Ipsilateral Breast Tumor Recurrence Following Breast-Conserving Surgery for Early-Stage Invasive Cancer

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Acta Oncologica Suppl. 13, pp. 9–17, 1999

Ipsilateral breast tumor recurrence (IBTR) following conservative surgery and radiation for early stage invasive cancer occurs in approximately 15% of all patients at 10 years and is diminished with surgical excisions which achieve negative margins. Treatment strategies of breast-conserving surgery with or without radiation that result in IBTR rates of 30–40% will impact negatively on survival and the magnitude of this effect will be influenced by the predominant pattern of local failure as well as initial and subsequent distant metastases. Optimal local control in early-stage invasive breast cancer is important to minimize the risk of a salvage mastectomy and maximize the potential for long-term survival.

In six prospective randomized trials radical or modified radical mastectomy was compared with breast-conserving surgery, axillary dissection, and radiation for stages I and II breast cancer (1–7). These trials have demonstrated the equivalence of the two approaches in terms of local-regional recurrence, distant metastases and overall survival and their results have been used to support the concept that variations in local-regional treatment will not affect survival since breast cancer is systemic at its inception. However, in all but one of the trials (7), the risk of a chest wall recurrence following mastectomy was similar to the risk of a recurrence in the conserved breast following radiation. Therefore, the variations in local-regional treatment evaluated in these trials proved to be comparable in terms of local control and would not have been expected to alter survival. Current debate has focused on the significance of an ipsilateral breast tumor recurrence and its impact on survival when variations in treatment result in significantly different risks of local recurrence. In this discussion I review ipsilateral breast tumor recurrence (IBTR) rates in patients treated with conservative surgery and radiation, the identification of factors associated with a significant risk of such a recurrence despite radiation, and the results of prospective randomized trials evaluating variations in breast conservation treatment which subsequently proved to have dissimilar rates of IBTR.

MAGNITUDE OF THE RISK OF AN IPSILATERAL BREAST TUMOR RECURRENCE FOLLOWING CONSERVATIVE SURGERY AND RADIATION

Table 1 presents local (chest wall or ipsilateral breast recurrence) rates reported by the prospective randomized trials comparing mastectomy to conservative surgery and radiation. Table 2 presents ipsilateral breast tumor recurrence rates at 5, 10, and 15 years reported by multiple retrospective series. Despite variations in patient selection, the extent of surgical resection, the technical aspects of radiation, and the use of adjuvant systemic therapy the results are relatively consistent with ipsilateral breast tumor recurrence rates in the range of 5–10% at 5 years, 10–15% at 10 years, and 15–20% at 15 years. For patients with negative resection margins or those undergoing quadrantectomy, ipsilateral breast tumor recurrence rates range from 2 to 12% at 10 years (3, 8–14).

FACTORS ASSOCIATED WITH A SIGNIFICANT RISK OF IBTR IN PATIENTS RECEIVING RADIATION

There is no general consensus on the magnitude of the risk of an IBTR which may be deemed ‘significant’. However, a risk that is two- to threefold greater than the average risk reported in Tables 1 and 2 or greater than the risk of a chest wall recurrence following mastectomy is not infrequently considered significant enough to warrant a recommendation for mastectomy. Quantitatively, this risk would fall in the range of 25–40%. Factors that have been associated with an IBTR rate of this magnitude are: young age, the presence of clinical gross multifocal or multicentric disease, and positive resection margins.

In several series IBTR rates have been reported in the range of 24–43% at 8 to 10 years in women ≤ 35 years of age treated with conservative surgery and radiation (11, 15–19). This increased risk has been attributed to a greater prevalence of primary tumors with an extensive intraductal component or adverse histopathologic factors such as high nuclear or histologic grade or tumor necrosis (16, 20–22). The risk has been decreased in some series by using wide excisions with negative margins and the addition of adjuvant chemotherapy (23–25). Of note is the observation that young women with a positive family history of breast cancer have a lower risk of IBTR than those without such a history (26–28). Robson et al. (29) reported an 11% crude breast recurrence rate (median follow-up 5.5 years) in 9 women < 42 years of age with breast cancers associated with the BRCA1 or 2-gene mutations treated with conservative surgery and radiation compared with a 25% rate (median follow-up 3.7 years) in 25 women of similar age with sporadic breast cancer.

