European Journal of Cancer (2014) xxx, xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre

Terri Patricia McVeigh [a,*], Lauren M. Hughes [a], Nicola Miller [a], Margaret Sheehan [b], Maccon Keane [c], Karl J. Sweeney [b], Michael J. Kerin [a]

[a] *Discipline of Surgery, National University of Ireland Galway, Ireland*
[b] *BreastCheck, Western Unit, Ireland*
[c] *Department of Oncology, Galway University Hospital, Ireland*

Received 19 April 2014; received in revised form 31 July 2014; accepted 3 August 2014

KEYWORDS
Breast cancer
Oncotype DX
Oncotype
Genomic profiling
Genomic assay
Recurrence score
Adjuvant chemotherapy
Chemotherapy
Individualised therapy

Abstract ***Introduction:*** The use of chemotherapy in node-negative, (O)Estrogen Receptor (ER)-positive breast cancer has changed significantly since the introduction of Oncotype DX to determine systemic recurrence risk based on tumour genomic signature.

Aims: This study aims to

1. Document longitudinal changes in chemotherapy use,
2. Assess the impact of new evidence on local protocol.

Methods: A cohort study was undertaken, including consecutive patients with early node-negative, ER-positive breast cancer diagnosed between 2006 and May 2013, including a period of prospective clinical trial (Trial Assigning Individualised Options for Treatment (TAILORx)) recruitment. Data were collected regarding patient demographics, tumour clinico-pathological features, Oncotype DX use and recurrence score and chemotherapy use. All therapeutic decisions were made following multidisciplinary discussion, with adherence to guidelines and consideration of trial protocol and Oncotype DX recurrence scores.

Results: 479 consecutive patients were included in the study, of whom 241 (50%) underwent Oncotype DX testing, 97 as part of the TAILORx clinical trial. Oncotype DX testing began on a trial basis in 2007 and until October 2011, only patients enrolled on TAILORx availed of genomic profiling. From October 2011, Oncotype DX was used in all eligible patients as per

* *Corresponding author:* Address: Discipline of Surgery, Clinical Sciences Institute, National University of Ireland Galway, Galway, Ireland. Tel.: +353 877912374.
E-mail address: terri.mcveigh@gmail.com (T.P. McVeigh).

http://dx.doi.org/10.1016/j.ejca.2014.08.002

National Cancer Control Programme (NCCP) guidelines. A total of 216 (45%) patients received chemotherapy. The use of chemotherapy changed in inverse proportion to the availability of the genomic assay. Of those patients in whom Oncotype DX was utilised, 138 (57%) were spared chemotherapy.

Conclusion: This study validates the use of molecular testing in the rationalisation of systemic therapy.

1. Introduction

1.1. Management of breast cancer

Disease free and overall survival rates from breast cancer have increased steadily over the last several years despite a trend towards less aggressive surgical techniques [1]. Breast conserving surgery represents the gold standard surgical approach to the breast, while the surgical management of the axilla is trending increasingly towards a more minimally invasive approach especially in the case of limited nodal disease burden [2]. Enhanced understanding of the molecular basis of breast cancer has allowed targeting of hormonal therapy or immunologic agents [3–5]. The use of systemic therapy in the management of breast cancer has led to a dramatic reduction in cancer-related mortality by virtue of eradication of micro-metastatic disease in the circulation [6]. The benefit of adjuvant chemotherapy is most apparent in those cases in which the cancer cannot be cured by local treatment alone [7,8]. In those patients with node-negative early-stage breast cancer, however, the absolute benefit of systemic treatment is modest [9], but the associated potential adverse effects are considerable. Therefore, in line with other breast cancer treatment modalities, the application of chemotherapy is becoming increasingly individualised, and over-treatment avoided wherever possible. To this end, international guidelines recommend inclusion of gene expression analysis in risk stratification and decision-making in prescription of adjuvant systemic therapy [10,11].

