The impact of margin status on local recurrence following breast conserving therapy for invasive carcinoma in Manitoba

by

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A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

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Abstract

Objective: The purpose of this research was: 1) to understand the relationship between margin status and local recurrence (LR) through a systematic review; 2) to determine the significance of margin status as a predictor of LR in Manitoba women with invasive breast cancer.

Methods: Results of the systematic review were presented descriptively and combined in a meta-analysis. A case-control analysis was performed using the Manitoba Cancer Registry between 1995 and 2004.

Results: From 22 studies in the systematic review, 8 of 11 comparing microscopically positive versus negative and 3 of 10 studies comparing close ($\leq$ 1, 2 or 3 mm) versus wider negative margins demonstrated an increased risk of LR for the smaller margin. In the meta-analysis, positive versus negative margins and close $\leq$ 2 mm versus > 2 mm margins were associated with a significantly increased risk of LR, odds ratio (OR) 3.0 (95% confidence interval [CI] 2.0 - 4.4) and OR 3.6 (95% CI 1.8 - 6.9), respectively. In contrast, close $\leq$ 1 mm margins were equivalent to > 1 mm margins, OR 1.2 (95% CI 0.5 - 2.7). In the case-control study, there were 50 cases of LR from 3017 patients who underwent BCT (median follow-up 60 months). Wider margins > 1 mm versus $\leq$ 1 mm and > 2 mm versus $\leq$ 2 mm were associated with a non-significant reduction in LR, OR 0.69 (95% CI 0.28 – 1.69) and OR 0.90 (95% CI 0.44 to 1.84), respectively.

Conclusions: The systematic review of the literature does not clearly support a margin greater than histologically negative. Similarly, the case-control study demonstrates that wider margins are not associated with a significant reduction in LR for Manitoba women with invasive breast cancer.

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Chapter 1: Literature Review

Epidemiology of Breast Cancer

Breast cancer is the most common cancer among Canadian women. One in nine women will be diagnosed with breast cancer in her lifetime. In 2007, it is estimated that 22 000 women will be diagnosed with breast cancer and more than 5 000 will die of this disease (Canadian Cancer Society, 2007). Breast cancer is second only to lung cancer as a cause of cancer death in women.

In Canada, the incidence of breast cancer increased by 1% per year from 1969 to 1999, or 30% over 30 years (Canadian Cancer Society, 2007). More recently the incidence of breast cancer has stabilized. With increasing participation in screening mammography and new advances in adjuvant therapy, there has also been a decline in breast cancer mortality. The age standardized mortality rate for breast cancer has fallen 25% since 1986 from 32 to 24.1 per 100 000 (Canadian Cancer Society, 2007).

The five-year relative survival for breast cancer diagnosed between 1996 and 1998 is 86% in Canada, excluding Quebec (Canadian Cancer Society, 2007). However, the five-year survival is only 79% for women under the age of 40 due to the more aggressive nature of breast cancer in young women. Because recurrences continue to present for many years following initial treatment, relative survival declines to 70% at 20 years (Canadian Cancer Society, 2007).

Risk factors for breast cancer can be considered in modifiable and non-modifiable categories. Non-modifiable risk factors include gender, age, family history of breast or ovarian cancer, BRCA1 or BRCA2 genetic mutations, personal history of breast cancer, race, previous abnormal breast biopsy, early onset of menses,

late menopause and previous chest irradiation (American Cancer Society, 2007 & Canadian Cancer Society, 2007). Modifiable risk factors include late age of first child bearing, combined estrogen and progesterone hormone replacement therapy, alcohol, and oral contraceptive use (Canadian Cancer Society, 2007). More controversial risk factors include smoking, diet, obesity and lack of physical activity (Canadian Cancer Society, 2007).

Breast Cancer Treatment

The management of breast cancer mandates a multidisciplinary approach with the expertise of surgical, medical and radiation oncology. When a patient presents with a newly detected breast lesion, a tissue diagnosis is usually sought prior to definitive surgery. Ultrasound or mammographic-guided core biopsy may confirm the diagnosis of invasive carcinoma and assist in treatment planning. Surgical exicision is the initial treatment of choice for women with early breast cancer. For patients with a diagnosis of invasive carcinoma on preoperative biopsy, lymph node staging is offered in the form of an axillary lymph node dissection or sentinel lymph node biopsy. Metastatic work-up generally consists of a chest radiograph and liver function tests. Bone scans and other investigations are performed as directed. Radiotherapy is incorporated into postoperative treatment for local tumor control. Chemotherapy and hormonal therapy are incorporated into the adjuvant treatment plan as indicated.

Breast Conserving Therapy versus Mastectomy

Breast conserving therapy (BCT) involves "the 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 (Schwartz et al., 2006)." With the widespread implementation of screening mammography, breast cancers are now detected at an earlier stage and are more often amenable to conservative surgery. BCT is considered a standard of care in the management of early invasive breast cancer. Six major randomized trials (Arriagada et al., 2003; Blichert-Toft et al., 1992; B. Fisher et al., 2002; Poggi et al., 2003; van Dongen et al., 2000; Veronesi et al., 2002) and a meta-analysis (Morris et al., 1997) have demonstrated equivalent disease-free and overall survival for BCT versus mastectomy in early breast cancer (Table 1). A comprehensive review by the Early Breast Cancer Trialists' Collaborative Group has also demonstrated equivalent survival for BCT (Early Breast Cancer Trialists' Collaborative Group, 1995). In 1990, the National Institute of Health Consensus Conference on Breast Cancer concluded that breast conserving surgery followed by radiotherapy is the preferred method of treatment for Stage I or II breast cancer (NIH, 1991).

Table 1. Local recurrence rate and overall survival from the randomized controlled trials of mastectomy versus BCT.

Study	Total Years	Segmental Margin Requirement	Intervention	No. Pts	LR (%)	DFS (%)	OS (%)	P value
Fisher et al. (NSABP-06*)	20	No tumor at inked margins	BCS BCS + RT TM	634 628 589	39.2 14.3 9	- - -	46 46 47	NS
Poggi et al. (NCI‡)	18	Grossly clear margins, micro negative not required	BCS + RT TM	121 116	26 7	63 67	54 58	NS
Arriagada et al. (Institut Gustave-Roussy)	22	2 cm margin around the lumpectomy	BCS + RT TM	88 91	16 10	- -	60 49	NS
Veronesi et al. (Milan)	20	2-3 cm margin and overlying skin & fascia	BCS + RT TM	352 349	8.8 2.3	- -	41.7 41.2	1.0
Van Dongen et al. (EORTC#)	10	1 cm margin, micro positive not excluded	BCS + RT TM	466 436	20 12	- -	65 66	0.11
Blichert-Toft et al. (Denmark)	6	Grossly clear margins	BCS + RT TM	430 429	4 3	70 66	79 82	NS

* NSABP – National Surgical Adjuvant Breast and Bowel
‡ NCI – National Cancer Institute
 # EORTC – European Organization for Research and Treatment of Cancer

Local Recurrence

The aim of BCT is to obtain adequate local control and satisfactory cosmesis without compromising overall survival (NIH, 1991). Many early breast cancers are amenable to BCT. The decision to pursue breast conservation involves consideration of surgical factors as well as patient preference. There is general consensus that tumors up to three centimeters in diameter can be managed with BCT, while larger tumors up to four or five centimeters may be treated with BCT if an acceptable cosmetic outcome can be achieved. Excision of large tumors and central lesions may require the application of oncoplastic procedures. In this case, plastic surgery techniques are used to remodel the conserved breast and achieve acceptable symmetry with the contralateral breast.

Historical studies examining mastectomy specimens have demonstrated the presence of tumor deposits several centimeters away from the primary breast lesion

(Carter, 1986; Holland, Veling, Mravunac, & Hendriks, 1985; Rosen, Fracchia, Urban, Schottenfeld, & Robbins, 1975). Because breast tumors are discontinuous in nature, there remains a definite risk of local recurrence within the residual breast following conservative surgery. The local recurrence rate following BCT is reported as approximately 1% per year (B. Fisher et al., 1991). In the NSABP B-06 trial, patients were randomized to mastectomy or breast conserving surgery with or without adjuvant radiotherapy. The local recurrence rate for the breast conserving surgery and radiotherapy arm was 10% at 12 years (B. Fisher et al., 1995) and 14.3 % at 20 years (B. Fisher et al., 2002). In contrast, the rate of local recurrence following mastectomy was only 3 to 5% at 10 years and 9% at 20 years (B. Fisher et al., 2002; B. Fisher et al., 1985).

At the time of diagnosis, 80% of local recurrences are invasive and 20% are non-invasive (Doyle, Schultz, Peters, Harris, & Solin, 2001). Local recurrence may present as a palpable mass detected by the patient or physician. Alternatively, it may present as mammographically detected calcifications. In a review by Dershaw et al., 42% of local recurrences were detected mammographically, 33% were detected by physical examination alone and 25% were discovered by both techniques (Dershaw, McCormick, & Osborne, 1992). Although postoperative surveillance mammography may be less sensitive at recognizing new lesions as a result of post-surgical and radiation changes (Dershaw, McCormick, Cox, & Osborne, 1990; Dershaw, Shank, & Reisinger, 1987), recurrences detected solely by mammography tend to be smaller (Orel et al., 1993) and are more likely to be non-invasive (72% of

mammographically detected lesions are noninvasive versus 7% of clinically detected lesions) (Dershaw, McCormick, & Osborne, 1992; Orel et al., 1993).

True local recurrences usually occur in the same quadrant of the breast as the primary tumor and are thought to represent inadequate excision of the primary lesion. In contrast, new primary tumors tend to present later and are frequently discovered in other quadrants of the breast (Fowble, Solin, Schultz, Rubenstein, & Goodman, 1990; Kurtz, Amalric et al., 1989). Kurtz et al. have demonstrated that 86% of recurrences within 5 years are located at the original tumor site and 75% of recurrences within 5 to 10 years are at the original site. In contrast, only 36% of recurrences are at the original site after 10 years (Kurtz, Amalric et al., 1989; Kurtz et al., 1987; Kurtz, Spitalier et al., 1990).

Histology and DNA analysis have been studied in an attempt to distinguish new primaries from true local recurrence. Haffty et al. reviewed 80 cases of local recurrence on the basis of tumor location, histology and DNA flow cytometry (Haffty et al., 1993). In this series, 59% of cases were classified as residual disease and 41% were classified as new primaries. The disease free interval was significantly shorter for recurrence due to residual disease than for new primaries.

Clinical Significance of Local Recurrence

Local recurrence following BCT is a significant event for the patient, associated with psychological morbidity and the stress of further surgery. While chest wall recurrence following mastectomy is an ominous event that is often followed by systemic disease, local recurrence following BCT is more frequently a limited event that can be successfully treated with additional surgery in the form of

mastectomy. Only 10% of patients with local recurrence will present with concurrent metastatic disease (Fowble, Solin, Schultz, Rubenstein, & Goodman, 1990; Kurtz, Jacquemier et al., 1989).

Some experts have argued for a causal relationship between local recurrence and distant metastases, while others have suggested that local recurrence is simply a marker of more aggressive disease. If local recurrence is a marker for developing distant disease rather than an actual cause, then the risk of metastases is predetermined regardless of treatment and the local recurrence event is simply a manifestation of this risk (Macmillan, Purushotham, & George, 1996). Alternatively, if local recurrence does lead to distant disease, then reducing the rate of local recurrence with various treatment approaches, including radiation, should result in a reduction in mortality. While the individual randomized trials of post-lumpectomy radiotherapy failed to demonstrate a mortality reduction associated with adjuvant radiotherapy, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group demonstrated a 5% reduction in breast cancer mortality and overall mortality with adjuvant radiotherapy (Clarke et al., 2005).

The overall prognostic significance of local recurrence remains controversial. The randomized trials of BCT versus mastectomy failed to demonstrate a statistical difference in distant metastases or overall survival, despite a significantly higher rate of local recurrence for BCT (Arriagada et al., 2003; Blichert-Toft et al., 1992; B. Fisher et al., 2002; Poggi et al., 2003; van Dongen et al., 2000; Veronesi et al., 2002). However, in further sub-analysis of the NSABP B-06 trial, local recurrence following BCT was associated with an increased risk of distant metastases (B. Fisher et al.,

1991). After nine years of follow-up, patients with local recurrence had a relative risk of developing distant metastases of 3.41 (B. Fisher et al., 1991). Based on the Milan quadrantectomy data, Veronesi also reported a hazard ratio for distant disease of 4.62 in patients with local recurrence (Veronesi et al., 1995). Decreased time to local recurrence predicted an increased risk of subsequent metastatic disease. Other nonrandomized studies have also demonstrated a reduction in distant disease-free and overall survival for local recurrence (Abner et al., 1993; della Rovere & Benson, 2002; B. Fisher et al., 1991; Fortin, Larochelle, Laverdiere, Lavertu, & Tremblay, 1999; Fowble, 1999; G. M. Freedman & Fowble, 2000; Haffty, Fischer, Beinfield, & McKhann, 1991; Haffty et al., 1996; Kemperman et al., 1995; Kurtz, Spitalier et al., 1990; Meric et al., 2003; Stotter et al., 1990; Touboul et al., 1999; Vicini, Kestin, Huang, & Martinez, 2003; Whelan, Clark, Roberts, Levine, & Foster, 1994).

