The Breast 21 (2012) 629–634

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Radiotherapy as sole adjuvant treatment for older patients with low-risk breast cancer

G.A. Walker [a,*], O. Kaidar-Person [b], A. Kuten [b], D.A.L. Morgan [a]

[a] Department of Clinical Oncology, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, United Kingdom
[b] Rambam Health Care Campus, Oncology Institute, Haifa, Israel

ARTICLE INFO

Article history:
Received 7 March 2012
Received in revised form
15 May 2012
Accepted 8 June 2012

Keywords:
Breast cancer
Adjuvant therapy
Endocrine therapy
Radiotherapy
Low risk

ABSTRACT

Partly as a result of screening, increasing numbers of older patients are presenting with 'low risk' breast cancer: tumours from which the likelihood of breast cancer death is minute; even so, these patients have a measurable risk of local recurrence if conservative surgery is not followed by some form of adjuvant treatment. However, it must be acknowledged that any such treatment has no detectable impact upon survival, and the value of all such interventions must be considered in the context of the individual patient's non-cancer life expectancy and the complex psychosocial factors that affect older patients.

If no impact on survival can be expected and the risk of local recurrence is high enough to warrant some post-operative treatment, the most powerful agent in this respect is radiotherapy. Whilst adjuvant endocrine treatment is becoming increasingly accepted as monotherapy in low risk patients, we propose that radiotherapy should not be forgotten as an alternative which, with its attendant benefits of shorter duration and high compliance, may be more suitable for a number of patients.

Introduction

In an era of mass mammographic screening, there is justifiable concern at the amount of 'over-treatment' that is given. It is widely accepted that many patients are being treated for conditions that left untreated, would have had no impact on the length of the affected individual's survival, nor upon the ultimate mode of death.[1] Similarly, there has always been interest in trying to identify 'low risk' groups who may be adequately treated by less aggressive interventions. The cooperative group trial CALGB 9343 proposes that endocrine agent monotherapy may be an acceptable adjuvant treatment in selected low risk patients over 70 years and this is a practice now supported by the St Gallen consensus meeting and National Comprehensive Cancer Network (NCCN)[2–4] While a number of randomised studies have addressed the issue of what value radiotherapy adds to endocrine therapy in these patients, no modern studies have asked the converse: what value does endocrine therapy add to radiotherapy in very low risk patients?

This article addresses this question and proposes that radiotherapy should not be overlooked, as a valuable and well-tolerated adjuvant treatment, with its own unique advantages over a five year course of endocrine treatment.

Search strategy and selection criteria

A selective review of the literature in the PubMed database, using the search terms "breast" and "cancer" and "radiotherapy" and "hormone" or "endocrine" was undertaken. The search was limited to Humans; Female; Clinical Trial; Meta-Analysis; Randomised Controlled Trial; Comparative Study; Controlled Clinical Trial; Aged 65 years and older. Cochrane library search was conducted using the above listed terms in "Title, Abstract or Keywords." Search for secondary end points was conducted without limitation for Meta-Analysis; Randomised Controlled Trial; Comparative Study; Controlled Clinical Trial and the terms "adherence", compliance", "adverse events", "partial breast irradiation", "QOL", "cost", "cost effectiveness" were added to the search. The articles were first evaluated by title, thereafter by abstract and full text. Guidelines and consensus statements, treatment recommendations and international meetings [US National Comprehensive Cancer Network (NCCN); *American Society of Clinical Oncology* (ASCO); American Society for Radiation Oncology (ASTRO), Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO), the American Brachytherapy Society (ABS), the American Society of

* Corresponding author. Tel.: +44 7809120890; fax: +44 115 8405879.
E-mail address: georgiewalker@doctors.org.uk (G.A. Walker).

0960-9776/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.breast.2012.06.008

Breast Surgeons, St. Gallen and *the San Antonio Breast Cancer* Symposium were also referred to.]

Endocrine therapy and radiotherapy: adjuvant treatments

Endocrine therapy reduces recurrence rates (local and distant), mortality and contralateral breast cancer in oestrogen receptor (ER) positive patients.[5] The St. Gallen Consensus Conference 2011 recommends that all ER-positive breast cancer patients should discuss adjuvant endocrine therapy, even those at very lowest risk.[4] Duration of treatment is typically five years, but can increase to eight years in higher risk patients, with extended endocrine therapy.[6,7]

Whole breast irradiation (WBI) after breast conserving surgery (BCS) reduces the risk of local recurrence (LR) by half, and results in similar long-term survival as mastectomy.[8] Conventional radiotherapy (RT) involves five weeks of treatment to the whole breast, often followed by a 'boost' to the tumour bed for patients at high risk of LR following BCS and clear margins. ASTRO and the St. Gallen 2011 panel endorse a hypofractionated regimen of 42·5 Gy in sixteen fractions over three weeks, since after ten years of follow-up, this schedule is as effective as five weeks in low risk patients.[4,6]

