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Original Article

# Outcomes for Patients with Non-metastatic Triple-negative Breast Cancer in New Zealand

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## Abstract

*Aims:* Triple-negative breast cancer (TNBC) has inferior outcomes to other subtypes of breast cancer. We studied the demographics and baseline breast cancer characteristics of patients in New Zealand with TNBC and assessed survival outcomes and prognostic/predictive factors.

*Materials and methods:* We searched the New Zealand breast cancer registry database and identified patients with TNBC without distant metastatic disease. We retrieved demographic, tumour characteristic and treatment information. Locoregional recurrence-free survival, breast cancer-specific survival (BSS), metastasis-free survival (MRFS) and overall survival were determined. Predefined univariate and multivariate analyses were carried out investigating the association of survival outcomes with treatment and tumour characteristics.

*Results:* In total, 1390 patients were identified, with a median follow-up of 3.5 years. The median age was 55 years. Thirty-eight per cent were node positive and 79% were grade III. Mastectomy was carried out in 53%, adjuvant radiation delivered in 66% and chemotherapy in 69%. The significant predictive factors for overall survival, BSS and MRFS were radiotherapy, chemotherapy and neoadjuvant chemotherapy. The significant prognostic indicators were lymphovascular invasion, nodal status and tumour size. On Kaplan–Meier analysis, the 5 year overall survival was 72%. The median time to death for those who died was 3.55 years with 92% of deaths within 5 years. Seventy-four per cent of patients had distant metastasis as a first recurrence and isolated local recurrences occurred in only 4.5%. Metastatic disease occurred in lung (55.9%) and was in multiple sites in 51%.

*Conclusion:* We report a large population-based series of TBNC without distant metastatic disease at diagnosis highlighting the unique behavioural characteristics of TNBC. Traditional therapies are positively associated with survival outcomes, and yet, particularly in the setting of recurrent disease, prognosis remains poor. Increased research into more effective systemic agents and the most effective timing of delivery of these may result in improved outcomes.



*Key words:* Chemotherapy; predictive factors; prognostic factors; radiotherapy; survival; triple-negative breast neoplasms

## Introduction

Triple-negative breast cancer (TNBC) has historically been defined as breast cancer low in expression of the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2). TNBC is a heterogeneous group, comprised of at least six different genetic subtypes. TNBC accounts for 15–20% of breast cancers [1,2], with increased prevalence in premenopausal women [3,4].

TNBC has a poorer prognosis compared with other subtypes, with decreased locoregional control, metastasis-free survival (MRFS) and overall survival [5,6]. Unlike other subtypes (ER/PR-positive, HER2-positive), no targeted therapies are available.

The aim of this study was to investigate the demographics, tumour characteristics and outcomes for non-metastatic TNBC patients in New Zealand and to study the impact of different treatments on the outcomes of locoregional control, MRFS, breast cancer-specific survival (BSS) and overall survival.

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## Materials and Methods

### *Case Identification*

Patients with non-metastatic TNBC were identified using the four prospectively collected New Zealand regional breast cancer registers. Inclusion in the registries required written consent. The registers were Waikato (established 1993), Auckland (established 2000), Christchurch (established 2009) and Wellington (since 2010). Included were patients from the earliest records available (1993) to December 2014. The data were reviewed and verified by the central data co-ordinator and discrepancies referred back to the local co-ordinator for revalidation. Missing data fields were in most cases able to be completed in this way.

The date of TNBC diagnosis was defined as the date of first histopathological diagnosis of TNBC. TNBC was defined as ER-negative, PR-negative and HER2-negative. ER and PR status was considered negative if Allred score was $\leq 2$ [7]. HER2 status was considered negative on immunohistochemistry (0 or 1+) or fluorescence *in situ* hybridisation (no amplification).

The tumour node metastasis (TNM) staging was verified as per the seventh edition of the American Joint Committee on Cancer (AJCC) staging system 2010 [8]. Tumour and nodal staging was evaluated clinically, radiologically and pathologically and the highest staging recorded. Systemic staging required radiological and/or histopathological confirmation. All patients with 'metastatic TNBC at diagnosis' were excluded. This was defined as metastasis diagnosed within 90 days of the initial TNBC diagnosis to allow for completion of staging investigations.