Fortin reviewed a series of 2 030 patients undergoing BCT. The relative risk associated with local recurrence was 5.1 for developing distant metastases and 3.6 for mortality. In patients with local recurrence, the rate of distant metastases peaked at 5 to 6 years. In contrast, the rate of distant metastases peaked at 2 years for patients without local recurrence (Fortin, Larochelle, Laverdiere, Lavertu, & Tremblay, 1999). Fortin proposed that this difference in time to distant metastases reflected an etiologic role for local recurrence. He argued that the time to distant disease would be the same between groups if local recurrence was a marker and not a cause of distant metastases (Fortin, Larochelle, Laverdiere, Lavertu, & Tremblay, 1999).

Several studies have demonstrated that a shorter disease free interval is associated with a reduction in overall survival. Brooks et al. analyzed the 18-year

data from the National Cancer Institute trial of BCT versus mastectomy (Brooks et al., 2005). Local recurrence within 5.3 years was associated with an increased hazard of death, while local recurrence after 5.3 years had survival equivalent to no local recurrence. Other groups have demonstrated lower distant disease-free survival (Elkhuizen, Hermans, Leer, & van d, 2001; Fourquet et al., 1989; Fredriksson et al., 2002; G. M. Freedman & Fowble, 2000; Haffty et al., 1996; Komoike et al., 2006; Kurtz, Spitalier et al., 1990; Le, Arriagada, Spielmann, Guinebretiere, & Rochard, 2002; Schmoor, Sauerbrei, Bastert, & Schumacher, 2000; Touboul et al., 1999; van der Sangen et al., 2006; Veronesi et al., 1995) and overall survival for earlier local recurrence (Doyle, Schultz, Peters, Harris, & Solin, 2001).

The randomized trials of postmastectomy radiotherapy in addition to chemotherapy provide strong causal evidence for a relationship between local recurrence and mortality. In the Danish pre-menopausal study (Overgaard et al., 1997), 1 708 women with Stage II or III invasive breast cancer were randomized to adjuvant chemotherapy plus chest wall irradiation or chemotherapy alone. There was a significant reduction in locoregional recurrence with radiation from 32% to 9%. Multivariate analysis demonstrated that chest wall irradiation after mastectomy significantly improved disease-free survival and overall survival, regardless of tumor size, number of positive nodes or histopathological grade. In the British Columbia trial (Ragaz et al., 2005), 318 patients were randomized to adjuvant chemotherapy with or without chest wall irradiation. After 20 years of follow-up, 90% of patients who received radiation were free from locoregional recurrence while only 74% of those who did not receive radiation were free from recurrence. There was significant

improvement in overall survival with radiation from 37% to 47%. The results of the postmastectomy radiotherapy trials support the theory of a causal relationship between local recurrence and mortality. As such, postmastectomy radiotherapy is now considered standard of care for high-risk patients.

Management of Local Recurrence

Most patients that experience a local recurrence following BCT undergo a mastectomy for management of the local disease. An extensive work-up is performed to rule out evidence of metastatic disease and consideration is given towards adjuvant therapy. While patients occasionally undergo a second BCT procedure for local recurrence, this is not viewed as the standard surgical option. Most patients have received adjuvant radiotherapy as part of their initial breast conservation, precluding the use of further radiotherapy following re-excision.

Margin Status

Margin status is consistently identified as one of the most important prognostic factors related to local recurrence (Huston & Simmons, 2005). The 2007 National Comprehensive Cancer Network guidelines from the United States require the following for optimal margin evaluation: orientation of the surgical specimen, description of the gross and microscopic margin status and reporting of the distance, orientation and type of tumor (invasive or ductal carcinoma in situ) in relation to the closest margin (NCCN, 2007).

Surgical margins are histologically classified as positive, close or negative. Positive margins may be further classified according to the extent of positivity as

focally, minimally, moderately or extensively positive. Recent series in the literature report a positive margin rate as high as 11 to 22% (DiBiase, Komarnicky, Heron, Schwartz, & Mansfield, 2002; Horiguchi et al., 1999; Jobsen, van der Palen, Ong, & Meerwaldt, 2003). Certain tumor characteristics have been associated with an increased risk of positive margins. These risk factors include increased tumor size (Luu, Otis, Reed, Garb, & Frank, 1999; Park et al., 2000; Peterson, Schultz, Reynolds, & Solin, 1999; Tartter et al., 2000), positive nodal status (Obedian & Haffty, 2000; Park et al., 2000; Peterson, Schultz, Reynolds, & Solin, 1999), young age (Obedian & Haffty, 2000; Tartter et al., 2000), family history (Tartter et al., 2000), the presence of extensive intra-ductal component (EIC) (Luu, Otis, Reed, Garb, & Frank, 1999; Park et al., 2000; Tartter et al., 2000), lymphovascular invasion (Borger et al., 1994; Park et al., 2000) and the presence of DCIS (Borger et al., 1994; Luu, Otis, Reed, Garb, & Frank, 1999; Tartter et al., 2000).

Several studies have demonstrated that positive margins predict the presence of residual carcinoma at re-excision (Cellini et al., 2005; Gwin et al., 1993; Kearney & Morrow, 1995; Papa et al., 1999; Scopa, Aroukatos, Tsamandas, & Aletra, 2006; Swanson, Rynearson, & Symmonds, 2002). Darvishian et al. correlated the findings on re-excision with the microscopic linear extent of positive margins on lumpectomy specimens (Darvishian, Hajdu, & DeRisi, 2003). These researchers found that positive linear margins greater than one centimeter on initial lumpectomy predicted findings of residual carcinoma at re-excision. Dillon et al. analyzed the presence of residual carcinoma according to the initial margin width (Dillon, Hill, Quinn, McDermott, & O'Higgins, 2006). Residual disease was present in 58%, 56% and

45% of patients with margin width < 1 mm, ≥ 1 mm to < 2mm, and ≥ 2 mm to < 5 mm, respectively. Wazer et al. demonstrated that moderate or extensively positive margins are associated with an increased risk of local recurrence compared to focally or minimally positive margins (Wazer et al., 1999). A retrospective review by Menes et al. (Menes et al., 2005) also confirmed that the number of excisions required to achieve negative histologic margins was associated with an increased risk of local recurrence.

A descriptive overview of margin status in invasive breast cancer by Klimberg et al. (Klimberg, Harms, & Korourian, 1999) concluded that most studies, although small and retrospective, favor obtaining negative margins when possible. Positive margins are not simply a risk factor for local recurrence. In some studies, they are also associated with an increased risk of systemic metastases and decreased disease-specific survival (DiBiase, Komarnicky, Heron, Schwartz, & Mansfield, 2002; Meric et al., 2003; Voogd et al., 2001).

Some institutions employ a pathologic category of close margins. While the definition of a close margin varies considerably, the most common definition in the literature appears to be two millimeters. The clinical significance of close surgical margins remains unclear. Breast cancers are not perfect spheres and the invasive or in situ disease often extends beyond the borders of the macroscopic tumor. Holland analyzed the extent of disease in the mastectomy specimens of 282 patients considered to be candidates for breast conserving surgery (Holland, Veling, Mravunac, & Hendriks, 1985). In this classic study, serial sections demonstrated invasive or in situ disease in 59% of patients one centimeter from the macroscopic

tumor edge, in 42% at two centimeters, in 17% at three centimeters and 10% at four centimeters. Other studies have demonstrated that limited excision may leave behind a considerable burden of tumor (Ghossein et al., 1992; Holland et al., 1990).

Not all experts advocate achieving widely negative margins of excision for invasive breast cancer. Several of the randomized trials of BCT required negative gross margins but did not require negative microscopic margins. These trials failed to detect a difference in disease-free or overall survival (Blichert-Toft et al., 1992; Jacobson et al., 1995; van Dongen et al., 2000). Cota et al. (Cota et al., 2005) reported a case series of breast conservation in which 54.3% of patients had close margins less than 2 millimeters. The overall local recurrence rate for the entire cohort at 5 and 10 years was 3.5% and 4.1%, respectively. A number of these patients received a 9 Gy boost to the tumor bed, which may have contributed to the low rate of local recurrence.

In a review of margin status by Singletary, 30 of the 34 studies demonstrated that a persistently positive margin was associated with an increased risk of local recurrence (Singletary, 2002). This relationship also held true for subgroup comparisons of negative versus positive, greater than one millimeter versus positive and greater than two millimeters versus positive margins. In the descriptive comparison, there was no obvious difference in local recurrence by margin width for close but negative margins, including one millimeter margins (0-7%, median 3%), two millimeter margins (3-10%, median 6%) and microscopically negative not otherwise specified (2-4%, median 2%). Ten studies had a close margin category. In three studies the local recurrence rate for close margins was equivalent to negative, in

four it was intermediate and in two it was equivalent to positive. Singletary concedes that the evidence does not clearly support a reduction in local recurrence with wider negative margins.

Preoperative Margin Assessment

Preoperative investigations may aid in identifying patients at risk for positive margins of resection. Microcalcifications on mammography predict a two fold increased risk of involved margins (Aitken et al., 1990). Mammography may also be used to identifying patients at risk of local recurrence. Lesions in multiple quadrants or diffuse residual calcifications on post-biopsy mammography predict an increased risk of recurrence (Klimberg, Harms, & Korourian, 1999). In some cases, magnification mammography may assist in demonstrating calcifications not visualized on standard mammography (Morrow, Schmidt, & Hassett, 1995).

The diagnosis of invasive cancer by fine needle aspiration (Cox et al., 1995) or core biopsy (King et al., 1998) can reduce the risk of positive margins. Preoperative diagnosis of an invasive component may lead the surgeon to perform a wider resection at the initial surgery. Smitt et al. demonstrated that 52% of women with a preoperative biopsy had negative margins, while only 29% of women undergoing excisional biopsy had negative margins (Smitt & Horst, 2007).

High contrast, high resolution magnetic resonance imaging (MRI) is an evolving technology in the field of breast cancer. MRI can assist in predicting the extent of tumor within the breast. The sensitivity of MRI may be as high as 94% compared to 55% for mammography and it has been shown to correlate well with margin status and the extent of disease on pathologic assessment (Harms, 1998).

Morrow has previously reviewed the literature on breast MRI (Morrow & Freedman, 2006). Some studies have demonstrated additional tumor foci in 11-31% of patients (Bedrosian et al., 2003; Berg et al., 2004; Bluemke et al., 2004; Boetes et al., 1995; Deurloo et al., 2005; Drew et al., 1999; Fischer, Kopka, & Grabbe, 1999; Liberman, Morris, Dershaw, Abramson, & Tan, 2003; Mumtaz et al., 1997; Orel et al., 1995). In contrast, MRI has identified additional tumor in up to 50% of patients with lobular carcinoma (Kneeshaw, Turnbull, Smith, & Drew, 2003; Munot et al., 2002; Quan et al., 2003; Schelfout et al., 2004; Weinstein et al., 2001). It has been suggested that MRI may be more useful in altering the management of lobular carcinoma by identifying those patients that would benefit from mastectomy. However, Morrow and Freedman (2006) argue that published series of BCT have demonstrated equivalent rates of local recurrence for both lobular and ductal carcinoma (Arpino, Bardou, Clark, & Elledge, 2004; Molland et al., 2004; Morrow et al., 2006; Peiro et al., 2000; Santiago, Harris, Qin, Hwang, & Solin, 2005; Weiss, Fowble, Solin, Yeh, & Schultz, 1992; White et al., 1994; Winchester et al., 1998). In the current era of adjuvant radiation and chemoendocrine therapy, local recurrence rates following BCT continue to decline and the clinical utility of the information on pathologic extent of tumor provided by MRI remains unknown. The role of MRI in the preoperative assessment of breast carcinoma continues to evolve.

Intraoperative Margin Assessment

Intraoperative margin assessment has been introduced in an attempt to reduce the incidence of positive margins following BCT. The ideal method of intraoperative assessment must be simple, rapid and affordable in order for it to be adopted into

routine practice. Although a variety of techniques have been evaluated, including gross margin assessment, touch prep cytology and frozen section analysis, these methods have achieved limited success. At present, there is no universally accepted method of intraoperative margin assessment (Lagios & Bennington, 1992).

The simplest intraoperative technique for determining margin status is gross margin assessment. This involves transecting the lumpectomy specimen and visually inspecting it for the absence of gross tumor involvement at the margins. Balch et al. reviewed a series of 255 lumpectomies, including 199 invasive and 56 noninvasive tumors, with intraoperative gross margin assessment (Balch, Mithani, Simpson, & Kelley, 2005). In total, 55% of patients had a re-excision based on positive margins. The final margin was histologically positive for 25% of patients. Balch concluded that this technique of gross intraoperative examination leads to an unacceptably high rate of positive margins. In contrast, Fleming et al. assessed 220 patients undergoing gross margin assessment and found that 21.4% of patients were spared a second operation because of intraoperative re-excision (Fleming et al., 2004). This was determined to be a significant reduction in secondary procedures.

