. METHODS: Three hundred and six women prescribed whole breast radiotherapy after tumour excision for early stage cancer were randomised to 3D IMRT (test arm) or 2D radiotherapy delivered using standard wedge compensators (control arm). All patients were treated with 6 or 10MV photons to a dose of 50Gy in 25 fractions to 100% in 5 weeks followed by an electron boost to the tumour bed of 11.1Gy in 5 fractions to 100%. The primary endpoint was change in breast appearance scored from serial photographs taken before radiotherapy and at 1, 2 and 5 years follow up. Secondary endpoints included patient self-assessments of breast discomfort, breast hardness, quality of life and physician assessments of breast induration. Analysis was by intention to treat. RESULTS: 240 (79%) patients with 5-year photographs were available for analysis. Change in breast appearance was identified in 71/122 (58%) allocated standard 2D treatment compared to only 47/118 (40%) patients allocated 3D IMRT. The control arm patients were 1.7 times more likely to have a change in breast appearance than the IMRT arm patients after adjustment for year of photographic assessment (95% confidence interval 1.2-2.5, p=0.008). Significantly fewer patients in the 3D IMRT group developed palpable induration assessed clinically in the centre of the breast, pectoral fold, infra-mammary fold and at the boost site. No significant differences between treatment groups were found in patient reported breast discomfort, breast hardness or quality of life. CONCLUSION: This analysis suggests that minimisation of unwanted radiation dose inhomogeneity in the breast reduces late adverse effects. Incidence of change in breast appearance was statistically significantly higher in patients in the standard 2D treatment arm compared with the IMRT arm. A beneficial effect on quality of life remains to be demonstrated.

Fentiman, I. S., C. Poole, et al. (1996). "Inadequacy of iridium implant as sole radiation treatment for operable breast cancer." Eur J Cancer **32A**(4): 608-611.

In order to avoid a prolonged course of external irradiation as part of breast conservation therapy, 27 patients received an iridium implant to the primary tumour bed as sole radiation treatment. Surgery was standardised comprising tumourectomy and axillary clearance. Using a rigid implant afterloading with iridium192 wires, 55 Gy was delivered on a continuous basis over 5 days. After 6 years median follow-up,

relapse of cancer within the treated breast has occurred in 10 of the 27 patients (37%). Compared with historical controls treated by similar surgery and iridium192 implant (20 Gy) with external radiotherapy (46 Gy), there was a significantly increased breast relapse rate in those treated by iridium implant alone. However, the incidence of distant metastases and overall survival was similar. Thus, a continuous iridium192 implant delivering 55 Gy in 5 days is not an effective means of achieving local control in patients with operable breast cancer.

Giordano, S. H., Y. F. Kuo, et al. (2005). "Risk of cardiac death after adjuvant radiotherapy for breast cancer." Journal of the National Cancer Institute **97**(6): 419-424.

BACKGROUND: Women with breast cancer who are treated with adjuvant radiation have a decreased risk of local recurrence but an increased risk of mortality from ischemic heart disease. Patients with left-sided breast tumors receive a higher dose of radiation to the heart than patients with right-sided tumors. Because radiation techniques have improved over time, we investigated whether the risk of death from ischemic heart disease after adjuvant breast radiotherapy decreased over time. METHODS: We used the 12-registry 1973-2000 dataset from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Women (n = 27,283) treated with adjuvant radiation for breast cancer diagnosed in 1973-1989 were included in the study. Ischemic heart disease mortality was calculated at 15 years and compared for women diagnosed during 1973-1979, 1980-1984, and 1985-1989. Cox proportional hazards models were used to calculate the hazard of death from ischemic heart disease for women diagnosed 1973-1988 and censored at 12 years. All statistical tests were two-sided. RESULTS: There were no differences in age, race/ethnicity, disease stage, or follow-up time between the 13 998 women with left-sided and 13 285 with right-sided cancer. For women diagnosed in 1973-1979, there was a statistically significant difference in 15-year mortality from ischemic heart disease between patients with left-sided (13.1%, 95% confidence interval [CI] = 11.6 to 14.6) and those with right-sided (10.2%, 95% CI = 8.9 to 11.5) breast cancer (P = .02); no such difference was found for women diagnosed in 1980-1984 (9.4%, [95% CI = 8.1 to 10.6] versus 8.7% [95% CI = 7.4 to 10.0], respectively, P = .64) or 1985-1989 (5.8% [95% CI = 4.8 to 6.8] versus 5.2% [95% CI = 4.4 to 5.9], respectively, P = .98). In the Cox model, the hazard ratio [HR] for ischemic heart disease mortality for women with left-sided versus women with right-sided disease was 1.50 (95% CI = 1.19 to 1.87) in 1979. With each succeeding year after 1979, the hazard of death from ischemic heart disease for women with left-sided versus those with right-sided disease declined by 6% (HR = 0.94, 95% CI = 0.91 to 0.98). CONCLUSIONS: Risk of death from ischemic heart disease associated with radiation for breast cancer has substantially decreased over time.