There is increasing interest in 'Accelerated Partial Breast Irradiation (APBI)'. Methods of delivery are listed in Table 1. By treating only part of the breast, there is reduced dose to the normal breast tissue, and organs at risk including heart and lungs. Treatment times are also shorter than standard WBI, which is of utmost important to patients with care-giving responsibilities, work commitments or who live far from the specialist centre, and also those older patients with significant co-morbidities or living in social isolation.[9] Even though follow-up beyond ten years is awaited, APBI is considered ethical in selected low risk patients, outside of the context of a clinical trial, due to the increasing body of evidence supporting effectiveness and safety comparable to WBI.[10] ASTRO, GEC-ESTRO, the American Brachytherapy Society and the American Society of Breast Surgeons have developed consensus guidelines, to identify 'low risk' patients who may be suitable for this conservative radiotherapy technique (Table 2). While APBI may be particularly appropriate for the group of patients here to be discussed, the argument we use applies to radiotherapy in general, not just to APBI or any of its various specific techniques.

Endocrine treatment and radiotherapy: degree of risk reduction

Trials over the years have investigated the role of RT and tamoxifen in low risk breast cancer patients, in terms of LR, distant metastasis-free survival (DMFS) and overall survival (OS.) Many of the trials are of factorial design. Key phase III randomised controlled trials are presented in Table 3. The definition of low risk patients has evolved, increasingly using such criteria as histological grade and molecular phenotype as well as tumour size and nodal status.[11] The risk a cancer poses to a patient, in terms of recurrence and survival, can be quantified by the use of prognostic scores. This can in turn guide the physician, in the prescription of adjuvant treatments. The Nottingham Prognostic Index (NPI) score is based on the following equation:

$$\text{NPI} = 0.2 \times \text{tumour size (cm)} + \text{grade (1–3)} + \text{lymph node stage (1–3)}$$

This index predicts survival of patients with invasive breast cancer, dividing patients into risk groups of excellent (NPI $\leq$ 2.4), good (2.41 $<$ NPI $\leq$ 3.4), moderate (3.41 $<$ NPI $\leq$ 5.4) or poor (NPI $>$ 5.4) prognosis. Patients with an NPI $\leq$ 2.4 have an equivalent survival to age-matched controls.[12] However, prognostic scores are never used in isolation, as other factors have been found to influence prognosis. HER-2 status, vascular invasion (VI) and patient age, should also be included when assessing risk.[13] For the purpose of this review, patients referred to as 'low risk' are over 70 years of age, of NPI $\leq$ 2.4, ER-positive, HER-2 negative and VI negative. It is patients with these characteristics who may be particularly suitable for treatment with radiotherapy alone, without prolonged endocrine therapy.

Important conclusions can be drawn from the trials of adjuvant WBI and endocrine therapy, and they will be summarized in turn:-

1. No risk group of breast cancers has been characterised in whom WLE alone (i.e. no use of RT or systemic therapy) will give a local ('in breast') recurrence rate of less than 10% after ten years of follow-up.[8,14]
2. RT and tamoxifen in combination following BCS in low risk patients, produces the lowest risk of LR, but no additional survival benefit above monotherapy.[2,8,15–17]
3. Following BCS, no recent trial has randomised patients to either RT or endocrine therapy, in a two-arm trial. However, in the factorial design studies, the risk of LR has been shown to be consistently higher, by up to eight times, with tamoxifen monotherapy, compared to tamoxifen and RT ($p < 0{\cdot}001$.)[2,15–17]
4. Not all patients will have a recurrence of their breast cancer following BCS, indicating that there will be some patients exposed to the risks of adjuvant treatments without benefit. In the NSABP B06 trial, 35·6% of patients remained free from breast cancer recurrence at twenty years, following BCS alone.[15,18,19]
5. The incidence of contralateral breast cancer has been shown to be significantly reduced by tamoxifen, compared to RT alone,

Table 1
Definitions of 'low risk' breast cancer patients, who may be considered for accelerated partial breast irradiation outside of a clinical trial.

Characteristic	GEC-ESTRO	ASTRO	ABS	ASBS
Age, years	>50	≥60	≥50	≥45
Histological sub-type	IDC, mucinous, tubular, medullary, colloid	Invasive ductal, other favourable[a]	Invasive ductal	Invasive ductal
Pure DCIS	No	No	No	Yes
Associated LCIS	Allowed	Allowed		
Histological grade	Any	Any	Any	Any
pT stage	pT1-2 (≤30 mm)	Up to and incl 2 cm	≤30 mm	≤30 mm
Surgical margins	≥2 mm	>2 mm	Negative	Negative
Multicentric or multifocal?	Unicentric, unifocal	Unicentric, unifocal		
EIC	No	No		
LVI	No	No		
ER/PR status	Any	+ve		
Nodal status	pN0	pN0 (i− or +)	pN0	pN0
Neoadjuvant therapy	No	No		

[a] Favourable sub-types include mucinous, tubular, colloid.[50–53]