Intraoperative ultrasound and specimen radiography have been employed as a means of achieving negative margins. Although visualization of DCIS calcifications is limited with ultrasound, various series have demonstrated low rates of positive margins employing this technique (Harlow, Krag, Ames, & Weaver, 1999; Moore et al., 2001; Smith, Rubio, Henry-Tillman, Korourian, & Klimberg, 2000; Snider & Morrison, 1999). Ultrasound is also limited by the availability of equipment and operator skill. Intraoperative specimen radiography, which involves imaging of the

entire specimen followed by inking, sectioning and serial imaging of the individual sections, does not ensure negative margins but it may assist in directing intraoperative re-excision (Oakley & Going, 1995).

Shave margins of the biopsy cavity have also been evaluated as a means of detecting residual unexcised breast cancer. DiBiase et al. demonstrated that the number of positive margins on shave biopsy correlated with the risk of local recurrence (DiBiase, Komarnicky, Schwartz, Xie, & Mansfield, 1998). However, the impact of shave margins on cosmesis remains uncharacterized.

Frozen section analysis is one of the most commonly employed techniques of intraoperative margin assessment. The results of frozen section analysis are robust in the hands of some experts. In a large series of 4436 patients undergoing frozen section analysis for breast cancer, there were no false positives, only 1.7% false negatives and 1.8% deferred cases (Fessia, Ghiringhello, Arisio, Botta, & Aimone, 1984). While frozen section analysis is quite accurate, the results are regarded as less reliable for small tumors. Niemann et al. demonstrated that the overall sensitivity of frozen section analysis is approximately 84% and the false negative rate is 3.3%. However, if the analysis is restricted to tumors larger than one centimeter, the overall sensitivity of frozen section analysis increases to 96% (Niemann, Lucas, & Marsh, 1996).

A number of technical factors limit the utility of frozen section analysis. Freezing of the adipose tissue and the associated artifact make the interpretation of margin status challenging. Frozen section analysis results in loss of tissue for

permanent section, especially when the primary lesion is less than one centimeter in diameter. There is also inherent sampling error associated with this technique.

Touch prep cytology, also known as imprint cytology, scrape cytology or cytologic smears (Klimberg, Harms, & Korourian, 1999), is a rapid, cost effective method of intraoperative margin assessment. The technique involves touching the margins of an oriented specimen onto glass slides. Tumor cells adhere to the slides, while adipose cells are left behind on the specimen. The cells are assessed for cytologic features of malignancy and categorized as negative, malignant, suspicious or indeterminate. Touch prep is more rapid than frozen section analysis, but it is limited by surface drying and cautery artifact (Klimberg, Harms, & Korourian, 1999). It also requires the expertise of cytopathologists, which limits its utility in smaller centers. Several studies have directly compared touch prep and frozen section analysis and, while touch prep is considered equivalent to frozen section analysis, it has not been uniformly adopted (Cox et al., 1991; Cox et al., 1998; Klimberg, Westbrook, & Korourian, 1998; Ku, Cox, Reintgen, Greenberg, & Nicosia, 1991).

Frozen section analysis was historically used in the absence of preoperative biopsy techniques to determine whether patients required a mastectomy for invasive cancer. However, tumors are now detected at an earlier stage by mammography and more patients are candidates for BCT. The histologic diagnosis of invasive cancer is often confirmed by preoperative core biopsy. As a result, the initial resection is generally therapeutic rather than diagnostic. The main utility of intraoperative techniques today is to permit intraoperative re-excision with the goal of achieving negative margins at the initial operative procedure. Even though frozen section and

touch prep analysis can be performed with acceptable results in certain centers, the reproducibility of such techniques is low. These procedures also require extensive resources and result in longer operative times. As such, the use of routine intraoperative margin assessment has not been widespread.

Specimen Handling & Postoperative Margin Assessment

The pathologic assessment of a lumpectomy specimen includes determination of the radial margins of invasive and non-invasive cancer. During specimen handling, the tumor holds its shape because of the secondary desmoplastic reaction. In contrast, the surrounding breast tissue may undergo distortion creating the false impression of positive margins. To avoid this problem, specimens are now routinely inked for margin determination.

Pathologic assessment of breast lumpectomy specimens is fraught with sampling error. A single hematoxylin and eosin (H&E) slide of a 2 to 3-mm block from a lumpectomy specimen visualizes less than one thousandth of the surface area of the lesion (McCready, 2004). Viewing the entire histologic margin of a lumpectomy specimen is simply unfeasible (Carter, 1986). Positive margins may, in fact, be misinterpreted as close margins due to sampling error. Breast cancers may also have separate foci in the same quadrant (multifocal) or other quadrants (multicentric) of the breast. Carter reviewed eleven studies assessing the multifocality of breast cancer (Egan, 1982; E. R. Fisher et al., 1975; Gallager & Martin, 1969; Holland, Veling, Mravunac, & Hendriks, 1985; Lagios, 1977; Noel et al., 1985; Qualheim & Gall, 1957; Rosen, Fracchia, Urban, Schottenfeld, & Robbins, 1975; Schwartz, Patchesfsky, Feig, Shaber, & Schwartz, 1980; Shah, Rosen, &

Robbins, 1973; Tellem, Prive, & Meranze, 1962). The incidence of multifocal tumor (invasive or non-invasive) ranged from 9-75%, depending on the definition and method of assessment, with a mean incidence of 32% (Carter, 1986).

The lumpectomy specimen is oriented by the surgeon at the time of the procedure. The surfaces are then differentially stained by the pathologist in order to facilitate directed re-excision of positive margins. Many centers use a multicolor inking system to mark the superior, inferior, anterior, posterior, medial and lateral surfaces of the specimen. The specimen is then serially sectioned and the margins of the tumor are grossly assessed. If intraoperative gross inspection is employed, concerning margins are further excised at the time of the initial procedure. The colored ink permits unequivocal identification of the appropriate surface for re-excision. If a single ink color is employed and the labeling sutures are removed for processing, the location of the positive margin cannot be accurately identified. In this case, re-excision of the entire cavity is performed rather than margin directed re-excision. A study by Gibson et al. demonstrated that colored ink directed re-excision results in similar local recurrence rates compared to whole cavity re-excision (Gibson et al., 2001). However, the mean weight of excised tissue is four fold greater for whole cavity re-excision. This may have significant cosmetic implications.

In order to improve the quality of pathology reporting, the College of American Pathologists introduced guidelines in 1998 designed to standardize the reporting of all cancer specimens (Compton, Hammond & Schramm, 1998). These guidelines employ standardized templates by organ and type of surgical specimen. They require reporting of macroscopic and microscopic tumor size, histologic type,

grade, margin orientation, margin status and TNM classification. A complete histologic description, including the Bloom Scarf Richardson Score and the extent/type of in situ involvement, is also required.

Wilkinson reviewed 100 consecutive pathology reports from lumpectomies performed for invasive cancer in western New York from 1998 to 1999 (Wilkinson, Shahryarinejad, Winston, Watroba, & Edge, 2003). This study highlighted the variability in overall quality of pathology reports. Surgical margins were inked in only 77% and the margins were oriented for only 25% of specimens. Microscopic margin status was reported in 94% but the distance to the closest margin was reported in only 69%. The presence or absence of lymphovascular invasion was reported in 57%, while the presence of in situ disease was reported in 71% of cases.

Many patients undergo re-excision for close or positive margins. A large proportion of these patients have grossly negative re-excisions with no obvious residual tumor. There is some controversy with regards to the extent of microscopic assessment that is required for these specimens. Abraham et al. (Abraham, Fox, Fraker, Solin, & Reynolds, 1999) reviewed the specimens from 97 cases of grossly negative re-excision. There were 47 specimens with residual DCIS or invasive carcimona. For 30 patients, there was a major change in management as a result of the review. It was estimated that if one block per centimeter was submitted and the remainder of the specimen was examined only if the initial sections demonstrated invasive or in situ carcinoma, then 901 blocks would have been processed (a 52% reduction in review). However, an average of 3.7 cases with a major change in therapy would have been missed. In contrast, if two blocks per centimeter were

assessed then an average of less than one case with major change in therapy would have been missed and 315 (17%) fewer tissue blocks would have been processed. Abraham recommended submitting two blocks per centimeter in grossly benign re-excisions, with examination of the remainder of the specimen only if carcinoma was detected on initial sections.

Lobular Carcinoma

Invasive lobular carcinoma represents approximately 10% of all breast cancers (Silverstein et al., 1994). Lobular carcinomas are usually larger, occur in older patients and are more difficult to diagnose than ductal cancer. They are also less likely to be node positive (Sastre-Garau et al., 1996; Silverstein et al., 1994) and may be associated with better survival (Silverstein et al., 1994). The influence of lobular histology on surgical margins is not well understood. Moore et al. demonstrated that invasive lobular cancer was more often associated with positive margins (51% vs 15%) (Moore et al., 2000). In another series of 416 women with invasive lobular carcinoma, the actuarial rate of local recurrence was only 3.5% at 5 years and 6.4% at 8 years (van den Broek et al., 2006). Most case series have suggested that the risk of local recurrence is similar for invasive lobular and ductal carcinoma (Chung, Cole, Wanebo, Bland, & Chang, 1997; Peiro et al., 2000; Sastre-Garau et al., 1996; Silverstein et al., 1994; Singletary, Patel-Parekh, & Bland, 2005).

Ductal Carcinoma in Situ and Margin Width

Invasive tumors are often surrounded by an extensive in situ component. The spread of ductal carcinoma in situ (DCIS) along ductal branches, in association with

the presence of skip lesions, may complicate margin assessment. In a meta-analysis of factors contributing to local recurrence for DCIS, margin status was one of the most important predictors of local control (Boyages, Delaney, & Taylor, 1999). Some experts have advocated for wider margins for pure DCIS tumors, ranging from 5 to 15 millimeters, although this is not universally accepted practice (Silverstein et al., 1999; Vicini et al., 2001). Singletary reviewed the studies assessing margin status for DCIS and noted an increased risk of local recurrence for positive margins (Singletary, 2002). Most negative margins in this review were only one or two millimeters and local recurrence rates were similar to those with invasive ductal carcinoma. It is not clear whether wider margins are required around an in situ component of an invasive tumor.

Management of Close or Positive Margins

Most consensus guidelines recommend re-excision of positive surgical margins (NCCN, 2007; EBCWG, 2001; Schwartz et al., 2006). At the Consensus Conference on Breast Conservation in Milan (2005), the panelists agreed that there should be "no evidence of tumor at the transected edge of the excision, per National Surgical Adjuvant Breast and Bowel Project (NSABP) guidelines" (Schwartz et al., 2006). While most panelists agreed that wider margins might result in a lower risk of recurrence, they acknowledged that there is "no evidence-based data to support this practice". There was no consensus between experts on the management of close margins, but the conference proceedings indicated that most radiation oncologists would accept one or two millimeter margins.

Extensive wide excision has been shown to reduce the rate of true recurrence but not the rate of new primaries. In the Milan II study of quadrantectomy and radiotherapy versus lumpectomy and radiotherapy, true local recurrence was defined as recurrent tumor within three centimeters of the surgical scar. Quadrantectomy required removal of the macroscopic tumor with a gross margin of two to three centimeters of normal breast tissue. Results of this study revealed a significant reduction in true recurrences with quadrantectomy but no difference in the rate of new primaries. More extensive surgery in the form of a quadrantectomy reduced the risk of local recurrence (13.3% vs. 5.3%) (Veronesi, Luini, Galimberti, & Zurrida, 1994).

Histologic margin assessment was incomplete for both arms of this study. Half of the quadrantectomy group had margin assessment and, of those evaluated, the rate of positive margins was 4.5%. In contrast, 83.8% of lumpectomies had margin assessment and 15.9% had positive margins. These patients were not re-excised. The rate of LR for positive margins was 17.4% compared to 8.6% for known negative margins.

While wider excision may reduce the rate of local recurrence, this is often at the expense of cosmesis. The improvement in local control in the Milan II trial was achieved at the cost of significantly less favorable cosmetic results (Veronesi et al., 1990). Patients are generally unsatisfied with the cosmetic outcome of breast conserving surgery when the volume of excision is greater than 10% of the breast volume (Cochrane, Valasiadou, Wilson, Al-Ghazal, & Macmillan, 2003). Wazer et al. have also demonstrated that a larger volume of excision is associated with less

satisfactory cosmetic outcome (Wazer et al., 1992). Overall, a careful balance must be achieved between adequate excision and acceptable cosmesis.

Radiotherapy and Margin Status

Individual randomized trials of adjuvant radiotherapy following lumpectomy for invasive cancer have demonstrated a significant reduction in local recurrence in the absence of a survival benefit (Liljegren et al., 1994; Veronesi et al., 1993; Veronesi, Luini, Galimberti, & Zurrida, 1994; Whelan, Clark, Roberts, Levine, & Foster, 1994). Given the significant improvement in local control afforded by radiation, it is now considered a standard of care for most women undergoing BCT for invasive tumors. The National Institutes of Health consensus conference on early breast cancer recommended post-lumpectomy radiotherapy as adjuvant treatment (NIH, 2001).