Magee, B., E. A. Young, et al. (1998). "Patterns of breast relapse following breast conserving surgery and radiotherapy." British Journal of Cancer **78**: 24-24.

Neumaier, C., E. Blank, et al. (2012). "TARGIT-E(lderly) - Prospective phase II study of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer." BMC Cancer **12**(1): 171.

ABSTRACT: BACKGROUND: Patients [greater than or equal to] 70 years with small, low-risk breast cancer who are operated but not irradiated show local relapse rates around 4% after 4 years. With adjuvant whole breast radiotherapy (WBRT) the local relapse rate drops to 1% after 4 years under Tamoxifen (5). It has been demonstrated (6, 12) that the efficacy of radiotherapy of the tumor bed only in a selected group can be non-inferior to WBRT. METHODS: This prospective, multicentric single arm phase II study is based on the protocol of the international TARGIT-A study. The TARGIT-E study should confirm the efficacy of a single dose of intraoperative radiotherapy (IORT) in a well selected group of elderly patients with small breast cancer and absence of risk factors. Patients will receive IORT (20 Gy with Intrabeam system/Carl Zeiss) during breast conserving surgery. In presence of risk factors postoperative WBRT will be added to complete the radiotherapeutic treatment according to international guidelines. Endpoints are the local relapse rate (within 2 cm of the tumor bed), ipsilateral in breast relapse, cancer-specific and overall survival and contralateral breast cancer as well as documentation of quality of life and cosmetic outcome. The expected local relapse rates are 0.5/1/1.5% after 2.5/5/7.5 years, respectively. Discontinuation of the trial is scheduled if rates of local relapse rates rise to 3/4/6% after 2.5/5/7.5 years. Power calculations result in 540 patients with a calculated dropout rate of 20% and loss to follow-up of 20%, an alpha of 0.01 and a beta 0.05. There will be a pre- and a post-pathology stratum (n=270 each). DISCUSSION: It is a pragmatic trial in which each participating centre has the option to modify entry criteria and criteria for WBRT according to this core protocol after consultation with the steering committee and local ethics committee (e.g. size, free margins). Only centers with access to the Intrabeam system (Carl Zeiss) can recruit patients into the trial. Its aim is to confirm the efficacy and toxicity of IORT in a well selected collective of elderly patients with breast cancer.

Orecchia, R. and M. C. Leonardo (2011). "Intraoperative radiation therapy: is it a standard now?" Breast **20 Suppl 3**: S111-115.

The question whether and for whom the gold standard of whole breast radiotherapy (WBRT) may be replaced by accelerated partial breast irradiation (APBI) is one of the most controversial issue in the adjuvant breast cancer setting. Among different APBI techniques, intraoperative radiation therapy (IORT) is particularly appealing to patients and physicians, because the procedure is fast, convenient, normal structures sparing and able to solve some clinical problems, like the integration with chemotherapy. Early findings from phase II and randomized phase III trials show the approach of APBI in selected patients at low risk for local recurrence is safe and well tolerated, but short follow-up creates some reservations. Since recurrences of breast cancer can occur after a considerably time delay, final assessment of APBI will only be valid after sufficient follow-up from prospective randomized trials with large patients number. Until then APBI should be considered experimental. Furthermore,

many questions regarding the appropriate patient selection criteria, treatment volume and dose fractionation still exist. In the context of risk-adapted RT, the key to success is the proper selection of the patients. Both the American and European Society of Radiology and Oncology provided a consensus statement regarding patient selection criteria based on tumour and patient-related features. The 5-year results of the non-randomized ELIOT study from Milan, using 21 Gy-full dose, identified a group of patients who may be good candidates for the treatment. The stratification of patients according to clinical phenotype or by molecular class and a widespread use of preoperative breast magnetic resonance imaging might be better identify patients eligible for APBI.

Pignol, J. P., I. Olivotto, et al. (2008). "A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis." Journal of clinical oncology : official journal of the American Society of Clinical Oncology **26**(13): 2085-2092.