Clinical gross multifocal or multicentric disease is defined as the presence of more than a single cancer in one breast demonstrated by physical examination and/or mammography. The distinction between multifocal and multicentric disease is based on the presence of the cancers in a single quadrant or separate quadrants. This clinical presentation is an infrequent occurrence in patients with stage I–II breast cancer. Three series have reported IBTR rates of 36–40% in these patients (30–32). The increased risk has been associated with both multifocal and multicentric disease and appears not to be diminished for lesions in close proximity to each other (31). Pathologic studies of similar patients treated by mastectomy have demonstrated a significant residual tumor burden following excision. In the series reported by Fowble et al. (33), residual disease was identified in two or more quadrants of the breast in 46% of the 57 mastectomy specimens examined.

Several recent studies have demonstrated that patients with microscopically positive resection margins (i.e. invasive cancer or ductal carcinoma in situ at the inked margin) have a two- to threefold increased risk of IBTR at 10 years (8, 34–37). The magnitude of the risk varies and has been correlated with patient age, histology, the extent of the margin positivity therapy (Table 3). Young women with positive margins have been reported to have a 22% and 27% IBTR rate at 10 years (35, 38). Gage et al. (39) reported a 27% 5-year crude breast recurrence in patients with positive margins with an extensive intraductal component (EIC) compared with 12% for EIC negative tumors with positive margins. Patients with EIC positive tumors have been noted to have a significant residual tumor burden despite gross excision. Holland et al. (40) reported that EIC positive tumors were more likely to have residual disease (primarily ductal carcinoma in situ) and disease at a greater distance from the primary than EIC negative tumors. Patients with invasive lobular cancers and positive margins have been reported to have a 40% IBTR rate (41). Diffuse margin involvement (i.e. > 3 lower power fields) has been associated with a 27% 8-year crude breast recurrence rate (42). DiBiase et al. (37) reported a 10-year actuarial IBTR rate of 26% for a single positive margin compared with 37% for 2 or more positive margins. In the Dana Farber Cancer Center randomized trial evaluating the sequencing of chemotherapy and radiation, patients with positive margins who received chemotherapy first had a 5-year crude breast recurrence rate of 26% (43).

Therefore, patients who appear to have a substantial risk of ipsilateral breast tumor recurrence despite radiation include those with clinically evident gross multifocal or multicentric disease, or patients with positive resection margins who are young or who have an EIC positive tumor or an invasive lobular cancer or have received adjuvant chemotherapy prior to radiation. DiBiase et al.

Table 1

Results of prospective randomized trials comparing conservative surgery and radiation (BCT) with mastectomy (M)

Trial	No. patients.	Stage	Surgery for primary	Percentage local recurrence		Interval reported years
				BCT	M	
Milan I (4, 5, 71)	701	I	Q, RM	7	4	18
IGR (1)	179	I	WE, MRM	9	14	15
NSABP B06 (3)	1 219	I–II	WE, MRM	10	8	12
NCI (7)	237	I–II	LE, MRM	16	6	10
EORTC (6)	874	I–II	LE, MRM	13	9	8
DBCG (2)	904	I–III	WE, Q, MRM	5	6	6

Abbreviations: IGR = Institut Gustave-Roussy; NSABP = National Surgical Adjuvant Breast and Bowel Project; NCI = National Cancer Institute; EORTC = European Organization for Research and Treatment of Cancer; DBCG = Danish Breast Cancer Group; Q = quadrantectomy; RM = radical mastectomy; MRM = modified radical mastectomy; LE = local excision; WE = wide excision with negative margins.

Table 2

Results of retrospective series—Ipsilateral breast tumor recurrence rates following conservative surgery and radiation at 5, 10 and 15 years

Reference	No. patients	Percentage breast recurrence		
		5-yr	10-yr	15-yr
Kini et al. (11)	400	4	10	
Pierce et al. (72)	429	4	9	
Clarke et al. (60)	436	5	7	
Leung et al. (73)	493		10	
Stotter et al. (56)	490	9	19	
Halverson et al. (74)	511	6	14	
Fowble et al. (75)	697	8	18	
Cowen et al. (67)	756	7	18	
Haffty et al. (58)	973	6	16	
Mansfield et al. (76)	1 070	7	14	
Clark et al. (77)	1 130	10	14	
Veronesi et al. (12)	1 232	4	8	
Elkhuizen et al. (17)	1 360	8	12	
Grosse et al. (78)	3 072	5	10	
Pierquin et al. (79)				
T1	99	3	8	8
T2	235	6	7	12
Fourquet et al. (24)	518	7	11	18
Dalberg et al. (80)	667	4	10	18
Harris (81)	811	10	17	23
Kurtz et al. (54)	1 593	7	14	18

(37) reported that the increased risk of IBTR in patients with positive margins translated into a statistically significant decrease in 10-year disease-free and overall survival when compared with negative margin patients.