The Early Breast Cancer Trialists' Collaborative Group combined individual patient data from the randomized trials of post-lumpectomy radiotherapy (Clarke et al., 2005). The ten individual trials all demonstrated a significant reduction in local recurrence but failed to demonstrate a survival benefit. Considering the combined results of the trials, the 5-year risk of local recurrence was reduced significantly from 26% to 7% and the breast cancer death rate was 0.83 (95% CI 0.75 – 0.91). There was also a significant reduction in overall mortality of 5.3% at 15 years ($p=0.005$).

Three prospective randomized trials investigating the application of an electron boost to the tumor bed following whole breast radiotherapy have demonstrated a statistically significant improvement in local control (Bartelink et al.,

2001; Polgar et al., 2001; Romestaing et al., 1997). In the largest trial by the European Organization for the Research and Treatment of Cancer (EORTC) (Bartelink et al., 2001), 5 569 patients with stage I or II invasive carcinoma were randomized to 50 Gray (Gy) of adjuvant radiotherapy to the entire breast or 50 Gy to the entire breast with a 16 Gy boost to the tumor bed. There were 5 318 patients with histologically negative margins included in the final report. With a median follow-up of 5.1 years, the 5-year actuarial local recurrence rate was 4.3% for those who received a boost and 7.3% for those who did not. Half of the in-breast recurrences were at a site distant from the original tumor. The greatest benefit was for patients under the age of 40 and the benefit for women over the age of 60 was non-significant.

While the randomized trials of boost radiotherapy were not designed to look at the subset of patients with close margins, there is some retrospective data to suggest that boost radiation to the surgical bed for close or focally positive margins may generate similar local recurrence rates as negative margins (Solin, Fowble, Schultz, & Goodman, 1991). Solin et al. analyzed a subset of node-negative patients that received boost radiotherapy with no adjuvant chemoendocrine therapy. The five-year rate of local recurrence was 0% for patients with positive margins. However, the selection criteria applied only to 30 patients and many of these had less than 55 months of follow-up. The group with "unknown" margins in this study was the largest cohort (346 patients) and this group actually had the worse disease-free survival, suggesting a selection bias.

Arthur et al. reviewed a group of 205 patients who underwent re-excision for positive or indeterminate margins and were found to have no residual tumor (Arthur

et al., 2006). Boost dose radiotherapy was omitted in this group and the local recurrence free survival was 92.4% at 15 years. Of note, 77.1% of patients received adjuvant chemotherapy and 36.7% received tamoxifen, which undoubtedly improved the recurrence free survival in this cohort.

To date, there is still considerable debate over the clinical significance of the small reduction in local recurrence associated with boost radiotherapy. Boost radiotherapy has been associated with a less satisfactory cosmetic outcome (Bartelink et al., 2001) and its role in local control on the basis of margin status remains undetermined.

Chemoendocrine Therapy

An extensive body of literature has demonstrated that adjuvant chemotherapy and hormonal therapy reduce the risk of local recurrence. Fisher et al. analyzed the combined results of three trials of adjuvant chemotherapy, including the NSABP B13, B19 and B23 (B. Fisher, Jeong, Anderson, & Wolmark, 2004). The cumulative incidence of local-regional treatment failure was 5% among women who received any form of postoperative chemotherapy, while the failure rate was approximately 14% in women who had undergone surgery only. When women in the CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or AC (adriamycin and cyclophosphamide) groups from NSABP B-19 and B-23 were compared with those who were in the surgery-alone group (B-13), there was a 58% reduction in recurrence and a 40% reduction in mortality at 8 years as a result of the chemotherapy. Other studies have demonstrated similar benefits to chemotherapy (Clahsen et al., 1996; B. Fisher et al., 1997).

In the NSABP B-14 study, the addition of tamoxifen for node-negative women reduced the rate of local recurrence from 4.3 to 1.9% (B. Fisher, Dignam, Bryant, & Wolmark, 2001). A meta-analysis of chemoendocrine therapy by the Early Breast Cancer Trialists' Collaborative Group assessed the benefit of 5 years of tamoxifen for estrogen receptor positive women (Effects of Chemotherapy, 2005). The annual recurrence rate ratio was 0.59 (standard error (SE) 0.03) and the breast cancer mortality was reduced by one third with a death rate of 0.66 (SE 0.04). Although there is a clear benefit to adjuvant therapy in terms of reducing local recurrence, the overall benefit of adjuvant chemoendocrine therapy on patients with close or positive margins, as compared to women with negative margins, is not well understood.

Other Predictors of Local Recurrence

Young age is consistently identified as a risk factor for local recurrence (Arriagada et al., 2002; Fourquet et al., 1989; G. M. Freedman, Hanlon, Fowble, Anderson, & Nicolaou, 2002; Jobsen, van der Palen, & Meerwaldt, 2001; Kroman, Melbye, & Mouridsen, 2002; Locker et al., 1989; Veronesi et al., 1995). However, there is an association between young age and other adverse prognostic factors, including multicentricity, multifocality, extensive intraductal component (EIC), grade and lymphovascular invasion (LVI) (de la Rochefordiere et al., 1993; Kurtz, Jacquemier, Amalric et al., 1990b; Richards et al., 1993). Young age may be a risk factor for local recurrence or it may simply be a marker for these other adverse prognostic factors.

The presence of an extensive intraductal component (EIC) has been associated

with an increased risk of local recurrence. EIC is defined as predominant intraductal carcinoma within the tumor (>25% of the tumor) as well as intraductal carcinoma in sections of grossly normal adjacent breast tissue. Vicini et al. demonstrated that the five-year local recurrence rate was 21% in a group of 166 patients with EIC and only 6% in a group of 418 patients without EIC (Vicini et al., 1992). Kurtz et al. reported that patients with EIC but negative margins have a significantly reduced risk of local recurrence. The rate of local recurrence was 31% for negative margins versus 67% for positive margins (Kurtz, Jacquemier, Amalric et al., 1990b). However, in this study surgical margins were assessed retrospectively and lumpectomy specimens were not routinely inked. Holland has also shown that EIC is associated with a greater probability of residual disease in mastectomy specimens (Holland et al., 1990).

A number of histologic factors have been variably associated with local recurrence. Lymphatic invasion was associated with local recurrence in the Milan overview (Veronesi et al., 1995) and other studies have also linked local recurrence to lymphatic invasion (Fourquet et al., 1989; Locker et al., 1989). Increasing nuclear grade has been associated with local recurrence (Kurtz, Jacquemier, Amalric, Brandone, Ayme, Hans, Bressac, Roth et al., 1990; Lindley et al., 1989; Locker et al., 1989). Multicentric or multifocal tumors have rates of local recurrence ranging from 36-40% (Kurtz, Jacquemier, Amalric et al., 1990a; Leopold et al., 1989; Wilson, Beinfield, McKhann, & Haffty, 1993). However, most studies show no association between tumor size and local recurrence (Asgeirsson, McCulley, Pinder, & Macmillan, 2003).

In 2001, Fisher published a 15 year update of the NSABP B-06 trial (E. R. Fisher et al., 2001). Treatment, patient age, nuclear grade, presence of intraductal carcinoma, and a lymphocytic tumor infiltrate were features that predicted local recurrence by multivariate analysis. Multivariate analysis also revealed that the presence of local recurrence, race, histologic tumor type, nodal status, nuclear grade, and blood vessel invasion affected survival independently. Irradiation reduced local recurrence from 36% to 12% in the analyzed cohort.

Summary

While BCT is considered a standard of care in the management of early breast cancer, there remains an increased risk of local recurrence. Margin status is clearly related to local recurrence. Histologically positive margins are generally considered unacceptable. Numerous intraoperative techniques of margin assessment have been introduced with limited success in an attempt to reduce the risk of positive margins. Most patients undergo re-excision for positive margins, while the indications for re-excision of close margins are less clear. There is currently no expert consensus on the management of close margins following BCT.

Chapter 2: Objectives

Overall Objective

The primary objective of this Master's Thesis was to determine whether there is a requirement for a margin greater than histologically negative following breast conserving therapy for invasive carcinoma.

Part I: Systematic Review

As part of the background for the Manitoba Case-Control study, the initial objective was to perform a systematic review of margin status and local recurrence following breast conserving therapy for invasive carcinoma in order to determine what is considered an appropriate margin.

Part II: Manitoba Study

The second objective was then to determine the significance of margin status as a predictor of local recurrence for Manitoba women with invasive carcinoma undergoing breast conserving therapy.

Chapter 3: Methods

Part I: Systematic Review

Search Strategy

A PubMed search (1966 - 2006) was conducted using the following MeSH headings: "Carcinoma, ductal, breast", "Mastectomy, segmental" and "Neoplasm recurrence, local". Select phrases (invasive breast cancer, breast conserving surgery, local recurrence) and keywords (margin, predictors) were also employed in the literature search. Embase and Web of Science (1988 - 2006) were searched using a similar strategy. Abstracts were reviewed by the primary author and studies were selected for inclusion. The primary author also performed a manual search of the references from the studies chosen for inclusion. The initial search strategy was not limited to the English language.

Studies selected for the review had to examine the relationship between margin status and local recurrence. Further inclusion and exclusion criteria are outlined in Table 2. Papers published by the same author had to involve different populations or different methods of classification of margin status for inclusion. Studies examining re-excision findings were included if they also attempted to quantify the relationship between margin status and local recurrence.

There is an extensive body of retrospective literature that examines all predictors of local recurrence including margin status. These studies were not designed to specifically address margin status and the majority did not provide sufficient information to examine close margins. Thus, a decision was made to exclude these papers from the review.

Table 2. Inclusion and exclusion criteria for systematic review.

Inclusion	Exclusion
BCT + radiotherapy > 1 margin assessed Invasive carcinoma +/- DCIS	Pure DCIS Studies with exclusively LCIS/Lobular carcinoma

Quality Assessment

A checklist for assessing the methodologic quality of papers was adapted from a previously published checklist for randomized and non-randomized studies (Downs & Black, 1998). This assessment included categories for data reporting, external validity, internal validity and analysis (Appendix A). Since the studies in the review were non-randomized, the few questions assessing quality of randomization were excluded.

Two reviewers, a surgical resident and fellow, scored each paper independently according to the checklist (maximum possible score 22). Six papers were initially reviewed and the results were discussed to clarify discrepancies in interpretation of the checklist items. Once each study was scored, the reviewers discussed and resolved score discrepancies. Outstanding discrepancies were resolved by a third reviewer, the senior member of the research team. Studies scoring less than 10 out of 22 on the methodologic checklist were excluded from subsequent analysis (Ikeda et al., 1999; Renton, Gazet, Ford, Corbishley, & Sutcliffe, 1996; Schmidt-Ullrich et al., 1989; Swanson, Rynearson, & Symmonds, 2002; Tartter et al., 2000).

Data Abstraction

The following data was abstracted from the studies: number of patients, median follow-up, definition of positive margin, definition of close margin, number of patients by margin category, number of local recurrences by margin category, crude or actuarial rates of local recurrence by margin category (when provided). In cases where the absolute number of local recurrences was not provided, it was estimated from actuarial data.

Data Analysis

Results were initially compiled descriptively. Local recurrence rate by margin category (positive, close $\leq$ 1 mm, close $\leq$ 2 mm, close $\leq$ 3 mm and negative) was compared using crude or actuarial rates published in the study and the longest follow-up provided.

The meta-analysis involved a statistical comparison of the proportion of local recurrences by margin category. The results of the longest follow-up were used. Analysis of local recurrence free survival or actuarial rate of local recurrence was not possible because the reporting of such values was inconsistent. Individual and summary odds ratios with 95% confidence intervals (CI) were calculated using a random-effects model for each margin category and represented in a standard Forest plot (NCSS Number Cruncher Statistical System, Kaysville, Utah 2007). Heterogeneity amongst studies was tested using Cochran's Q test. This value is computed by summing the squared deviations from each study's estimate that contributes to the overall estimate, weighting each study's contribution to the same degree as in the meta-analysis (Cochran, 1954). A significant p value for Cochrane's

Q indicates that the studies are heterogeneous. Since Cochran's Q lacks power when there are few studies in the analysis, a cut-off value of $p < 0.10$ rather than $p < 0.05$ was adopted in order to reduce the risk of type II error (Hardy & Thompson, 1998). Reporting a combined result from a meta-analysis following a significant Cochran's Q is controversial (Stroup et al., 2000). Although combined result with significant heterogeneity must be viewed with caution, the summary OR for each margin category, including those that demonstrated heterogeneity, was reported. Sub-analysis by length of follow-up (< 5 or ≥ 5 years), first year of accrual (before and during/after 1980) and according to the median quality score (< 13 and ≥ 13) was also performed to examine other factors that may be associated with local recurrence and/or improve homogeneity.

Part II: Manitoba Study

Study Design

A matched case-control design was selected to examine the impact of close or positive margins on local recurrence following BCT for invasive carcinoma.

Ethics Approval

Ethics approval was obtained from the University of Manitoba Health Research Ethics Board and from the Manitoba CancerCare Research Resource Impact Committee. Annual renewal of approval was obtained for the duration of the project.