PURPOSE: Dermatitis is a frequent adverse effect of adjuvant breast radiotherapy. It is more likely in full-breasted women and when the radiation is distributed nonhomogeneously in the breast. Breast intensity-modulated radiation therapy (IMRT) is a technique that ensures a more homogeneous dose distribution. PATIENTS AND METHODS: A multicenter, double-blind, randomized clinical trial was performed to test if breast IMRT would reduce the rate of acute skin reaction (notably moist desquamation), decrease pain, and improve quality of life compared with standard radiotherapy using wedges. Patients were assessed each week during and up to 6 weeks after radiotherapy. RESULTS: A total of 358 patients were randomly assigned between July 2003 and March 2005 in two Canadian centers, and 331 were included in the analysis. Breast IMRT significantly improved the dose distribution compared with standard radiation. This translated into a lower proportion of patients experiencing moist desquamation during or up to 6 weeks after their radiation treatment; 31.2% with IMRT compared with 47.8% with standard treatment (P = .002). A multivariate analysis found the use of breast IMRT (P = .003) and smaller breast size (P < .001) were significantly associated with a decreased risk of moist desquamation. The use of IMRT did not correlate with pain and quality of life, but the presence of moist desquamation did significantly correlate with pain (P = .002) and a reduced quality of life (P = .003). CONCLUSION: Breast IMRT significantly reduced the occurrence of moist desquamation compared with a standard wedged technique. Moist desquamation was correlated with increased pain and reduction in the quality of life.

Vaidya, J. S., D. J. Joseph, et al. (2010). "Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial." Lancet **376**(9735): 91-102.

BACKGROUND: After breast-conserving surgery, 90% of local recurrences occur within the index quadrant despite the presence of multicentric cancers elsewhere in the breast. Thus, restriction of radiation therapy to the tumour bed during surgery might

be adequate for selected patients. We compared targeted intraoperative radiotherapy with the conventional policy of whole breast external beam radiotherapy. METHODS: Having safely piloted the new technique of single-dose targeted intraoperative radiotherapy with Intrabeam, we launched the TARGIT-A trial on March 24, 2000. In this prospective, randomised, non-inferiority trial, women aged 45 years or older with invasive ductal breast carcinoma undergoing breast-conserving surgery were enrolled from 28 centres in nine countries. Patients were randomly assigned in a 1:1 ratio to receive targeted intraoperative radiotherapy or whole breast external beam radiotherapy, with blocks stratified by centre and by timing of delivery of targeted intraoperative radiotherapy. Neither patients nor investigators or their teams were masked to treatment assignment. Postoperative discovery of predefined factors (eg, lobular carcinoma) could trigger addition of external beam radiotherapy to targeted intraoperative radiotherapy (in an expected 15% of patients). The primary outcome was local recurrence in the conserved breast. The predefined non-inferiority margin was an absolute difference of 2.5% in the primary endpoint. All randomised patients were included in the intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT00983684. FINDINGS: 1113 patients were randomly allocated to targeted intraoperative radiotherapy and 1119 were allocated to external beam radiotherapy. Of 996 patients who received the allocated treatment in the targeted intraoperative radiotherapy group, 854 (86%) received targeted intraoperative radiotherapy only and 142 (14%) received targeted intraoperative radiotherapy plus external beam radiotherapy. 1025 (92%) patients in the external beam radiotherapy group received the allocated treatment. At 4 years, there were six local recurrences in the intraoperative radiotherapy group and five in the external beam radiotherapy group. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1.20% (95% CI 0.53-2.71) in the targeted intraoperative radiotherapy and 0.95% (0.39-2.31) in the external beam radiotherapy group (difference between groups 0.25%, -1.04 to 1.54; p=0.41). The frequency of any complications and major toxicity was similar in the two groups (for major toxicity, targeted intraoperative radiotherapy, 37 [3.3%] of 1113 vs external beam radiotherapy, 44 [3.9%] of 1119; p=0.44). Radiotherapy toxicity (Radiation Therapy Oncology Group grade 3) was lower in the targeted intraoperative radiotherapy group (six patients [0.5%]) than in the external beam radiotherapy group (23 patients [2.1%]; p=0.002). INTERPRETATION: For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks. FUNDING: University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre, UCLH Charities, National Institute for Health Research Health Technology Assessment programme, Ninewells Cancer Campaign, National Health and Medical Research Council, and German Federal Ministry of Education and Research (BMBF).

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