RESULTS OF PROSPECTIVE RANDOMIZED TRIALS COMPARING CONSERVATIVE SURGERY WITH OR WITHOUT RADIATION

In six prospective randomized trials the role of radiation following breast-conserving surgery in women with stage I–II breast cancer was evaluated. The results in terms of IBTR recurrence rates are presented in Tables 4 and 5. For T1 node-negative breast cancer, IBTR rates at 5 years are 12–18% without radiation and 2% with radiation (4, 5, 44, 45). For primary tumors <4 to 5 cm with negative axillary nodes, breast recurrence rates without radiation range from 21 to 40% and with radiation 4 to 18% (3, 46–48). For axillary node-positive patients receiving adjuvant chemotherapy and no radiation, breast recurrence rates range from 27 to 42% compared with 4 to 20% with radiation (3, 4, 47, 48). These trials have identified women at greatest risk for an IBTR without radiation as those with an extensive intraductal component (4), intralymphatic extension (15), estrogen receptor negative (47), close (≤ 2 mm) margins (48), and positive axillary nodes (3, 4, 47, 48). For each of the trials the addition of radiation resulted in a significant decrease in IBTR rates. The absolute improvement in local control ranged from 10 to 36% (Table 6). These trials, therefore, compared effective versus less effective local treatments.

The survival results of the trials are presented in Table 6. The absolute improvement in overall survival ranges from 0 to 4% for all patients, from 1 to 4% for axillary node-negative patients and 8% for the single trial which reported results for axillary node-positive women.

THE SIGNIFICANCE OF AN IBTR IN RELATIONSHIP TO SURVIVAL

The absence of a statistically significant survival benefit in the trials comparing conservative surgery with or without radiation has again been interpreted as additional evidence that variations in local-regional breast cancer treatment will not impact on ultimate outcome. However, the majority of these trials did demonstrate a modest survival benefit with the improvement in local-regional control achieved with radiation. For the most part, the lack of

Table 3

Clinical and pathologic factors associated with a significant risk of ipsilateral breast tumor recurrence (IBTR) in patients with positive margins

Factor	IBTR		Interval reported yrs
Young age	$\leq$40 yrs	$>$40 yrs	10
Dewar et al. (35)	22%	11%	
	$\leq$45 yrs	$>$45 yrs	10
Wazer et al. (38)	27	13	
Pathology			
EIC	Yes	No	
Gage et al. (39)	27%	12%	5 crude
Invasive lobular			
Bouvet et al. (41)	40%	–	5 act.
Extent of margin positivity			
	Diffuse	Focal	8 crude
Park et al. (42)	27%	14%	
	$\geq$2 margins	1 margin	10 act.
DiBiase et al. (37)	37%	26%	

Table 4

Results of prospective randomized trials comparing conservative surgery with or without radiation for axillary node-negative patients

	Primary size (cm)	Surgery	Percentage IBTR		Interval reported yrs
			No XRT	XRT	
Swedish (44)	≤2	Q	18 (197)	2 (184)	5 act.
Milan III (5, 45)	<2.5	Q	12 (273)	2 (294)	3 act.
NSABP B06 (3, 4)	<4	WE	33 (361)	13 (375)	12 act.
Ontario (46)	<4	WE	40 (421)	18 (416)	10 act.
Scottish (47)	≤4	WE	21 (212)	4 (230)	5.7 med.
British (48)	≤5	WE	32 (125)	9 (148)	5

( ) no. pts.

Table 5

Results of prospective randomized trials comparing conservative surgery and chemotherapy with or without radiation for axillary node-positive patients

	Chemo	Primary size (cm)	Surgery for primary	Percentage IBTR		Interval reported yrs
				Chemo	Chemo+XRT	
Milan III (4)	CMF	<2.5	Q	27 (91)	4 (92)	3 act.
NSABP B06 (3)	Alk, 5-FU	<4	WE	42 (209)	6 (192)	12 act.
Scottish* (47)	CMF	≤4	WE	38 (70)	9 (63)	5.7 med.
British (48)	CMF	≤5	WE	39 (66)	20 (76)	5

* Includes node-negative.
( ) no. pts.
Abbreviations: C = cyclophosphamide; M = methotrexate; Alk = alkeran; 5-FU = 5-fluorouracil.