### *Treatment*

Patients were treated using prevalent national guidelines adapted according to clinician and patient preference. Radiation was used after wide local excision (WLE) and in higher risk postmastectomy patients (node-positive, close margin). Adjuvant chemotherapy was used when the benefit was seen to outweigh the risks. At this time, neoadjuvant chemotherapy was used for larger and/or node-positive tumours. Patients with clinical concern or higher risk (larger primary or nodal disease) underwent staging using a computerised tomography scan and a whole-body nuclear medicine bone scan.

### *Outcomes Assessed*

The outcomes evaluated included locoregional recurrences, development of metastases, BSS and overall survival. Outcomes for patients who received neoadjuvant chemotherapy were assessed separately.

The length of follow-up is defined as the time from diagnosis to the date of last clinical or radiological review or death. Locoregional recurrence-free survival (LRRFS) time is defined as the time from diagnosis to clinical, histopathological or radiological recurrence in ipsilateral breast/chest wall or regional lymph nodes at axillary, supraclavicular, infraclavicular or internal mammary regions. Metastatic recurrence-free survival time is the time from diagnosis to recurrence at a site more distal than locoregional sites. BSS time is defined as the time from diagnosis to death from a breast cancer-specific event and the overall survival time is the time to death from any cause.

The prognostic factors studied include tumour size, nodes (number of positive nodes), tumour grade, lymphovascular space invasion (LVI), chemotherapy given at diagnosis and type, radiotherapy (adjuvant/neoadjuvant), neoadjuvant chemotherapy, surgery (WLE or mastectomy), menopausal status (premenopausal: currently menstruating; perimenopausal: last menstrual period between 6 and 12 months ago; postmenopausal: last menstrual period greater than 12 months ago or age above 55 years) and family history of breast cancer. The treatments at presentation studied were chemotherapy (adjuvant/neoadjuvant and agent used) and adjuvant radiation (including dose, dose per fraction and volumes covered). We also analysed survival outcomes based on type of chemotherapy used (taxane versus other), time from tissue diagnosis to the start of chemotherapy (3/6 months versus longer), time from surgery to adjuvant chemotherapy (3/6 months versus longer) and year of treatment. The effect of neoadjuvant chemotherapy on downstaging was reported. We noted whether an immediate or delayed breast reconstruction was carried out.

### *Statistical Analysis*

Standard descriptive statistics were used to describe patient characteristics. Kaplan–Meier estimates of event-free rates and 95% confidence intervals were calculated for overall survival, BSS, MRFS and LRRFS. Prognostic factors for these outcomes were evaluated using univariate and multivariate Cox regression models to compute hazard ratios and 95% confidence intervals. Estimates were considered statistically significant for the values of $P < 0.05$.

## Results

There were 1390 patients with non-metastatic TNBC identified between May 1993 and December 2014. The median length of follow-up was 3.5 years. There was one patient with incomplete follow-up data as she had moved from New Zealand; four patients had died of causes other than breast cancer, with an unknown breast cancer status.

### *Demographics*

The clinical characteristics are depicted in Table 1. The median age at diagnosis was 55 years, with 59.6% postmenopausal. The mean body mass index was 28. The mean tumour size was 23 mm, with 10.5% of all patients with T3/T4 tumour stage and 37.8% lymph node positive (N1: 23%; N2: 8.5%; N3: 6.3%). Around 80% were high-grade tumours (grade III). LVI occurred in 31.5% of patients.

**Table 1**
Patient and tumour characteristics (total $n = 1390$)

| Characteristics | *n* (%) |
|---|---|
| Age at diagnosis (years) | |
| Median (range) | 55 (2–95) |
| Gender | |
| Female | 1390 (100) |
| Male | 0 (0) |
| Menopausal status | |
| Premenopausal | 504 (36) |
| Perimenopausal | 58 (4) |
| Postmenopausal | 828 (60) |
| Tumour stage (T) | |
| T1 | 606 (44) |
| T2 | 631 (45) |
| T3 | 95 (6) |
| T4 | 51 (4) |
| Tx | 7 (1) |
| Nodal stage (N) | |
| N0 | 843 (60) |
| N1 | 319 (23) |
| N2 | 119 (9) |
| N3 | 86 (6) |
| Nx | 23 (2) |
| Histological type | |
| Ductal | 1219 (88) |
| Lobular | 35 (3) |
| Other | 132 (9) |
| Unknown | 4 (0) |
| Tumour grade | |
| 1 | 29 (2) |
| 2 | 239 (17) |
| 3 | 1095 (79) |
| Unknown | 27 (2) |
| Lymphovascular space invasion | |
| No | 938 (67) |
| Yes | 438 (32) |
| No primary surgery | 14 (1) |

