The Warwick Experience of the Oncotype DX[®] Breast Recurrence Score[®] Assay as a Predictor of Chemotherapy Administration

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Keywords

Oncotype DX · Recurrence Score · Multigene assay · Chemotherapy

Summary

Introduction: Oncotype DX[®] analyses the expression of 21 genes within tumour tissue to determine a Recurrence Score[®] (RS). RS is a marker of risk for distant recurrence in oestrogen receptor-positive early breast cancer, allowing patient-specific benefit of chemotherapy to be evaluated. Our aim was to determine whether the introduction of Oncotype DX led to a net reduction in chemotherapy use. **Methods:** Consecutive patients that underwent Oncotype DX at Warwick Hospital were reviewed. Patients were anonymised and re-discussed at a multidisciplinary team meeting (MDM; without RS), and treatment recommendations were recorded. This was compared to the original MDM outcome (recommendations made with RS). Differences were analysed using Wilcoxon signed-rank test. **Results:** 67 patients were identified. Proportions of high, intermediate and low risk were 28, 33 and 39% (n = 19/22/26), respectively. Without RS, 56 (84%) patients were recommended for chemotherapy and 3 were not. The remaining 8 patients were deemed borderline for requiring chemotherapy and referred for discussion with an oncologist. With availability of RS, 34 (50%) patients were recommended for chemotherapy, and 24 (43%) patients were spared chemotherapy (p < 0.0005). The net reduction in chemotherapy was 33%. **Conclusion:** There has been a significant reduction in chemotherapy usage in patients at Warwick since the introduction of Oncotype DX.

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Introduction

Breast cancer is the most commonly diagnosed cancer in the UK, with over 55,000 new cases diagnosed in 2015 [1–4]. Greater than 80% of these cancers are diagnosed at an early stage (stage I–II) [2]. Around three-quarters of all breast cancer patients undergo surgical resection [5]; however, subsequent decision-making for adjuvant treatments can prove challenging.

Chemotherapy can reduce the risk of breast cancer recurrence, but the yields are small and variable [6]. Complications of chemotherapy can be life-threatening and therefore must be balanced against the benefits. Traditional methods of selecting patients for chemotherapy according to patient and tumour characteristics are vague and unscientific. Factors such as age, menopausal status, oestrogen receptor (ER) status and lymph node involvement may be taken into consideration. Patients with tumours associated with poorer prognosis may be offered chemotherapy [7]. Online resources such as Adjuvant! Online and PREDICT can be used to reinforce decisions. Both are web-based prognostication tools. Uniquely, PREDICT uses an algorithm that considers human epidermal growth factor receptor 2 (HER2) status, Ki67 status and mode of detection. It was developed using a UK-based cancer registry and validated in a second UK-based registry. It is a free resource that is accessible to both clinician and patient [8]. The accuracy of PREDICT has been criticised, especially in patients under 35, hence why clinicians are advised to interpret results with caution [9].

Oncotype DX[®], developed by Genomic Health (Redwood City, CA, USA), was marketed in 2004, becoming available in the UK on the National Health Service (NHS) in 2007. It provides predictive information for ER-positive and HER2-negative breast cancers where the benefit of chemotherapy remains uncertain. The Oncotype DX assay analyses a panel of 21 genes from the tumour

specimen using reverse transcription polymerase chain reaction. The result is given as a Recurrence Score® (RS); it helps predict the benefit of chemotherapy and 10-year risk of distant recurrence. The RS is a continuous value (0–100) and allows for individualised adjuvant treatment decisions with regards to chemotherapy. Retrospective analysis of data from the NSABP-14 and B-20 trials has enabled validation of the RS; an RS of greater than 30 is deemed to indicate a high risk of disease recurrence. This group of patients would benefit significantly from chemotherapy [10, 11].

Warwick Hospital began utilising Oncotype DX in 2012. Our routine practice is to discuss all breast cancer patients at the multi-disciplinary team meeting (MDM), including whether or not individuals should be offered adjuvant chemotherapy. The outcomes of such meetings are typically based upon the opinions of healthcare professionals (surgeons, oncologists, pathologists and radiologists) discussing the clinical and histological characteristics for each case. Oncotype DX use has been associated with a noticeable reduction in adjuvant chemotherapy being offered to breast cancer patients. The aim of this study is to quantify this impact of Oncotype DX.