Table 6

Results prospective randomized trials comparing conservative surgery with and without radiation

	Percentage absolute improvement local control			Interval reported yrs
	With radiation	Survival (%)		
		CS	CS+XRT	
All patients				
Milan III (4)	+16	92	92	5 act.
NSABP B06 (3)	+25	58	62	12 act.
Scottish (47)	+18	85	88	5.7 med.
Node-negative				
Swedish (44)	+16	90	91	5 act.
Milan III (45)	+10	95	98	3 act.
NSABP B06 (3)	+20	74	78	10 act.
Ontario (46)	+22	72	74	10 act.
Node-positive				
NSABP B06 (70)	+36	62	70	8 act.

statistical significance reflects inadequate patient numbers resulting in insufficient power to detect these modest differences.

The potential for a survival benefit with an improvement in local control is illustrated by the schema in Fig. 1. An ipsilateral breast tumor recurrence that is salvaged with subsequent treatment will not adversely affect survival (pattern A). Similarly, patients who develop a local failure in association with distant metastases (pattern B) will have their survival influenced by the distant disease rather than

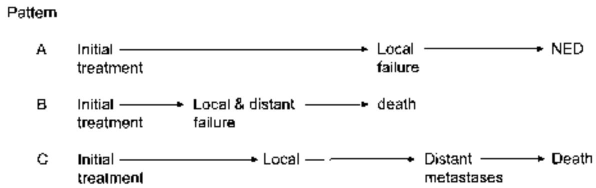

Fig. 1. Patterns of initial local failure.

the local failure. Pattern B supports the concept of a local failure as a marker for established distant disease (49). The prevention of a local failure that subsequently results in fatal distant metastases has the sole potential for a survival benefit (pattern C), with improved local treatment. Pattern C supports the argument for a causal relationship between local failure and distant metastases.

Several studies have evaluated the prognosis of an ipsilateral breast tumor recurrence. Six to 14% percent of all patients who develop an IBTR will have simultaneous distant metastases (pattern B) (19, 24, 50–57). Factors which correlate with this pattern of failure are not well defined but would logically include those that are associated with an increased risk of initial distant metastases, i.e., large primary tumor size and positive axillary nodes. Gage et al. (50) reported that 44% of patients whose IBTR manifested as a skin recurrence had distant metastases either simultaneously or within 2 months compared with 5% of the patients with a parenchymal breast recurrence. Patients with a skin recurrence usually had a larger primary tumor, lymphatic invasion, positive axillary nodes with extracapsular extension, and a shorter interval to failure. The median time to failure for patients with a skin recurrence was 3.2 years compared with 5 years for a parenchymal recurrence.

Table 7

Survival following salvage surgery for isolated ipsilateral breast tumor recurrence

	No. patients	5-yr survival (DFS) %
Clark et al. (60)	11	81
Calle et al. (82)	20	75
Kemperman et al. (83)	28	66
Dubois et al. (84)	30	70
Osborne et al. (59)	46	76 (54)
Stotter et al. (56)	49	63
Fowble et al. (70)	52	84 (59)
Cowen et al. (67)	61	67
Elkhuizen et al. (17)	68	64
Haffty et al. (58)	73	76
Grosse et al. (78)	85	61
Clark et al. (77)	87	55
Abner et al. (55)	123	79 (59)
Veronesi et al. (69)	151	69
Kurtz et al. (54)	159	69
Giard et al. (85)	193	85

DFS = disease-free survival.

Five-year survival rates following salvage surgery for an isolated breast recurrence in patients whose initial treatment included radiation are presented in Table 7. It appears that overall 30–40% of these patients will develop fatal distant metastases following a local recurrence. Factors which correlate with successful salvage of an IBTR (pattern A) include a long interval to failure, initial T1 tumor, negative axillary nodes, localized recurrence without skin involvement, and a recurrence in a location separate from the original primary, and one which is non-invasive, i.e. ductal carcinoma in situ (24, 51, 54, 55, 58–63). Information regarding surgical salvage of a breast recurrence following conservative surgery alone is limited. Subsequent distant metastases have reportedly ranged from 0 to 48% (64–66).

The development of distant metastases subsequent to an isolated IBTR (pattern C) has been correlated with the interval to failure, young age, initial T2 tumor size, initial positive axillary nodes, and the extent of the recurrence (17, 19, 53, 55, 56, 63, 67). Sixty percent of patients whose IBTR appears within 2 years of initial treatment have been reported to develop distant metastases compared with 27–38% after 2 years (49, 53). In contrast, only 16–18% of patients whose interval to IBTR is beyond 5 years developed distant metastases compared with 44–47% before 5 years (1, 49, 58).