**Table 2**
Treatment administered (total $n = 1390$)

| | |
|---|---|
| Chemotherapy | |
| Adjuvant | 877 (63) |
| Neoadjuvant | 71 (5) |
| Unknown | 8 (1) |
| No | 434 (31) |
| Breast surgery | |
| Wide local excision | 610 (44) |
| Mastectomy | 761 (55) |
| Axillary surgery only | 5 (0) |
| No primary surgery | 14 (1) |
| Radiotherapy | |
| Yes | 911 (66) |
| No | 475 (34) |
| Unknown | 4 (0) |

The New Zealand national breast screening programme started in December 1998 for women aged between 45 and 69 years. In our study population, 805 patients fell into this category and in 312 (38.8%) detection was by screening mammogram.

*Treatments*

The treatments received are summarised in Table 2. Reconstruction was carried out in 19% who underwent a mastectomy (141/761).

Of the 911 patients receiving radiotherapy, 485 (53%) received hypofractionated radiation (greater than the standard 2 Gy per fraction) and 421 (46%) received standard fractionation. Additional radiation to the tumour bed (boost dose) was given to 178 (20%). Radiation was given most commonly to the breast or chest wall only, with 126 (14%) patients also receiving axillary radiation, 243 (27%) radiation to the supraclavicular fossa and only five (0.6%) received radiation to the internal mammary chain.

Adjuvant chemotherapy contained an anthracycline in 746/948 cases (78%), a taxane in 482/948 (49%) and a platinum-based compound in 3/948 (0.3%). For 69/948 (7.2%) patients the regimen was cyclophosphamide, methotrexate and fluorouracil (CMF). Chemotherapy was given to 423/828 (51%) postmenopausal women and 465/562 (83%) premenopausal women.

Neoadjuvant chemotherapy in anticipation of breast surgery was planned for 71 patients, most under the age of 60 years (55/71, 77.5%). Surgery was completed in 90% (64). Most were clinically T4 before chemotherapy (30 patients, 45.3%) with only five patients T1 (7.8%). A pathological complete response was achieved in five patients. Anthracyclines were included in the regimen in 57.7% of cases and taxane in 56.3%. A mastectomy was carried out for 58 patients (90.6%) and WLE in six (9.4%).

*Survival Outcomes*

There were 340 deaths, 259 due to breast cancer. The median overall survival was 12.9 years (95% confidence interval 11.8–14) with 5 year overall survival 72% (95% confidence interval 69.5–75.1) and 10 year overall survival 61% (95% confidence interval 56.5–65.3) (see Figure 1). The median BSS was 15.1 years (95% confidence interval 14.1–16); 5 year BSS was 76.8% (95% confidence interval 76.52–77.08) and 10 year BSS was 71.5% (95% confidence interval 67.9–75.1) (see Figure 2). The median MRFS was 13 years (95% confidence interval 12–14); 5 year MRFS was 69.8% and 10 year MRFS was 60.9%. The median LRRFS was 15.3 years (95% confidence interval 14.1–16.4); 5 year LRRFS was 83.2% and 10 year LRRFS was 72.7%.

*Prognostic/Predictive Factors*

The significant prognostic and predictive factors for overall survival on univariate and multivariate analyses were radiotherapy, chemotherapy (adjuvant/neoadjuvant), neoadjuvant chemotherapy, LVI, nodal status and T staging (Table 3). Similar results were seen for BSS and MRFS. Breast surgery was significant on univariate but not on