Case Definition & Inclusion Criteria

The population of interest included all women in the province of Manitoba undergoing BCT for invasive breast cancer from January 1995 to December 2004. Cases from this population were defined as women experiencing local recurrence following BCT. Local recurrence was further defined as any recurrence, invasive or non-invasive, within the ipsilateral breast occurring six months or more following BCT, with or without simultaneous axillary or distant failure. Patients were not censored if they developed a subsequent contralateral primary. The distinction between true local recurrence due to microscopic residual disease versus grossly inadequate excision of the primary was not straightforward. It was felt that a time interval of six months from breast conservation to local recurrence was an appropriate definition and that earlier recurrence would reflect grossly inadequate excision.

Exclusion Criteria

Cases were excluded if the patient failed to complete a full course of adjuvant radiotherapy as planned by the radiation oncologist.

Control Matching

Each case was matched to three controls who had undergone breast conserving therapy for Stage I or II invasive cancer and were free of local recurrence. For most cases, the controls were matched within an age range of 5 years above or below the case age. For 2 cases, the age criterion was relaxed to 10 years above or below the case age in order to match three controls and in one case the age range had

to be relaxed to 17 years above or below the case age. The controls were also matched by tumor grade (I-III), pathologic stage (I, IIa or IIb, AJCC v5 1995-2002 and v6 2003-2004) and the use of adjuvant chemotherapy (within one year after diagnosis). CancerCare Manitoba charts were used to collect demographic data and determine margin status for the controls.

Datasets

1. Manitoba Cancer Registry (MCR)

All malignancies in the province of Manitoba are reportable (as per the *Diseases and Dead Bodies Regulation* of the *Public Health Act*) to the Manitoba Cancer Registry. This database receives reports on all cases of cancer in Manitoba, regardless of whether the patient is treated at CancerCare Manitoba or not.

The patient file in the Registry contains basic patient identifiers such as name, gender, birth date and residence. The tumor file contains features of the tumor including the site and morphologic type of the cancer as well as pathologic summary stage. Stage at diagnosis for breast cancer has been collected since 1995. Treatment information is available from the treatment file, particularly for patients receiving treatment at CancerCare Manitoba.

Treatment information in the Registry is tumor specific and includes surgeries (e.g. segmental mastectomy, axillary node dissection (AND), mastectomies) and some adjuvant therapies (chemotherapy, radiotherapy and hormone therapy).

The Cancer Registry is part of a linked data resource that also incorporates administrative data maintained by Manitoba Health as part of the management of the provincial health care insurance plan.

2. Manitoba Health Data

Manitoba Health collects basic identifying information about all registrants of the provincial health care insurance plan (i.e., all Manitoba residents) and patient-specific information about contacts with the health care system, notably hospital discharges and physician visits. The records of the health care system identify the patient, the service provider, and the location, type and date of the services rendered. All databases contain a personal health identification number (PHIN), which is unique for each individual. The PHIN allows linkage of data between databases.

3. Manitoba Cancer Registry at Manitoba Health

The MCR and the Manitoba Health data are linked each year using a probabilistic matching algorithm. This allows Manitoba Health's unique Personal Health Identification Number (PHIN) to be attached to each cancer record. All subsequent linkages of the Manitoba Cancer Registry with Manitoba Health administrative databases for research purposes was deterministic, based on exact match of PHIN for the databases of interest.

4. The Medical Claims File

The Medical Claims File was started in 1969 and is generated by claims filed by physicians for payments. Aside from the billing tariff code, it also includes an ICD-9 code for one diagnosis.

Search Strategy

The Manitoba Cancer Registry was used to identify all women with Stage I or II invasive breast cancer in Manitoba who underwent BCT (segmental resection and adjuvant radiotherapy to the remaining breast) between 1995 and 2004. The Registry captures more than 99.5% of all cases of cancer in the province of Manitoba (Kostyra, 2005). Staging information has been captured routinely for breast cancers diagnosed after January of 1995. Cases diagnosed from 1995 to 2002 were staged using the fifth edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual (Fleming et al., 1997); cases diagnosed in 2003 were staged using the AJCC's sixth edition (Greene et al., 2002) and cases diagnosed after 2003 were staged using the Collaborative Staging System (Collaborative Staging and Coding Manual, 2007). The Collaborative Staging Task Force formed in 1998 with a mission to develop a translation or method between the AJCC TNM staging system and the SEER Extent of Disease (EOD) and Summary Staging System.

Several search strategies were employed to identify cases from the Registry. All women diagnosed with loco-regional progression more than six months following BCT were selected for review. As this field is not routinely captured in the Manitoba Cancer Registry, the database was also searched electronically for women undergoing ipsilateral mastectomy at least six months following BCT. ICD-9 codes appropriate

for this search have been previously described (Turner, 2007). The provincial Medical Claims data, which captures all physician claims in the province of Manitoba, was also queried using a similar search strategy. While mastectomy is considered a standard procedure for the treatment of local recurrence, patients may uncommonly undergo a second BCT procedure. Thus, the Registry was also searched for patients undergoing ipsilateral breast conservation more than six months following their original procedure. The CancerCare Manitoba charts of potential cases were reviewed by the primary author. Local recurrence was confirmed from the clinical progress notes and the confirmatory biopsy or mastectomy pathology.

Data Collection

The following demographic and pathologic data was collected from the CancerCare Manitoba charts or, when possible, from the electronic patient record: date of birth, date of BCT, presenting history, tumor stage, pathologic features (tumor size, histology, grade, margin), adjuvant radiotherapy dose, local recurrence event, date of mastectomy, pathology confirming local recurrence and use of adjuvant chemotherapy when available.

Margin status was determined directly from the official pathology report in the cancer clinic chart. If tumor was present at the inked margin, the margin was recorded as "positive". The closest margin was recorded as an absolute value in millimeters when it was reported. If the margin was said to be free of tumor without a specific measurement, it was recorded as "negative not otherwise specified (NOS)". If the patient had a re-excision procedure and there was no tumor on final pathology, the margin was recorded as "no residual". When the margin was indeterminate

according to the pathology report, it was recorded as "unknown". If expert pathology review was obtained, this report was used to determine the final margin status.

Based on informal discussion with local pathologists, a report of "negative NOS" margins was typically used when the margins were greater than 2 millimeters. In order to assess the validity of this assumption, the cases with "negative NOS" margins were reviewed by a senior pathology resident and an attending pathologist with an interest in breast cancer. However, the original pathology report was used to determine margin status in all subsequent analyses, as the pathology review could not be performed for the entire group of cases and controls.

Sample Size Calculations

The local recurrence rate following BCT with negative margins is approximately 1% per year in large randomized studies with long-term follow-up (Huston & Simmons, 2005). A clinically significant difference was considered a doubling of this rate to 2% per year for close or positive margins. Table 3 demonstrates sample size calculations based on 85% negative and 15% close or positive margin rates. The frequencies indicated by the asterisks (*) were inserted into PS Sample Size Calculator as dichotomous values with inputs: two proportions, independent, prospective, Fisher's exact test, alpha=0.05, power=0.80 P0=0.15 M=3 (for 3:1 controls to cases). Requested output for sample size was 146. A 3:1 control to case ratio would require 438 controls.

Table 3. Sample size calculations for local recurrence based on 85% negative and 15% close or positive margin rates.

	Wide Margin	Narrow Margin (<2 mm)	Total
% Subjects	0.85	0.15	1.00
Local Recurrence Rate	0.01	0.02	-
1 – Local Recurrence Rate	0.99	0.98	-
What does the LR group look like? (LRR*%subjects)	0.0085	0.003	0.0115
Distribution of each margin type in the LR group (ie. 0.0085/0.0115)	0.74	0.26*	1.00
How large is the group left without recurrence? (%subjects-% with LR)	0.8415	0.147	0.9885
Distribution of each margin type in non-LR group (ie. 0.8415/0.9885)	0.85	0.15*	1.00

Similar calculations were completed for rates of narrow margins up to 35% (Table 4). Previous local reviews of DCIS suggest the rate of close or positive margins approximates 25%. A very conservative estimate of a 15% narrow margin rate was assumed, such that the study would require 146 cases of local recurrence and 438 controls. In Manitoba, approximately 800 women are diagnosed with breast cancer annually, among which 700 are invasive. Half of these women (350) undergo BCT. Based on these estimates and the local recurrence rate of 1% per year, the 10 years of patients available for this study appeared to be able to provide a sufficient number of cases and controls to detect a doubling of the local recurrence rate due to narrow margins if it existed.

Table 4. Results of sample size calculations based on various proportions of narrow margins (≤ 2 mm).

Proportion Narrow Margins (≤ 2 mm)	# Cases	# Controls
0.15	146	438
0.2	125	375
0.25	107	321
0.3	102	306
0.35	95	285

Data Analysis

The odds ratio of local recurrence by margin category was determined using a conditional logistic regression model (SAS v9.1), which accounts for matching in the analysis. The median follow-up for the entire cohort of BCT patients was calculated based on the time from diagnosis to local recurrence or, alternatively, censored at the end of 2004 or until the last coverage date by Manitoba Health.

Time to local recurrence (as identified by the recurrence date or, if this could not be determined, the mastectomy date) was calculated. In the absence of a recurrence date or surgery date cases were censored using the last cancellation date in the Manitoba Health Registration file (if a cancellation date exists, this means that the patient was lost to follow-up) or, in the absence of a cancellation date, cases were censored at February 28, 2006. This date was chosen because the latest recurrence/surgery date in the cases was February 24, 2006.

Chapter 4: Results

Part I: Systematic Review

The search identified 412 titles from which 26 relevant abstracts were selected for review. Five abstracts failed to meet inclusion criteria and were excluded from the review, leaving 21 relevant studies. An additional 6 studies were added after reviewing the references of these papers. In total, 27 studies were identified for the systematic review, including 25 retrospective case series and 2 post-hoc analyses of prospective trials (Anscher et al., 1993; Assersohn et al., 1999; Aziz et al., 2006; Chism, Freedman, Li, & Anderson, 2006; DiBiase, Komarnicky, Heron, Schwartz, & Mansfield, 2002; DiBiase, Komarnicky, Schwartz, Xie, & Mansfield, 1998; G. Freedman et al., 1999; Gage et al., 1996; Ghossein et al., 1992; Horiguchi et al., 1999; Ikeda et al., 1999; Jobsen, van der Palen, Ong, & Meerwaldt, 2003; Kunos et al., 2006; Leong et al., 2004; Obedian & Haffty, 2000; Park et al., 2000; Peterson, Schultz, Reynolds, & Solin, 1999; Pittinger, Maronian, Poulter, & Peacock, 1994; Renton, Gazet, Ford, Corbishley, & Sutcliffe, 1996; Schmidt-Ullrich et al., 1989; Schnitt et al., 1994; Smitt et al., 1995; Solin, Fowble, Schultz, & Goodman, 1991; Spivack, Khanna, Tafra, Juillard, & Giuliano, 1994; Swanson, Rynearson, & Symmonds, 2002; Tartter et al., 2000; Wazer et al., 1999).

Quality Assessment

The methodologic quality checklist was applied to the 27 papers. There were only 11 discrepancies out of 567 possible responses between the initial two reviewers. Eight of these were resolved by discussion. The third reviewer was required to resolve the remaining three discrepancies. Five studies were excluded on the basis of

poor methodologic quality (score < 10/22). As summarized in Table 5, the remaining 22 studies had quality scores ranging from 10 to 18 (median 13).

Table 5. Results of the methodologic quality checklist for 22 papers.

	Median Score	Range	Base Score
Reporting	7	5 - 10	12
External Validity	2	0 - 2	2
Internal Validity (Bias/Confounding)	5	3 - 7	7
Analysis	0	0	1
Overall	**13***	**10 – 18***	**22**

* Median and range of overall scores (not sum of individual categories)

Summary of Individual Study Results

Appendix B provides a summary of the 22 studies retained in the review. Eleven studies provided a statistical comparison of microscopically positive versus negative margins (Anscher et al., 1993; DiBiase, Komarnicky, Schwartz, Xie, & Mansfield, 1998; G. Freedman et al., 1999; Gage et al., 1996; Ghossein et al., 1992; Jobsen, van der Palen, Ong, & Meerwaldt, 2003; Leong et al., 2004; Obedian & Haffty, 2000; Peterson, Schultz, Reynolds, & Solin, 1999; Solin, Fowble, Schultz, & Goodman, 1991; Spivack, Khanna, Tafra, Juillard, & Giuliano, 1994). Local recurrence following a positive margin ranged from 2 – 31%, while local recurrence following a negative margin ranged from 2 – 13%. Overall, three quarters of these studies (8 of 11) demonstrated an increased risk of local recurrence for positive margins with a median difference of 8.0% (range –5 to 25%).

Three additional studies used a definition of positive margins that included close margins of 1, 2 or 5 mm, making the results difficult to interpret. The studies that included 2 and 5 mm margins found a significantly increased risk of recurrence compared to negative margins (DiBiase, Komarnicky, Heron, Schwartz, & Mansfield, 2002; Horiguchi et al., 1999). No difference between positive and negative margins was found in the 1 mm margin study but the numbers were small (Assersohn et al., 1999).