Factors that correlate with an earlier pattern of IBTR and therefore reflect a greater likelihood of subsequent distant metastases include young age, a recurrence in the vicinity of the original primary, the presence of skin involvement, a diffuse recurrence, high histologic grade, and the presence of lymphatic or vascular invasion (19, 50, 54, 57, 68, 69). Factors that correlate with a later pattern of IBTR and therefore fewer subsequent distant metastases include initial T1 primary tumor size, axillary node-negative and location of the recurrence distinct from the original primary (54, 58, 62).

Several series have analyzed factors that are predictors for a local failure, distant or both, primarily in axillary node-negative patterns with negative margins (52, 67, 69). The presence of an extensive intraductal component has been associated with an increased risk of IBTR but not distant metastases (52, 69). In two series, young age has been found to predict for both a local and a distant failure (67, 69). In one series the presence of lymphatic invasion correlated with both a local and a distant failure (69). Tumor multifocality has predicted for an increased risk of IBTR in two series (52, 67) but distant metastases in one (67). Tumor size, positive axillary nodes, and an IBTR have been the primary predictors for distant metastases (52, 67, 69).

Therefore, patients who are mostly likely to achieve a survival benefit with an improvement in local control with radiation following breast conservation surgery (pattern C) are those who experience a recurrence within 2–5 years after treatment, are young, have T2 primary tumors, and limited or no axillary node involvement. It should be noted that these patients have a 30–40% IBTR rate in the absence of radiation (3, 4, 15, 47, 48). The addition of radiation reduces this rate to approximately 10%. Since overall 10% of patients who experience a breast recurrence will have simultaneous distant metastases (pattern B), 30% will develop a distant failure after a local recurrence (pattern C), and 60% will be salvaged (pattern A); the survival benefit that could be anticipated from a 20–30% absolute improvement in local control would be 6–9%, i.e., 30% of the difference in local control (pattern C). A survival benefit with radiation of this magnitude was observed in NSABP B06 in the axillary node-positive patients but was probably not statistically significant because of inadequate patient numbers (70). The trials evaluating radiation following conservative surgery for T1 pathologically node-negative breast cancer would be expected to have a smaller absolute survival benefit since these patients have a lower initial IBTR rate, and following such a recurrence are more likely to be salvaged (pattern A) and less likely to develop subsequent distant metastases (pattern C). For example, in the Milan III or Uppsala–Örebro trials, the 10–16% absolute improvement in local control would translate into an estimated survival benefit of 2–4% since only 25% of these patients would be expected to develop distant metastases after a local failure (53, 67). At 3 and 5 years the actual improvement in overall survival reported by these trials was 3% and 1%, respectively (Table 6). As the period of observation increases, the survival benefit will also increase, since the appearance of distant metastases and subsequent death after an initial isolated local failure may require years to become evident.

For patients whose risk of an IBTR is in the range of 30–40% despite radiation, mastectomy has the potential for a survival benefit if this procedure results in a significant reduction in the risk of a local recurrence. This has been demonstrated for patients with gross multicentric disease (33) and those with an extensive intraductal component (71). As previously noted, DiBiase et al. (37) reported a 10-year actuarial IBTR rate and overall survival of 13% and 84% for patients with negative margins treated with conservative surgery and radiation compared with 31% and 78% for those with positive margins. There were no statistically significant differences between the two groups for axillary nodal positivity or the risk of adjuvant chemotherapy or hormonal therapy. This study provides further evidence for a significant adverse effect on survival when IBTR rates approach 30%, despite radiation. In a recent study of 2030 patients treated with conservative surgery and radiation, close or positive surgical margins were significant predictors for decreased local control and survival (63). For young women, an increased risk of local recurrence has been observed following either mastectomy or conservative surgery and radiation.

SUMMARY

For most patients the risk of an IBTR following conservative surgery and radiation is in the range of 10–15% at 10 years and is equal to the risk of a chest wall recurrence following mastectomy. However, certain patients have been found to have a significant risk of IBTR despite radiation, and mastectomy may diminish this risk and result in an improved survival. The omission of radiation after conservative surgery for stage I–II breast cancer results in a significantly increased risk of IBTR which approximates 30–40% in patients with T2 tumors, lymphatic invasion, or positive axillary nodes. The prevention of an IBTR in these patterns has the potential for a 6–9% improvement in survival. For patients with T1 node-negative tumors the expected survival benefit with improved local control would be less than 5%. These estimates are based on patterns of initial local failure and the potential for distant metastases occurring synchronously, metachronously, or not at all. Regardless of any survival benefit, it can be argued that efforts should be directed to minimize the risk of an IBTR in order to avoid the psychological impact of such a recurrence and the need for salvage mastectomy.

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