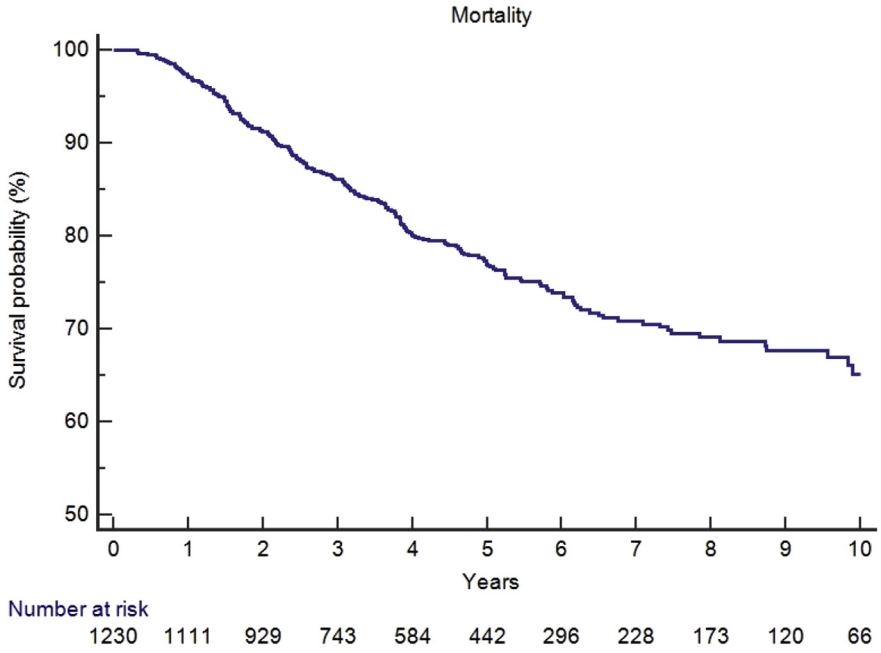


**Fig 1.** Overall survival of women with triple-negative breast cancer without distant metastatic disease at diagnosis.

multivariate analysis. For LRRFS the significant prognostic/predictive factors remained, except that breast surgery became significant and neoadjuvant chemotherapy was not. The type of chemotherapy (taxane versus other) did not have a statistically significant association with survival ($P = 0.369$; 95% confidence interval 0.835–1.165), nor did the year of treatment ($P = 0.204$; 95% confidence interval 0.546–0.788). When the time from surgery to chemotherapy was studied there was a trend to increasing mortality as the delay increased. The odds ratios for overall survival when delay to chemotherapy was compared with ≤30 days was 0.620 (0.281–1.369) for 30–60 days and 0.893 (95% confidence interval 0.646–1.235) for ≥60 days.

*Recurrence*

In total, 343 patients (25%) had a first recurrence; 88 were locoregional, 49 were concurrent locoregional and systemic and 206 were systemic only. Thus, 74% of first recurrences were systemic. The median time to

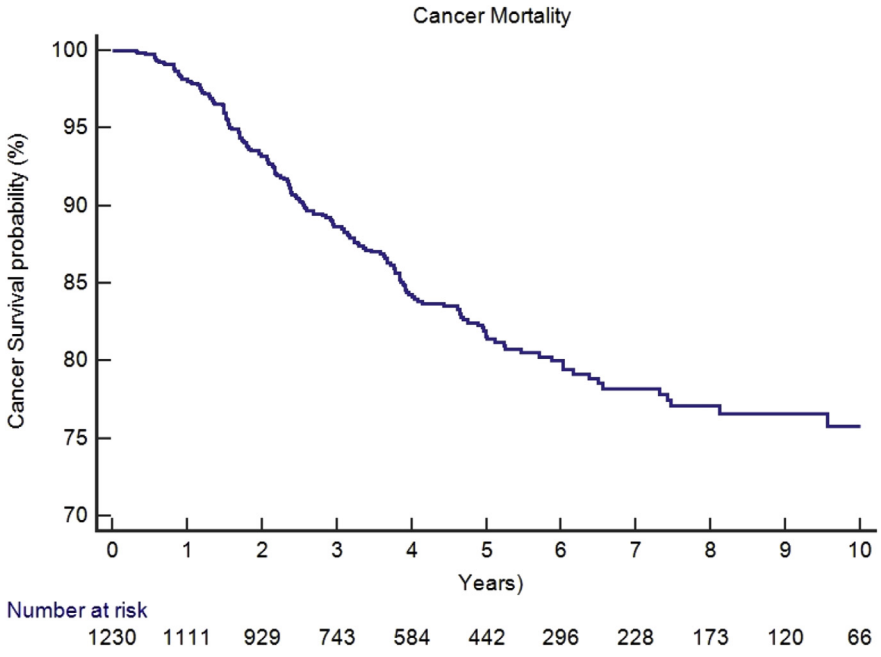


**Fig 2.** Breast cancer-specific survival with triple-negative breast cancer without distant metastatic disease at diagnosis.