Three studies provided a statistical comparison of focally or diffusely positive versus negative margins. Two studies demonstrated a greater risk of local recurrence for diffusely positive versus focally positive margins (range 27 - 28% versus 9 - 14%, respectively) (Gage et al., 1996; Park et al., 2000) and the third study demonstrated increased local recurrence for diffusely positive versus any other margin (Schnitt et al., 1994). Two of these studies also compared focally positive versus negative margins. Focally positive margins were associated with increased local recurrence, although the results were intermediate between negative and diffusely positive (Gage et al., 1996; Park et al., 2000). A fourth study included categories of focally and diffusely positive margins but did not analyze them individually (Smitt et al., 1995).

Three studies compared close ≤ 1 mm versus negative > 1 mm margins (Gage et al., 1996; Park et al., 2000; Schnitt et al., 1994). Local recurrence following a ≤ 1 mm negative margin ranged from 2 - 7%, while local recurrence following a negative >1 mm margin ranged from 0 - 7%. All 3 studies demonstrated no significant increase in local recurrence for close margins (median difference 0%, range -1 to 4%).

Six studies compared close ≤ 2 mm versus negative > 2 mm margins (G. Freedman et al., 1999; Kunos et al., 2006; Obedian & Haffty, 2000; Peterson, Schultz, Reynolds, & Solin, 1999; Smitt et al., 1995; Solin, Fowble, Schultz, & Goodman, 1991). Local recurrence following ≤ 2 mm negative margin ranged from 2.1 - 17%, while local recurrence following a negative > 2 mm margin ranged from 2 - 8%. Only three of the six studies demonstrated a statistically significant increase in local recurrence for close margins with a median difference of 6.9% (range -0.1 to 14%).

A single study compared negative ≤ 3 mm against > 3 mm margins (Pittinger, Maronian, Poulter, & Peacock, 1994). This demonstrated equivalent local recurrence in both groups (risk difference –0.4%).

Meta-Analysis

Twenty of the 22 studies reported crude data that could be extracted for comparison in the meta-analysis. Only the eighteen studies that had information on positive and negative margin categories were included. The three studies that combined close margins (1, 2 and 5 mm) with positive margins were subsequently excluded in order to compare microscopically positive versus negative margins. The fifteen remaining studies defined a positive margin as tumor at the inked margin.

Positive margins were associated with a significantly increased risk of local recurrence, OR = 3.0 (95% CI 2.0 - 4.4, Figure 1). The Cochran's Q value of 35.09 indicated significant heterogeneity between the studies (p = 0.001). This corresponded to an overall absolute risk difference of 7.8% (95% CI 4.3 – 11.3). Sub-analysis with the studies further stratified according to the duration of follow-up,

starting time of accrual and quality checklist score yielded similar odds ratios (Table 7). It should be noted that the test for heterogeneity was significant for all sub-groups except the group commencing accrual during or after 1980.

Figure 1. Odds ratio of local recurrence for positive versus negative margins.

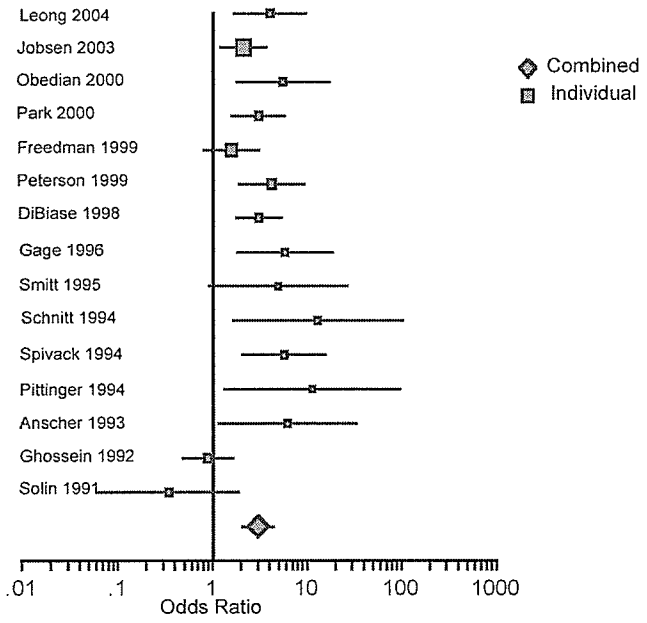


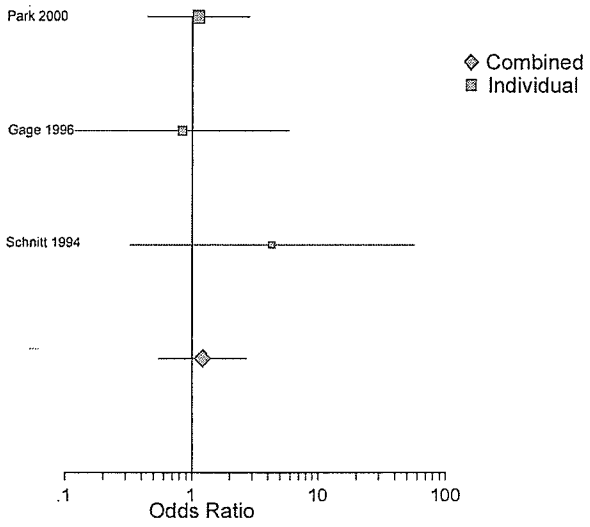
Table 6. Sub-analysis of studies comparing positive and negative margins.

Comparison	No. Studies	OR (95% CI)	Cochran's Q	P value*
First Year of Accrual				
Before 1980	10	2.6 (1.6 – 4.1)	26.71	0.002*
During/After 1980	5	4.6 (2.1 – 9.7)	7.22	0.125
Duration of Follow-up				
< 5 Years	5	3.3 (1.4 to 7.9)	9.88	0.043*
≥ 5 Years	10	2.9 (1.8 to 4.4)	23.68	0.005*
Quality Score (/22)				
< 13	6	2.6 (1.2 to 5.3)	15.82	0.007*
≥ 13	9	3.4 (2.3 to 5.0)	13.43	0.098*

*Significant p value <0.10

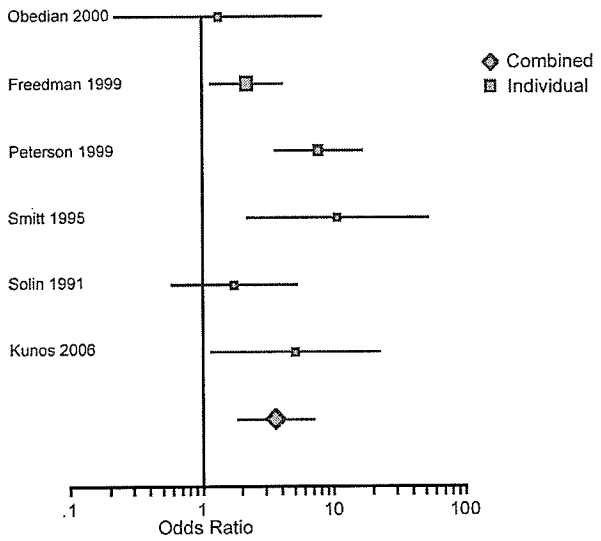
There was no significant increase in local recurrence for the three studies comparing close ≤ 1 mm margins with negative margins, OR = 1.2 (95% CI 0.5 - 2.7, Figure 2). Cochran's Q test of heterogeneity was non-significant with a value of 1.58 (p = 0.454). The overall absolute risk difference was 0.9% (95% CI –2.9 – 4.7).

Figure 2. Odds ratio of local recurrence for close ≤ 1 mm versus negative > 1 mm margins.



For the six studies that compared close ≤ 2 mm and negative margins, the risk of local recurrence was significantly higher for close margins, OR = 3.6 (95% CI 1.8 - 6.9, Figure 3). The test for heterogeneity was significant with a Cochran's Q value of 11.15 (p = 0.048). This corresponded to an overall absolute risk difference of 5.9% (95% CI 1.9 – 9.8).

Figure 3. Odds ratio of local recurrence for close ≤ 2 mm versus negative > 2 mm margins.



There were no obvious quality or methodologic discrepancies among the nine studies with a 1 or 2 mm margin category. The overall quality scores ranged from 10 to 18. Further subgroup statistical analysis was not conducted due to the small number of studies with a close margin category.

Part II: Manitoba Study

There were 3017 BCT procedures in Manitoba from January 1995 to December 2004 with a median follow-up of 60 months. There were 58 potential cases identified as having locoregional progression in the Manitoba Cancer Registry. The initial search for patients undergoing mastectomy six months following BCT revealed 76 potential cases, while Medical Claims demonstrated an additional 30

potential cases. After final review of these charts, there were 48 cases of confirmed local recurrence. Two other cases of local recurrence were discovered in review of the control charts. These cases had undergone post-lumpectomy mammographic surveillance and were found to have recurrent invasive carcinoma confirmed on mastectomy pathology.

The 50 cases were matched in a 3:1 manner to 150 controls. The demographic and pathologic data for these groups is summarized in Table 7. Cases were staged by the AJCC method up to 2003 and by the Collaborative Stage method after 2003. Because all of the cases occurred prior to 2004, they were matched on the bases of pathologic stage using the AJCC classification. The final margins status for all cases and controls is summarized in Table 8. One case had an unknown margin due to specimen handling and was excluded from subsequent analysis. Only 11 cases underwent re-excision (22 %), with a single case undergoing secondary re-excision. In contrast, 63 controls (42 %) underwent a re-excision procedure. This may account for the higher proportion of patients with no residual tumor in the control group.

Table 7. Summary of demographic and pathologic data for the cases and controls.

Characteristic	Cases n=50 (%)	Controls n=150 (%)
Mean Age at Diagnosis	51	52
Tumor Grade		
1	3 (6)	9 (6)
2	22 (44)	66 (44)
3	17 (34)	51 (34)
Unknown	8 (16)	24 (16)
Path Stage*		
I	27 (54)	81 (54)
IIa	15 (30)	45 (30)
IIb	8 (16)	24 (16)
Chemotherapy	28 (56)	84 (56)

* AJCC v5 1995-2002 or v6 2003-2004

Table 8. Summary of pathologic margin classification for cases and controls.

Margin Category	Cases n=50 (%)	Controls n=150 (%)
Positive	3 (6)	4 (3)
≤ 1 mm	8 (16)	19 (13)
≤ 2 mm	6 (12)	19 (13)
>2 mm	10 (20)	35 (23)
Negative NOS	15 (30)	36 (24)
No residual	7 (14)	37 (25)
Unknown	1 (2)	0 (0)

Slide review was performed for 13 "negative NOS" cases that had accessible slides in order to confirm whether they had widely negative (> 2 mm) margins. One case had a positive margin on review which was suspected according to the wording of the initial pathology report. One case had a ≤ 1 mm margin, three cases had ≤ 2 mm margins and the remaining 8 of 12 cases (67%) had > 2 mm margins. We considered our assumption of > 2mm for margins "negative NOS" reasonable.

Positive margins were associated with an increased, but not statistically significant, risk of local recurrence when compared to close ≤ 1 or 2 mm margins, OR 1.65, 95% CI 0.31 – 8.75 and OR 2.07, 95% CI 0.42 – 10.17, respectively. As the general standard of care in Manitoba is to re-excise positive margins, there were few cases or controls with positive margins.

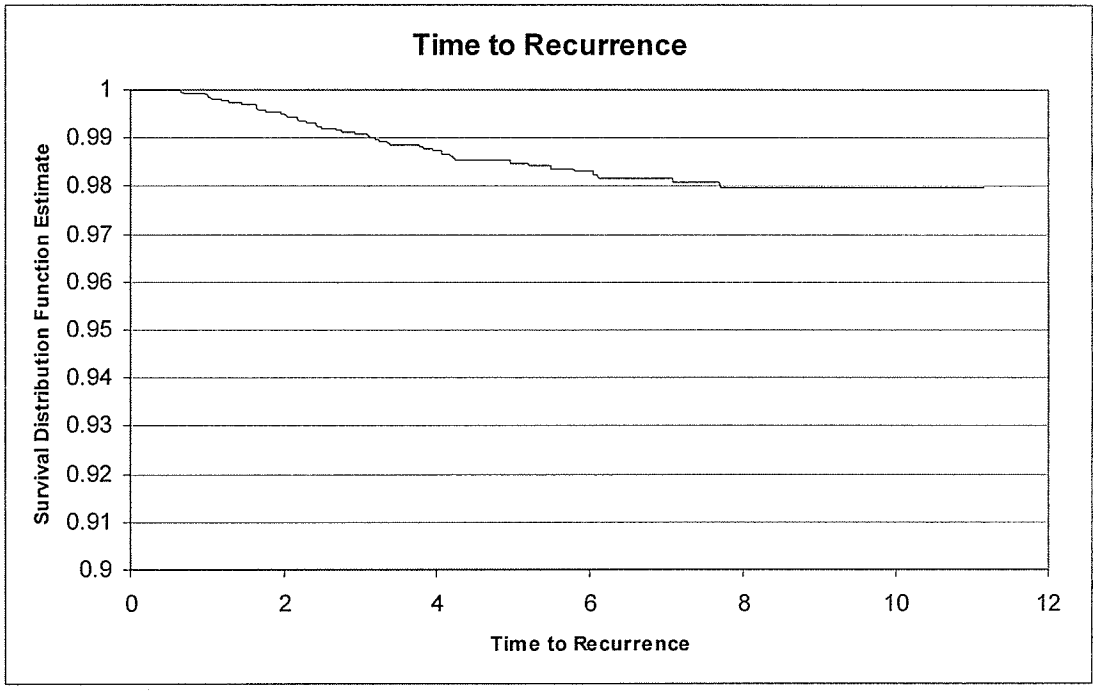
A comparison was made between close ≤ 1 or ≤ 2 mm margins and any wider margin, including negative NOS or no residual margins within the wide margin category. Wide > 1 or > 2 mm negative margins were not associated with a reduction in local recurrence compared to close ≤ 1 mm or ≤ 2 mm margins. These results were unchanged when the wide margin category was broken down into sub- categories, including the negative NOS and no residual categories (Table 9).