Materials and Methods

A prospectively collected database of all Oncotype DX requests between February 2012 and November 2016 was analysed. All were ER-positive and HER2-negative. Patients were anonymised and re-discussed at an MDM without the knowledge of the RS, and recommendations for chemotherapy were recorded. This information was compared to the original MDM outcome where recommendations were made with the knowledge of each RS. Differences were analysed using Wilcoxon signed-rank test.

Results

A total of 76 patients were identified from our Oncotype DX database between February 2012 and November 2016. Of these, 9 patients were excluded due to a lack of data. Patient and tumour characteristics are summarised in table 1. Axillary lymph node macrometastases were present in 4 patients, and micrometastases in 5. No patients had isolated tumour cells present. The mean tumour size measured 28.3 mm (range 2–100 mm). Proportions of high, intermediate and low risk were 28, 33 and 39% ($n = 19/22/26$), respectively.

Without the knowledge of the RS, 56 (84%) patients were recommended for chemotherapy at the MDM. 3 cases did not warrant chemotherapy. The remaining 8 (12%) patients were deemed borderline for requiring chemotherapy as the benefits were thought to be uncertain. These patients were referred to the oncology department for further discussion (fig. 1).

Following the availability of each RS, the MDM recommended 34 (51%) patients for chemotherapy. Of the 56 patients who were recommended for adjuvant chemotherapy at the MDM without RS, 24 (43%) were spared chemotherapy ($p < 0.0005$). 1 of the 3 patients initially deemed to not require chemotherapy was offered chemotherapy following an unexpectedly high RS.

Table 1. Patient and tumour demographics

Number of patients, <i>n</i>	67
Median age, years	51 (range 34–71)
Average tumour size, mm	28.3 (range 2–100)
<i>T</i> stage, <i>n</i>	
T1	24
T1a	1
T1b	3
T1c	20
T2	35
T3	8
Grade, <i>n</i>	
1	5
2	31
3	31
Nodal status, <i>n</i>	
Macrometastases	4
Micrometastases	5
Isolated tumour cells	0
Recurrence Score, <i>n</i>	
High	19
Intermediate	22
Low	26

Fig. 1. Chemotherapy recommendations with and without knowledge of Recurrence Scores.

Fig. 2. Percentage of patients recommended for chemotherapy by risk group, with and without knowledge of Recurrence Scores.

Of the 8 patients who had unclear chemotherapy benefits, only 1 was recommended for chemotherapy with an available RS. In total, 49% of patients had a change in treatment recommendation, and there was a net reduction in chemotherapy of 33%.

The low RS group underwent the greatest reduction in chemotherapy use at 66%. In the intermediate RS group, there was an absolute reduction of 23%. There was no reduction in chemotherapy use in the high RS group, with 95% being recommended for chemotherapy (fig. 2).

Discussion

Oncotype DX has been incorporated into many breast units around the world. NICE approved its use in 2007, and although the uptake was initially slow, perhaps due to cost, it is now available on the NHS for selected patients. Traditional methods for chemotherapy decision-making in ER-positive, HER2-negative disease have been imprecise in the past. Although the wealth of experience harnessed within an MDM should not be underestimated, there may be a tendency to overtreat patients. Traditionally, nodal status was the mainstay of predicting the future outcome of the patient; this can lead to gross overtreatment. The SWOG-8814 trial demonstrated that only 5% of patients with node-positive disease benefited with a survival advantage at 10 years after adjuvant chemotherapy. For 95% of patients, no survival advantage exists, yet they will suffer the side effects of chemotherapy [12]. Long-term side effects of chemotherapy such as cardiac toxicity and neurotoxicity can have a detrimental effect on a patient's quality of life. Younger patients undergoing chemotherapy may suffer with significant issues surrounding sexual wellbeing and fertility [13]. There may also be an increased risk of developing secondary cancers such as acute myeloid leukaemia and myelodysplastic syndrome [14].

A Canadian report demonstrated a decrease in workplace productivity, whereby nearly 50% of respondents noted a reduced physical ability to work following breast cancer treatment. Patients undergoing chemotherapy were more likely to suffer a greater loss of income and to require longer than 4 months of leave [15]. Chemotherapy is undoubtedly disruptive to the patient at a personal level but also at an economical level.