1.2. Breast cancer genomics

Our understanding of tumour behaviour may be enhanced by gene expression analysis. The risk of distant spread or recurrence of a tumour may not simply be a function of increasing size or temporal acquisition of metastatic ability, but may exist as an inbuilt property of the tumour from the very beginning of the neoplastic process [8]. The use of chemotherapy is based traditionally on factors providing prognostic information, but the genomic profile of a tumour may provide additional information in predicting the recurrence risk of a tumour, and the degree of benefit associated with chemotherapy [8,9].

Oncotype DX (Genomic Health Inc., Redwood City, CA) is a clinically validated twenty-one-gene genomic assay that can quantify the risk of breast cancer recurrence [12–14]. The gene panel includes five reference genes and sixteen cancer-related genes, including those associated with cell proliferation, invasion and hormone response. The test generates a recurrence score between 0 and 100 that correlates to the likelihood of disease recurrence within 10 years of diagnosis. Prospective validation of the assay was carried out using a cohort from the National Surgical Adjuvant Breast and Bowel Project (NSABP), trial B-14 and B-20 [13,14]. Patients in these trials were divided into low-, intermediate- and high-risk groups based on recurrence scores ($<$18, 18–30 and $\geqslant$31, respectively). The additional chemotherapy benefit when added to hormonal therapy compared to hormones alone was large in the high-risk group, and minimal in the low-risk group. The benefit in the intermediate group was unclear [14]. The protocol of TAILORx (Trial Assigning Individualised Options for Treatment) has assigned different definitions to risk categories, with 'low risk' defined as scores less than 10, high-risk greater than 26 and intermediate between 11 and 25, inclusive. This new 'intermediate-risk' group is randomised to receive either hormonal therapy alone or combination chemotherapy and hormonal therapy [15,16]. This trial will hopefully increase our understanding of the utility of adjuvant systemic therapy in this group. TAILORx recruitment in Ireland was run through the All Ireland Cooperative Research Oncology Group (ICORG), and interested and participating oncologists were provided with information and educational materials at ICORG meetings, by post and online.

The Health Service Executive (HSE) provides health and personal social services for every Irish resident, using taxation accrued public funds. A substantial proportion of the Irish population also avails of private health insurance from a variety of insurance brokers. Ireland was among the first European countries to publicly reimburse the Oncotype DX test from October 2011. Prior to this date, Oncotype DX had been available for use in this patient cohort in Ireland on trial basis only, as part of the TAILORx trial [16]. From October 2011, Oncotype DX was used in all eligible patients as per national Irish Society of Medical Oncology and National Cancer Control Program guidelines [17]. Recruitment for this trial began in our institution

Please cite this article in press as: McVeigh T.P. et al., The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.08.002

in September 2007 and continued until May 2010. Between May 2010 and October 2011, Oncotype DX was included in only a small proportion (20%) of private health insurance policies, and was not publicly available. The test was therefore not routinely used in clinical practice.

2. Aims

This study aims to document longitudinal changes in the uptake of genomic profiling technologies and systemic chemotherapy, and to assess the impact of new evidence on local protocol.

3. Methods

A retrospective cohort study was undertaken. Patients were included if their disease fulfilled the following criteria: unilateral, stage T1 or T2, between 10 and 50 mm in size, node-negative, (O)Estrogen Receptor (ER)-positive and Her2/neu negative. The study group comprised 471 consecutive female patients diagnosed between January 2006 and May 2013. Patient demographic and tumour clinico-pathological data, Oncotype DX recurrence scores and information regarding chemotherapy treatment regimes, complications and patient outcomes were obtained by chart review. Oncotype DX testing was performed centrally at the Genomic Health Laboratory, using paraffin-embedded tissue samples taken from the tumour. All tumour specimens were analysed in-house in the department of pathology, and interpretation validated by a dedicated breast pathologist. All reports were discussed at a weekly monthly disciplinary meeting. Tumour grade was scored using Elston–Ellis modification of the Scarff–Bloom–Richardson grading system (Nottingham grading system) [18], based on assessment of tubule formation, nuclear pleomorphism and mitotic count. Tumours were staged as per TNM staging system [19].