Table 9. Odds ratio of local recurrence for wider margins compared to close ≤ 1 or ≤2 mm margins.

Margin Comparison	Reference Category	Odds Ratio	95% CI
Any wide > 1mm	≤ 1 mm	0.69	0.28 – 1.69
Subcategories			
> 1 mm	≤ 1 mm	0.62	0.22 – 1.74
Negative NOS	≤ 1 mm	1.03	0.38 – 2.83
No residual	≤ 1 mm	0.38	0.11 – 1.30
Any wide > 2mm	≤ 2 mm	0.90	0.44 – 1.84
Subcategories			
> 2 mm	≤ 2 mm	0.86	0.34 – 2.19
Negative NOS	≤ 2 mm	1.33	0.56 – 3.14
No residual	≤ 2 mm	0.49	0.16 – 1.48

Recurrence-free survival for the 3017 women undergoing BCT for invasive carcinoma is demonstrated in Figure 4. At 5 years, 98.5% of women are free from local recurrence.

Figure 4. Recurrence-free survival for the 3017 women undergoing BCT for invasive carcinoma between 1995-2004.



Chapter V. Discussion

Margin Status and Local Recurrence

The literature addressing margin status and local recurrence consists primarily of retrospective case series of intermediate methodologic quality. Overall, there appears to be little support for margins greater than microscopically negative in the treatment of invasive breast cancer with BCT in the literature or in this Manitoba study.

Current consensus guidelines on BCT recommend achieving negative microscopic margins of excision (EBCWG, 2001; McCready et al., 2005; NCCN, 2007; Schwartz et al., 2006). Most studies in the descriptive review found that microscopically positive margins were associated with an increased risk of local recurrence compared to microscopically negative ones (median difference 8.0%). Although the meta-analysis also demonstrated an increased risk of recurrence with positive margins, the combined odds ratio for the results must be viewed with caution as the test for heterogeneity was significant. A descriptive review by Singletary had similar findings (Singletary, 2002). In that review, 30 of 34 studies demonstrated that persistently positive margins were associated with an increased risk of local recurrence. Singletary's review had broader inclusion criteria than this review and her primary objective was not necessarily an assessment of margin status as a predictor of local recurrence.

In our case-control study, positive margins were also associated with a trend towards increased local recurrence. However, the odds ratio did not reach statistical significance due to small numbers. There were only 3 cases (6%) and 4 controls

(2.7%) with positive margins. This is lower than the rate of positive margins reported in most recent case series, which is in the range of 11-22% (DiBiase, Komarnicky, Heron, Schwartz, & Mansfield, 2002; Horiguchi et al., 1999; Jobsen, van der Palen, Ong, & Meerwaldt, 2003). This may reflect the practice of re-excising positive margins in Manitoba. As well, many patients now undergo preoperative core biopsy to document invasive carcinoma. The use of preoperative tissue diagnosis has been associated with a reduction in positive margins, as these patients tend to have a wider excision at the time of initial surgery (Cox et al., 1995; King et al., 1998; Smitt & Horst, 2007).

Some studies have suggested that extensively positive margins are associated with a higher risk of local recurrence than focally positive margins (Gage et al., 1996; Park et al., 2000; Schnitt et al., 1994). The systematic review confirmed this finding. It appears that focally positive margins may be of intermediate risk between extensively positive and negative margins. In the Manitoba data, there were insufficient cases with positive margins to assess the influence of focal or diffusely positive margins on local recurrence.

The use of boost dose radiotherapy for positive margins is not well studied. The EORTC trial of boost dose radiotherapy excluded patients with positive margins from final analysis (Bartelink et al., 2001). Of note, the 2007 National Comprehensive Cancer Network (NCCN) guidelines acknowledge that: "It may be reasonable to treat (*with radiotherapy)* selected cases with breast conserving therapy with a microscopically focally positive margin in the absence of an extensive

intraductal component. For these patients, the use of a higher radiation boost dose to the tumor bed should be considered" (NCCN, 2007).

The results of the systematic review indicate that positive surgical margins should be re-excised. Based on the findings in the case-control study, this is the accepted practice in Manitoba since 1995.

The management of close surgical margins is more complex. In the systematic review, the comparison of close margins to wider negative margins was, at best, associated with a modest reduction in local recurrence. While most studies appear to favor wider margins, only three of the nine studies with a close margin category found a statistically significantly improvement in local control. The results for close ≤1 mm and close ≤ 2 mm margins were counterintuitive, as the median difference in local recurrence was 0% and 7%, respectively. One would anticipate that closer ≤1 mm margins would be associated with a greater risk of local recurrence. If one believes that combined results are acceptable in a meta-analysis in which heterogeneity has been shown, then the meta-analysis results demonstrate the same discrepancy for close ≤1 mm and close ≤ 2 mm margins. This heterogeneity in the close ≤ 2 mm margins likely reflects the confounding variables associated with retrospective studies. It is also interesting to note that the differences for positive versus negative margins are very similar to close ≤ 2 mm margins versus >2 mm margins.

The Manitoba case control study also did not find an advantage for wide versus close margins in terms of local recurrence. In the results of the case-control analysis, wider margins > 1 mm versus ≤ 1 mm and > 2 mm versus ≤ 2 mm were

associated with a non-significant trend towards reduction in local recurrence. The small number of local recurrences in this study resulted in wide confidence limits, particularly around the odds ratio for ≤ 1 mm margins. Although very wide excision in the form of a quadrantectomy is associated with a reduction in local recurrence, it may be difficult to demonstrate a benefit to negative but close margins. The small sample size and low rate of local recurrence in this study does not definitively exclude a benefit to slightly wider margins.

The results of the systematic review and the Manitoba study are in keeping with the pathologic analysis of residual tumor in mastectomy specimens. Holland analyzed the extent of disease in the mastectomy specimens of 282 patients considered to be candidates for breast conserving surgery and demonstrated invasive or in situ disease in 59% of patients one centimeter from the macroscopic tumor edge, in 42% at two centimeters, in 17% at three centimeters and 10% at four centimeters (Holland, Veling, Mravunac, & Hendriks, 1985). The recent literature on MRI supports these findings. Additional tumor foci have been demonstrated in 11-31% of patients (Bedrosian et al., 2003; Berg et al., 2004; Bluemke et al., 2004; Boetes et al., 1995; Deurloo et al., 2005; Drew et al., 1999; Fischer, Kopka, & Grabbe, 1999; Liberman, Morris, Dershaw, Abramson, & Tan, 2003; Mumtaz et al., 1997; Orel et al., 1995). The clinical significance of such findings is unclear. Because tumor deposits are known to extend several centimeters from the main tumor, it is not surprising that the difference in local recurrence between one and two millimeter margins is negligible.

There was extensive debate over the management of close margins at the Consensus Conference on Breast Conservation in Milan in 2005 (Schwartz et al., 2006). The only consensus that could be reached was on achieving negative microscopic margins. The controversy over the management of close margins is fuelled by the paucity of reliable evidence, as documented in this systematic review, as well as differences in expert opinion on what constitutes a clinically important difference in local recurrence. For example, it has been suggested that, for patients over the age of 70 with small tumors treated with tamoxifen alone, it may be reasonable to accept an increase in loco-regional recurrence of 6% at a median follow-up of 7.9 years in order to avoid adjuvant radiotherapy (Hughes, 2006). In contrast, a 3% reduction in local recurrence at 10 years has been suggested to support the use of a 16 Gy boost following standard radiotherapy (Bartelink, 2006).

One could strengthen the argument for obtaining wider negative margins if the improvement in local control was associated with a mortality effect. The Early Breast Cancer Trialists' overview examined the impact of radiotherapy on local recurrence and survival following breast conservation. In this review of the randomized trials of adjuvant radiotherapy following breast conservation, the combined results estimated that a 20% reduction in local recurrence at 5 years would results in a 5.2% reduction in mortality at 15 years related to improved local control (Clarke et al., 2005). The findings of the review suggested that, in the absence of any other causes of death, one breast cancer death would be avoided over the next 15 years for every four local recurrences avoided. While adjuvant radiotherapy may provide a clinically meaningful reduction in local recurrence with long-term follow-up, it is unlikely that

re-excision of close margins could share a benefit of such magnitude given that the reduction in local recurrence is at best a few percent.

There are disadvantages to increasing the minimum margin width. The Milan II study demonstrated that more extensive surgery in the form of a quadrantectomy reduced the risk of local recurrence from 13.3% to 5.3% (Veronesi, Luini, Galimberti, & Zurrida, 1994). However, this improvement in local control was achieved at the cost of significantly less favorable cosmetic outcome (Veronesi et al., 1990). Cochrane et al. have also demonstrated that patients are generally unsatisfied with the cosmetic outcome of breast conserving surgery when the volume of excision is greater than 10% of the breast (Cochrane, Valasiadou, Wilson, Al-Ghazal, & Macmillan, 2003). Other data suggests the cosmetic outcome is more satisfying following a smaller volume of excision (Al-Ghazal, Blamey, Stewart, & Morgan, 1999; Cochrane, Valasiadou, Wilson, Al-Ghazal, & Macmillan, 2003). Based on the data from this case-control analysis, 25% of patients had close margins that would require re-excision in order to obtain > 2 mm margins. Although local recurrences are a source of significant anxiety, re-excision to reduce this further may not be worth the cosmetic sequelae.

Systematic Review: Limitations

The objective assessment of methodologic quality for a systematic review poses many challenges. A purposeful attempt was made to select a checklist that was previously validated. There are few methodologic quality checklists in the literature that address both randomized and nonrandomized studies. Overall, the quality

checklist employed in the systematic review demonstrated face validity and was useful in objectively assessing the quality of studies. There were few discrepancies between the reviewers on the checklist items. Recognizing the controversy with regards to weighting studies by quality using an ad hoc quality checklist (Stroup et al., 2000), the scores were instead used to stratify the studies in the sub-group analysis.

Meta-analysis of retrospective or observational data is particularly controversial because of the inherent biases in the studies and the variability of study design (Stroup et al., 2000). However, such reviews can help provide a more objective assessment of the quality of the literature and the overall findings. There was significant heterogeneity between the studies evaluated in the systematic review. This heterogeneity was likely a result of the confounding variables that are not easily controlled for in retrospective analyses, including the presence of an extensive intraductal component (EIC) (Elkhuizen et al., 1999; E. R. Fisher et al., 2001; Hurd et al., 1997; Kurtz, Jacquemier, Amalric et al., 1990b; Schnitt, Connolly, Harris, Hellman, & Cohen, 1984; van Dongen et al., 1992; Vicini et al., 1992), lymphatic invasion (Fourquet et al., 1989; Veronesi et al., 1995), increasing nuclear grade (Dewar et al., 1995; Elkhuizen et al., 1999; E. R. Fisher et al., 2001; Kurtz, Jacquemier, Amalric, Brandone, Ayme, Hans, Bressac, Roth et al., 1990; Lindley et al., 1989; Locker et al., 1989; Nixon et al., 1996), multicentric or multifocal tumors (Kurtz, Jacquemier, Amalric et al., 1990a; Leopold et al., 1989; Wilson, Beinfield, McKhann, & Haffty, 1993) and young age (Arriagada et al., 2002; E. R. Fisher et al., 2001; Fourquet et al., 1989; G. M. Freedman, Hanlon, Fowble, Anderson, &

Nicolaou, 2002; Jobsen, van der Palen, & Meerwaldt, 2001; Kroman, Melbye, & Mouridsen, 2002; Kurtz, Amalric et al., 1989; Kurtz, Jacquemier, Amalric, Brandone, Ayme, Hans, Bressac, Roth et al., 1990; Locker et al., 1989; Nixon et al., 1994; Veronesi et al., 1995). There was also considerable variation in radiotherapy technique and the use of adjuvant chemoendocrine therapy. Most studies attempted to account for such confounding variables. However, there were numerous occasions when the data was unavailable or was not appropriately addressed. This attests to the limitations of meta-analysis for observational studies with confounding variables.

Case-Control Study: Limitations

There are advantages to using administrative data as it can be used to measure health related outcomes in an efficient and cost-effective manner. In this study, the Manitoba Cancer Registry was used to examine local recurrence and margin status following BCT on a population-based level. By using this population-based data set, patterns of care and outcomes are representative of the standard of care for the province of Manitoba. The disadvantages of this study are largely inherent in its retrospective design and the small number of patients identified with a local recurrence, which limits the exclusion of clinically important differences in local recurrence as the result of margin status.