Therefore, the need to provide objective evidence to the patient and allow for informed decision-making has never been greater. The Oncotype DX can assist doctor-patient discussions and allow for more accurate, scientifically based decisions to be made.

The TAILORx trial is a multicentre prospectively conducted trial of over 10,000 women with early-stage breast cancer, exploring the predictive value of the RS within this population. The trial has demonstrated that patients with an RS of <11 have a <1% chance of distant recurrence at 5 years if treated with hormone therapy alone [16]. The trial is ongoing to accrue patients with intermediate risk (RS 11–25), and we await the next interim analysis to be published. PlanB, a trial using the RS as a key tool in decision-making for chemotherapy, has already demonstrated disease-free survival rates of 94% in women with RS between 11 and 25, treated with hormone therapy alone [17].

This study allowed us to gain insight into our own practice and undoubtedly reflects the practices of other units in the UK. It adds to the current body of evidence, mirroring these outcomes and

demonstrating a significant reduction in chemotherapy use through the use of Oncotype DX. This is beneficial to patients, clinicians and healthcare providers. The uncertainty of chemotherapy benefit was reflected in 8 of our patients without RS. It can be challenging to counsel this group of patients about chemotherapy without personalised and objective evidence. With the knowledge of the RS, nearly all of these patients were spared chemotherapy. Additionally, there are likely to be cost savings to the healthcare provider, although a formal cost evaluation has not been performed in this study.

In many countries, utilisation of Oncotype DX is not yet feasible due to its cost. However, sparing patients from expensive chemotherapy agents is likely to be more cost effective in the long term. A recent Turkish study demonstrated that 27% of patients were spared chemotherapy due to Oncotype DX testing, which is highly likely to result in a cost saving overall [18]. Within the UK, a recent study calculated a cost saving of approximately GBP 75,000 in a study population of 201 patients, when considering the cost of testing all patients plus the costs for the 37% of patients undergoing chemotherapy [19]. This has large-scale implications on a public health service such as the NHS in the UK and others worldwide.

International breast units have produced comparable results with regard to chemotherapy usage. A Hong Kong study revealed an absolute reduction of 14.4% ($p < 0.001$). The demographics of these patients were similar to ours in terms of tumour characteristics [20].

A pooled analysis of 4 European studies involving a total of 527 patients boasts an overall net reduction in chemotherapy of 26%, and a change in treatment recommendation of 32%. Across the individual studies, conclusions were homogenous with the systematic review [21].

Despite a growing body of evidence in favour of Oncotype DX, its limitations are beginning to surface. A case report has emerged of a 62-year-old female who was initially diagnosed with a node-negative, 16-mm, grade 2, HER2-negative, ER-positive, invasive ductal carcinoma. Following breast-conserving surgery, Oncotype DX testing was ordered on the tissue sample and an RS of 0 was returned. No chemotherapy was recommended; however, halfway through radiotherapy the patient developed symptoms of cord compression, and magnetic resonance imaging revealed bone metastases. The spinal canal was decompressed, and tissue biopsy from surgery confirmed metastatic breast carcinoma with neuroendocrine differentiation. The authors suggest that Oncotype DX should not be used in rare histological subtypes of breast cancer [22].

Despite our study being limited by small numbers, the net reduction in chemotherapy in our unit was clinically and statistically significant. When compared to the larger systematic studies mentioned, our net chemotherapy reduction rate was greater. Although our secondary MDM (without knowledge of RS) was anonymised, the primary MDM outcome (with RS knowledge) was not reconfirmed; therefore, changes in practice over time were not accounted for. There were also differences in the number of clinicians present at each MDM, which may have influenced outcomes.

In conclusion, Oncotype DX can significantly reduce chemotherapy rates and greatly improve decision-making for patients originally thought to have borderline benefit from chemotherapy. Healthcare services, particularly those which are fund-restricted,

are likely to benefit from potential cost saving without compromising outcomes of breast cancer patients, but clinicians should be aware of rare and emerging shortcomings of the test.

Disclosure Statement

The authors declare no conflicts of interest.

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