**Table 3**
Multivariate Cox proportional hazard models for overall survival and locoregional recurrence-free survival

| | Hazard ratio (95% confidence interval) | *P* value |
|---|---|---|
| Overall survival | | |
| Radiotherapy | 0.66 (0.52–0.84) | <0.001 |
| Chemotherapy | 0.38 (0.30–0.493) | <0.001 |
| Neoadjuvant chemotherapy | 3.29 (1.95–5.54) | <0.001 |
| Lymphovascular invasion | 1.62 (1.27–2.06) | <0.001 |
| Node positive | 2.59 (2.01–3.35) | <0.001 |
| T stage | | <0.001 |
| T2 compared with T1 | 2.14 (1.61–2.83) | <0.001 |
| T3 compared with T1 | 3.64 (2.42–5.46) | <0.001 |
| T4 compared with T1 | 3.27 (1.82–5.85) | <0.001 |
| Locoregional recurrence-free survival | | |
| Radiotherapy | 0.40 (0.28–0.58) | <0.001 |
| Chemotherapy | 0.47 (0.34–0.64) | <0.001 |
| Lymphovascular invasion | 1.56 (1.13–2.15) | 0.006 |
| Node positive | 2.82 (2.02–3.95) | <0.001 |
| Breast surgery | 0.55 (0.37–0.81) | 0.002 |
| T stage | | 0.001 |
| T2 compared with T1 | 1.47 (1.06–2.05) | 0.022 |
| T3 compared with T1 | 2.53 (1.41–4.53) | 0.002 |
| T4 compared with T1 | 3.60 (1.71–7.57) | 0.001 |

development of recurrence was 1.6 years. Table 4 shows sites of recurrence based on surgery type.

The most common site of distant recurrence was lung (55.9%). Other sites were bone (44.4%), liver (30.9%) and brain (21.9%). In 51% of cases the metastases occurred at multiple sites.

## Discussion

We report a large database study of all patients diagnosed with TNBC, to our knowledge the first report of this kind in Australasia. There were 1390 patients included. The median age was 55 years, with the majority postmenopausal. At diagnosis, 38% of patients had node-positive disease and most were grade III. About 40% were detected by screening and just over half were treated with mastectomy, with low reconstruction rates. Most received radiation and chemotherapy. The significant predictive factors for overall survival, BSS and MRFS on univariate and multivariate analyses were radiotherapy, chemotherapy (adjuvant or neoadjuvant), neoadjuvant chemotherapy and the prognostic factors LVI, nodal status and T staging. On Kaplan–Meier analysis, the 5 year overall survival was 72% and the median time to death from breast cancer was 3.55 years, with 92% of the breast cancer deaths occurring within 5 years. Recurrences occurred early (median 1.6 years) and for 74% there was a component of systemic spread at first recurrence. Isolated local recurrences were rare (4.5%). Metastases were visceral and frequently at multiple sites.

Although traditionally considered a premenopausal cancer, in our series 60% were postmenopausal. This is similar to other series reporting a median age of 55 years [9] and 54 years [10], with 60.3% of patients postmenopausal [9]. The median age at diagnosis for non-TNBC, however, is older at 60 years [10], suggesting an earlier age of onset for TNBC.