Identification of local recurrences in the CancerCare Registry required a carefully devised search strategy, as there was no direct classification of local recurrence. Patients were marked in the Registry as having locoregional recurrence or metastatic disease, although this classification system was not reliable. The

category of locoregional recurrence also included axillary recurrence, which is a distinct entity in terms of pathogenesis and prognostic significance. These patients with axillary recurrence had to be excluded by hand review of charts.

The search strategy required that certain assumptions be made with regards to the timing and treatment of local recurrence. As most local recurrences represent inadequate local excision, rather than new primary disease, the timing of true local recurrence along this continuum is a matter of debate. While it was assumed that most patients undergo a mastectomy for treatment of local recurrence, the Registry was also searched for BCT procedures more than six months following initial surgery and four cases of local recurrence treated with BCT were discovered. As well, there were four patients that did not have surgical therapy for their local recurrence. These patients had metastatic disease and were felt to have a limited life span. Overall, there is significant potential for the Registry to improve its classification system for the purpose of future data collection and analysis.

While the CancerCare Registry proved to be a relatively reliable source of data, it is interesting to note that there were 30 potential cases of recurrence found in the Medical Claims data based on physician procedure billing that were not identified in the original search of the Registry. Only two of these were subsequently confirmed as cases of local recurrence. The Registry is thought to capture 99.5% of cases of cancer in the province of Manitoba (Turner, 2007). Yet, it may not be as accurate when more complex search strategies for specific cohorts are employed. In this study, an additional 2 cases were identified from manual search of the control population charts. These patients underwent mastectomy for treatment of their local

recurrence but they were not captured in the search strategy. As there were 150 controls and just over 3000 patients in the overall study, perhaps a total of 40 additional cases might have been identified if all charts were reviewed. However, the low rate of local recurrence may also reflect the low incidence of positive margins or advances in adjuvant therapy over time compared to other case series reported in the literature, which often extend back several decades.

A doubling of the rate of local recurrence from 1% per year to 2% per year was felt to be a clinically significant effect for the purpose of sample size calculation. With an estimated 350 women undergoing BCT annually and a close or positive margin rate of 15%, the required sample size was calculated as 146 cases and 438 controls. There were 3017 BCT procedures over 10 years in our series, which was close to the estimate. However, the rate of close or positive margins was much higher at 25%. With a close or positive margin rate of 25%, 107 cases would have been required which is twice the number of confirmed local recurrences.

There were also considerable limitations in the quality of pathology reporting. Fifteen of the 50 cases (30%) with negative margins did not describe the margin width. These cases were classified as "negative NOS" for the purpose of analysis. In conversation with local expert pathologists, it appears that surgical margins were usually reported as 'negative NOS" when they were greater than 2 mm. In order to assess the validity of this assumption, a review of the cases with negative "NOS" margins was performed. It would have been preferable to perform a pathology review of all cases and controls, but resources did not permit such an extensive review. As such, the original pathology reporting was used for the case-control

analysis. Based on the pathology review that was performed, most patients with "negative NOS margins" were wider than 2 mm and the assumption that "negative NOS" margins could be placed in the > 2 mm margin category for the purpose of comparison appeared reasonable. Even when these individuals with "negative NOS" margins were excluded and only the patients with definite margins were analyzed, there was no benefit to wider margins.

The Registry is also limited in its ability to capture data on adjuvant hormonal therapy. Tamoxifen and the newer chemotherapy regimens are known to have an impact on local recurrence and overall survival (Effects of chemotherapy, 2005). However, the pharmaceutical data in the CancerCare Registry is of limited accuracy and it is difficult to quantify the duration of therapy or patient compliance. The data for hormone receptor status is also inaccurate. For this reason, the use of hormonal therapy was not controlled for in the analysis. With further advances in the Registry and improved linking to pharmaceutical data, it may be possible to utilize this information for ongoing breast cancer research.

Overall, this is the first attempt to quantify local recurrence following breast conservation in the province of Manitoba. Most other literature on this topic is also retrospective and has similar limitations. However, the local recurrence rate on a population basis appears well within the accepted rate of 1% per year.

Future Recommendations

1. Current evidence supports a histologically negative margin with no required minimum. It would be difficult to design a randomized study to assess the benefit of excising close margins. Even if the outcome was local recurrence, it would require an excessively large sample size and long follow-up. There is likely insufficient equipoise in the medical community to conduct such a study. However, that assumption could be examined in a survey.

2. The Manitoba Cancer Registry should be expanded to capture cancer recurrence information. Our data suggests that the local recurrence rate following BCT in may be less than 1% per year, likely as a result of advances in adjuvant chemoendocrine therapy and radiation, including boost radiotherapy. Knowing the true local recurrence rate will help to tailor treatment recommendations and could potentially reduce the use of re-excisions and boost therapy.

3. As local recurrence does not appear to be related to margin status other than microscopically negative in Manitoba, an audit could be conducted to examine current patterns of practice in the province with regards to margins and BCT.

4. There were significant limitations in the pathologic reporting of lumpectomy margins. Earlier reports were more likely to omit a measurement of the microscopic margin. More recently, it appears that the use of synoptic reporting has improved the

reporting of surgical margins. This could be reviewed for the purpose of quality assurance.

5. Pathologic studies and new MRI data confirm that patients often have microscopic disease several centimeters beyond gross tumor. Thus, the difference between 1 and 2 mm margins is intuitively negligible. The new debate is what to do with the disease that is documented on MRI but not seen on mammography. The randomized trials of BCT in the pre-MRI era showed low local recurrence rates and no difference in survival when these deposits were left unresected. More aggressive resection based on the MRI may lead to unnecessary mastectomies. Further studies are required to determine the role of MRI in margin assessment and operative planning.

5. Recommendations for what constitutes an acceptable margin following BCT should be made based on the information contained in this study and consensus of the Breast Disease Site Group at CancerCare Manitoba.

Chapter VI: Summary

In summary, the literature addressing margin status and local recurrence following BCT for invasive carcinoma consists primarily of retrospective case series of intermediate methodologic quality. Positive margins are associated with an increased risk of local recurrence and re-excision for local control is reasonable. In contrast, the absolute benefit of converting close margins to negative margins remains poorly defined in the literature. The case-control study from Manitoba data did not demonstrate a reduction in local recurrence with wider histologically negative margins. Considering the lack of good quality evidence in the systematic review, the discrepancy between data for 1 and 2 mm margins and the modest absolute difference between close and negative margins found in the meta-analysis and case-control study, it is difficult to uniformly recommend a margin greater than microscopically negative following BCT for invasive carcinoma.

Appendix A. Methodologic Checklist

Data Reporting

1) Is the hypothesis/aim/objective clearly described?

Yes = 1 No = 0

2) Are the main outcomes to be measured clearly described in the Introduction or Methods?

If the main outcomes are first mentioned in the results section, the question should be answered no.

Yes = 1 No = 0

3) Are the characteristics of the patients included in the study clearly described?

Inclusion and exclusion criteria should be given. In case-control studies a case definition and source for controls should be given.

Yes = 1 No = 0

4) Are the interventions of interest clearly described?

Treatment and placebo (when relevant) to be compared should be clearly described.

Yes = 1 No = 0

5) Were all important confounders accounted for in the paper? If not, list these confounders.

Yes = 1 No = 0

6) Are the distributions of principal confounders in each group of subjects to be compared clearly described?

Yes = 2 Partially = 1 No = 0

7) Are the main findings of the study clearly described?

Simple outcome data (numerators/denominators) should be reported for all major findings so that the reader can check the major analyses.

Yes = 1 No = 0

8) Does the study provide estimates of random variability in the data for the main outcomes?

In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or CI should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and answer yes.

Yes = 1 No = 0

9) Have all important adverse events that may be a consequence of the intervention been reported?

Answer yes if the study demonstrates a comprehensive attempt to measure adverse events.

Yes = 1 No = 0

10) Have the characteristics of the patients lost to follow-up been described?

Answer yes is no losses or losses so small that findings would be unaffected by their inclusion. Answer no if does not report number lost to followup.

Yes = 1 No = 0

11) Have actual probability values been reported (0.035 rather than <0.05) for the main outcomes, except when the probabiliy value is less than 0.001?

Yes = 1 No = 0

External Validity

12) Were the subjects asked to participate in the study represenatative of the entire population from which they were recruited?

Study must identify the source population and how patients were selected. Patients considered representative if entire source, an unselected sample of consecutive patients or a random sample. Random sampling is only feasible when a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the answer should be unable to determine.

Yes = 1 No = 0 Unable to determine = 0

13) Were the staff, places and facilities where the patients were treated representative of the treatment the majority of patients received?

Study should demonstrate that the intervention was representative of that in use in the source population. Answer no if intervention, for example, took place in a specialist hospital unrepresentative of the hospitals most of the source population would attend.

Yes = 1 No = 0 Unable to determine = 0

Internal Validity

14) If any of the results of the study were based on "data dredging" was this made clear?

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes = 1 No = 0 Unable to determine = 0

15) In trials and cohort studies, do the analyses adjust for different lengths of followup of patients, or in case-control studies, is the time period between intervention and outcome the same for cases and controls?

Where follow-up was the same for all study patients the answer is yes. If different lengths of followup were adjusted for by, for example, survival analysis the answer should be yes. Studies where the differences in follow-up are ignored should be answered no.

Yes = 1 No = 0 Unable to determine = 0

16) Were the statistical test used to assess the main outcomes appropriate?

The statistical tests used must be appropriate to the data. For example, non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data is not

described, it must be assumed that the estimates used were appropriate and answer yes.

Yes = 1 No = 0

17) Was complaince with the intervention reliable?

Where there was noncompliance with the allocated treatment or where there was contamination, the question should be answered no. For studies where the effect of any misclassifications was likely to bias any association to the null, the question should be answered yes.

Yes = 1 No = 0 Unable to determine = 0

18) Were the main outcome measures used accurate (valid and reliable)?

For studies where the outcome measures are clearly described, the answer is yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the answer is yes.

Yes = 1 No = 0 Unable to determine = 0

19) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

In non-randomised studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made, answer should be no.

Yes = 1 No = 0 Unable to determine = 0

20) Were losses of patients to followup taken into account?

If the numbers of patients lost to followup are not reported, the question should be answered unable to determine. If the proportion lost to followup was too small to affect the main findings, answer yes.

Yes = 1 No = 0 Unable to determine = 0

Analysis

21) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

Sample sizes have been calculated

Yes = 1 No = 0

Is there a discrepancy between reviewers with respect to component ratings?

Oversight = A
Difference in interpretation of criteria = B
Difference in interpretation of study = C

Appendix B. Summary of 22 studies included in systematic review.

Author (Year)	Accrual Period	Median F/U (mos)	No. Patients	OR Positive (95% CI)	OR Close (95% CI)
Azziz (2006)	1987 - 1997	-	1430		
Chism (2006)	1974 - 2001	80.4	1044		
Kunos (2006)	1996 - 2002	56	341		5.1 (1.2 – 22.1)†
Leong (2004)	1979 - 1994	80	452	4.0 (1.7-9.6)	
Jobsen (2003)	1983 - 1999	78	1697	2.1 (1.2 – 3.6)	
DiBiase (2002)	1978 - 1994	52	641	3.7 (2.3 – 5.7)	
Obedian (2000)	1970 - 1990	156	871	5.5 (1.8 – 17.0)	1.4 (0.2 – 8.2) †
Park (2000)	1976 - 1987	127	533	3.0 (1.6 – 5.8)	1.1 (0.5 – 2.8)*
Freedman (1999)	1979 - 1992	76	1262	1.6 (0.8 – 3.1)	2.2 (1.2 – 4.1) †
Peterson (1999)	1977 - 1992	73	1021	4.2 (1.9 – 9.2)	7.7 (3.6 - 16.4) †
Assersohn (1999)	1991 - 1995	57	184	1.7 (0.4 – 7.5)	
Horiguchi (1999)	1991 - 1997	47	161	11.5 (1.7 – 75.9)	
Wazer (1999)	1982 - 1994	86	105		
DiBiase (1998)	1978 - 1994	45	453	3.0 (1.8 – 5.2)	
Gage (1996)	1976 - 1986	109	343	5.8 (1.8 – 18.5)	0.8 (0.1 – 5.8)*
Smitt (1995)	1972 - 1992	72	289	4.9 (0.9 – 26.4)	10.7 (2.2 – 51.5) †
Schnitt (1994)	1982 - 1985	86	181	25.9 (1.5 – 443.9)	8.6 (0.3 – 219.0)*
Spivack (1994)	1982 - 1990	48 (mean)	272	5.7 (2.1 – 15.6)	
Pittinger (1994)	1985 - 1990	54	211	11.3 (1.3 – 95.1)	
Anscher (1993)	1983 - 1988	44	259	6.2 (1.2 – 33.0)	
Ghossein (1992)	1967 - 1985	72 (mean)	503	0.9 (0.5 – 1.6)	
Solin (1991)	1977 - 1985	58	697	0.3 (0.1 – 1.9)	1.7 (0.6 – 5.2) †

* 1 mm; † 2 mm

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