The use of chemotherapy in patients enrolled to the TAILORx clinical trial was based on recurrence score and randomisation as per protocol. The use of chemotherapy in patients managed outside this trial was guided by recurrence score and decided based on a case-by-case discussion at the multidisciplinary meeting, and in full consultation with patients. All patients received adjuvant hormonal therapy, and in the case of breast conserving surgery, adjuvant radiotherapy. The standard chemotherapy regime consisted of Docetaxel and Cyclophosphamide or Doxorubicin and cyclophosphamide.

A comparative analysis was carried out across four time intervals:

1. Period prior to availability of Oncotype DX in Ireland (2006–September 2007).
2. Period during TAILORx recruitment (September 2007–May 2010).
3. Period following TAILORx recruitment and prior to public reimbursement (May 2010–October 2011).
4. Period in which Oncotype DX testing is part of routine clinical practice (October 2011–May 2013).

All data were analysed using SPSS version 20.

4. Results

4.1. Patient demographics

Criteria for inclusion in this study included a diagnosis of unilateral, stage T1 or T2 tumours ($\leqslant$50 mm in maximum diameter), node-negative, ER-positive HER2-negative breast cancer. Three patients had tumours less than 1 cm and were excluded from analysis. Five hundred consecutive female patients were diagnosed with tumours fitting this molecular profile over the study period. Twenty-five of these patients were excluded from analysis in the case of bilateral disease, ipsilateral concomitant second tumour of different morphology or if the diagnosis pertained to a disease recurrence. Two patients had multifocal disease but overall tumour burden measured <50 mm maximally. A total of four hundred and seventy-three tumours in four-hundred and seventy-one patients were then included in the final analysis. Patient and tumour clinico-pathological data are outlined in Table 1. The majority of patients were aged between 50 and 65 years ($n = 250$, 53%).

4.2. Time intervals

The use of Oncotype DX testing and adjuvant chemotherapy across four intervals is outlined in Table 2.

Table 1
Patient and tumour characteristics.

Age at diagnosis (years)	Median (range)	58 (30–89)
Age groups (*n* (%))	<40	18 (4)
	40–49	78 (16)
	50–64	250 (53)
	>65	125 (27)
Size (mm)	Median (range)	20 (10–50)
T-stage	*n* (%)	
	T1	240 (51)
	T2	233 (49)
Histological subtype	*n* (%)	
	Ductal	364 (77)
	Lobular	56 (12)
	Colloid	23 (5)
	Tubular	12 (3)
	Mixed	5 (1)
	Other	13 (3)
Grade	*n* (%)	
	1	66 (14)
	2	317 (67)
	3	90 (19)

Please cite this article in press as: McVeigh T.P. et al., The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.08.002

Table 2
Treatment intervals, Oncotype DX and chemotherapy use.

Time period	2006–2007	2007–May 2010	June 2010–October 2011	October 2011–May 2013	Total
Oncotype DX test availability	Oncotype not Available	Oncotype available on trial only	Oncotype not publicly reimbursed	Oncotype in clinical use	
Number of patients treated	54 (12)	198 (42)	73 (15)	147 (31)	471
Oncotype DX use (*n* (%))	0 (0)	96 (48)	19 (26)	125 (85)	240
Chemotherapy use (*n* (%))	34 (63)	100 (51)	33 (45)	47 (32)	216
Proportion of population with private health insurance	49%	47%	48%	46%	

Table 3
Recurrence risk groups and chemotherapy use.

Recurrence risk	Oncotype score	Trial	Number of patients (*n*)	Chemotherapy used (*n* (%))
Low	0–17		118	16 (14)
		TAILORx	41	16 (39)
		Off-trial	77	0 (0)
Intermediate	18–30		100	65 (65)
		TAILORx	43	25 (58)
		Off-trial	57	40 (70)
High	⩾31		16	16 (100)
		TAILORx	7	7 (100)
		Off-trial	9	9 (100)

The application of the test in clinical practice has increased exponentially since it has been available for use in the public sector. Eighty-five percent of patients ($n = 125$) managed in the most recent interval underwent genomic profiling of their tumours as part of their treatment. The use of chemotherapy has undergone a stepwise reduction over the four intervals, having been used in 63% of cases in the interval pre-Oncotype DX availability, compared to 32% of cases in the interval of routine Oncotype DX testing.