At presentation, 41% had T1 disease, lower than reported for non-TNBC, with 62% T1 at presentation, but similar to TNBC rates reported in other literature of 36.5% [11] and 41% [9]. Node-positive disease occurred in 37.8% of patients, similar to rates of non-TNBC nodal positivity in 45.6% and

**Table 4**
Site of relapse

| Relapse type | Mastectomy ($n = 761$) | Wide local excision ($n = 610$) |
|---|---|---|
| First recurrence | 229 (30%) | 105 (17%) |
| Local and regional or regional only | 16 (7%) | 8 (8 %) |
| Local and regional or regional alone with systemic | 34 (15%) | 15 (14%) |
| Systemic only | 152 (66%) | 46 (44%) |
| Local only | 27 (12%) | 36 (34%) |
| Systemic disease after local recurrence | 13/27 (48%) | 12/36 (33%) |
| Systemic disease after locoregional recurrence | 22/43 (51%) | 17/44 (40%) |

other series of TNBC reporting nodal positivity in 54.4% and non-TNBC, 46.1% [5]. The similar nodal positivity reported for non-TNBC is consistent with series that suggest that for a given T size, TNBC has relatively less nodal involvement with a propensity for haematogenous spread [11]. TNBC in our series were predominantly ductal (87.7%) and grade III (78.8%). The predominance of grade III disease is similar to other series [9,11], but markedly increased compared with non-TNBC series reporting 28.3% grade III disease [5].

Of the 805 eligible for breast cancer screening, 38.8% had their cancer screen detected, similar to the overall rates of screen detection in New Zealand reported in 2008 as 37% [12]. Other series reported lower rates of screen-detected cancers in TNBC. One series reported a statistically significant difference between TNBC and other breast cancers in the rate of screen detection (19.5% compared with 36% for non-TNBC, $P = 0.00080$ [13]).

Just over 50% underwent mastectomy. This figure is similar to an audit of patients diagnosed with all non-metastatic breast cancer in New Zealand, which reported that 52.9% underwent mastectomy [12]. The reconstruction rate was 20%. Although this rate is lower than in other series [14] this may reflect local practice rather than being a consequence of TNBC. In Christchurch, the rate of immediate reconstruction for all patients undergoing a mastectomy is similar to the TNBC rate at 21% (207/990).

Radiation treatment was delivered to 65.5%; 92% of patients who underwent a WLE and 46% of those undergoing a mastectomy. This is similar to rates for New Zealand breast cancer patients overall, with 95% of WLE and 42.5% of mastectomy patients receiving radiation [12].

Chemotherapy was given to 68.2% at diagnosis, higher rates than reported for breast cancer patients in general in New Zealand (54%), but also higher than a similar series of TNBC [5,12]. A greater proportion of premenopausal patients received chemotherapy, perhaps due to increased comorbidities in postmenopausal women or this may reflect under-treatment of this group.

The significant prognostic and predictive factors for overall survival, BSS and MRFS on univariate and multivariate analyses were radiotherapy, chemotherapy (adjuvant/neoadjuvant), neoadjuvant chemotherapy, LVI, nodal status and T staging. Menopausal status, family history and grade were not statistically significant. This may be due to small numbers with lower grade and positive family history. Menopausal status was not significantly associated with survival outcomes. One could hypothesise that TNBC is not hormonally driven and thus less affected by menopausal status. A further series reported similar prognostic factors but also found an effect on disease-free survival for age less than 65 years [9]. In our series, younger age was a marker for a higher risk of relapse but did not have an effect on overall survival on multivariate analysis. Breast surgery was a significant predictive factor for overall survival, BSS and MRFS, significant on univariate analysis but not on multivariate analysis. For LRRFS, the extent of breast surgery (lumpectomy versus mastectomy) was significant on both univariate and multivariate analysis. This may reflect an increase in local recurrence rates in the setting of breast conservation with no effects on the overall survival, as salvage surgery is usually possible. This would be supported by data in the literature that suggests a higher local recurrence in breast TNBC patients undergoing breast conservation compared with other forms of breast cancer [15]. In our series, however, the local recurrence rate after breast conservation was low at 5.8%. Some have argued for more aggressive surgery in TNBC due to local recurrence concerns. We have found no evidence to support this. The type of chemotherapy and year of treatment were also not significant. The effect of differing chemotherapy agents may be diluted by different numbers of cycles, dose density and differing chemotherapy combinations.

On Kaplan–Meier analysis, the 5 year overall survival was 72%, similar to other series at 68.2% [9] and 82.3% [16]. The breast cancer survival curve is steepest in the initial 5 years and seems to plateau beyond this, with 5 year BSS 76.8% and 10 year BSS 71.5%. For those who died, the median time to death from breast cancer was 3.55 years and 92% of the deaths occurred within 5 years. This propensity for early breast cancer death is reflected in other TNBC series, which reported for those who died that 70% of deaths occurred within the first 5 years with a median time to death of 4.2 years [5] and contrasts with 44% of deaths within the first 5 years for non-TNBC and a median time to death of 6 years [6].

Recurrences occurred early with TNBC at a median of 1.6 years, similar to a Dutch series with a median time to recurrence of 1.6 years [16].

A large proportion who had a first recurrence had a component of systemic failure (74%). Indeed, an isolated local first recurrence only occurred in 4.5%. Isolated locoregional recurrence was associated with subsequent development of systemic metastatic disease in 40–50%. Other studies found a similar low rate of isolated locoregional recurrences, with a component of systemic failure in 53.3% of those with a first recurrence [16] and a local recurrence prior to a systemic recurrence of 25% [5].

The first recurrence was more likely systemic than locoregional for patients treated with mastectomy compared with breast conservation. For those undergoing breast conservation, the number developing a first recurrence that was locoregional (7.2%) and those developing a first recurrence that was systemic (7.5%) was very similar. For those undergoing a mastectomy, a systemic recurrence (20%) was much more common than locoregional only (5.6%).

The site of development of metastatic disease differs markedly from non-TNBC. The recurrence in TNBC is more likely visceral and occurs in multiple sites. In non-TNBC the first site of metastasis is bone in 62% of patients, with lung, liver and brain all less than 20% [17]. The rate of bone metastases (44%) was higher than reported in other series (10%), which may relate to detection methods [17].

Neoadjuvant chemotherapy was carried out as a response to high T/N stage. Pathological complete responses were low at less than 10% compared with 30–60% rates reported in the literature [18]. This may be explained by the use of older chemotherapy regimens, which did not

always include a taxane and predated the use of platinum-based chemotherapy, vascular endothelial growth factor monoclonal antibodies [18], poly ADP-ribose polymerase 1 (PARP) inhibitors and immunotherapy; agents currently being explored. There is evidence from meta-analysis that capecitabine in combination with standard chemotherapy for patients who do not achieve a pathological complete response may improve disease-free survival and overall survival in selected patients with TNBC [19].

There is recent evidence that the time to starting chemotherapy after surgery is important, with one series indicating a detrimental effect on both overall survival and BSS with delays to adjuvant chemotherapy [20]. We found a trend for decreasing overall survival with delay in chemotherapy after surgery, but this effect may have been diluted by differences in the types, dose intensity and combinations of agents used and was not statistically significant. The high systemic relapse rates in our series may suggest a need for prompt commencement of systemic chemotherapy and may give weight to consideration of neoadjuvant chemotherapy.

TNBC is known to be a heterogeneous group with multiple molecular subtypes [21]. Knowledge of the molecular subtype of the TNBC is becoming available and is expected to guide treatment strategies in the future.

The strength of this study is that it was a prospective study of all registry cases, including patients not routinely included in randomised controlled trials, such as the older and unwell. This allows us to understand the outcomes for the population of patients in New Zealand with TNBC, including how the patients and subsequent outcomes may differ from those in clinical trials and to gain insights into how we can work to improve the outcomes.

Although prospectively collected, this was a database study and hence there may be inconsistencies in the collection of data, despite rigorous quality assurance. Inherent in a study of this type is confounding bias. For example, younger, fitter patients or those with a worse prognosis may be considered for treatment ahead of others. The lack of collection of molecular data also limits the analyses able to be carried out. During the period of reporting treatment our understanding of TNBC and treatment strategies has changed and hence our results may not be completely applicable to current patients.

## Conclusion

This population-based series confirms that the behaviour of TNBC differs from non-TNBC and highlights that particularly in the setting of relapse, TNBC has an aggressive course. Traditional treatments such as surgery, radiation treatment and traditional chemotherapy are significantly associated with improvement in survival outcomes. However, the fact that recurrence rates remain high confirms the ongoing need for further trials of additional effective therapies to prevent recurrence and improve the prognosis for this group of patients and participation in these trials should be encouraged. The timing of systemic therapy needs further investigation in light of high systemic relapse rates and evidence suggesting delays may have an impact on survival outcomes.

## Conflict of Interest

The authors declare no conflict of interest.

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