4.3. Chemotherapy drug costs

Chemotherapy drug-related costs reduced dramatically in 2010 following the expiration of the patent on Docetaxel. The cost in our institution of four cycles of the TC (Docetaxel/Cyclophosphamide) fell from €5965 in 2006 to €483 in 2013.

4.4. Recurrence scores

A total of 240 (51%) Oncotype DX genomic tests were performed over the study period. Of these, 96 were performed as part of the TAILORx trial. Patients were stratified into low-, moderate- and high-risk groups based on recurrence scores, as per the definitions outlined by Paik et al. [14,20]. The majority of patients ($n = 118$, 50%) had a low recurrence score. A minority ($n = 16$, 7%) had a score in excess of 31 (high-risk). The remaining patients ($n = 100$, 43%) were of intermediate risk. All patients with a high-risk score received adjuvant chemotherapy ($n = 16$, 100%). Of patients with a low-risk score, 16 received chemotherapy ($n = 16$, 14%). All 16 patients were enrolled to the TAILORx trial, and had a recurrence score in excess of 11, and were randomised to chemotherapy as per protocol [16]. Sixty-five (65%) of patients deemed to be of intermediate recurrence risk were prescribed adjuvant chemotherapy. Patients in this risk category were far more likely to receive chemotherapy if they were not being managed as part of the TAILORx trial (40 (70%)-versus-25 (58%)) (Table 3).

4.5. Chemotherapy use

Univariate analyses were performed to investigate which factors influenced use of chemotherapy (Table 4). Chemotherapy was more often prescribed in the case of tumours of increasing grade (<0.001, X^2), increasing size ($p = 0.012$, Mann–Whitney) and increasing recurrence score ($p < 0.001$, Mann–Whitney). The use of chemotherapy correlated inversely with age at diagnosis ($p < 0.001$, Mann–Whitney). Chemotherapy use was also significantly influenced by the time period during which patients were treated ($p < 0.001$, X^2). Four patients declined chemotherapy. Three of these patients did not undergo genomic assessment, and the other patient had an intermediate risk score and was not on a clinical trial. One other patient withdrew from participation in a clinical trial and did not have systemic chemotherapy treatment.

These factors were then included in a multivariate model (binary logistic regression, Table 5). Considering traditional prognostic indicators such as grade and

Please cite this article in press as: McVeigh T.P. et al., The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.08.002

Table 4
Univariate analysis: factors influencing prescribing of chemotherapy.

		N	Chemotherapy used	*p*-Value
Interval	Prior to Oncotype	54	34 (63)	<0.001*
	Trial period	198	100 (51)	
	Prior to reimbursement	73	33 (45)	
	Publicly reimbursed	147	47 (32)	
Grade	1	66	12 (18)	<0.001*
	2	317	153 (48)	
	3	90	51 (57)	
Age groups (years)	⩽39	18	14 (78)	<0.001*
	40–49	78	52 (67)	
	50–64	250	119 (48)	
	65	125	29 (23)	
Oncotype DX risk groups	Low	118	16 (14)	<0.001*
	Intermediate	100	65 (65)	
	High	16	16 (100)	
		Chemotherapy prescribed	No chemotherapy	
Median age (range)/years		54 (31–77)	62 (30–89)	<0.001†
Median tumour size (range)/mm		22 (7–50)	19 (10–49)	0.012†
Median Oncotype score (range)		24 (11–61)	14 (4–28)	<0.001†

* Chi-squared test.
† Independent Samples Mann–Whitney *U* test.

tumour size, as well as patient age and interval of treatment, all factors retained significance in influencing decision-making as regards prescription of chemotherapy. However, when recurrence score was included in the multivariate model (Table 6), the traditional prognostic indicators (grade and tumour size) were not shown to be independent factors in guiding chemotherapy use. Patients were 1.32-times more likely to receive chemotherapy with each unit increase in recurrence score ($p < 0.001$). The interval during which patients underwent treatment remained a significant predictive factor ($p = 0.04$).

In those patients in whom Oncotype DX was not used, traditional prognostic factors such as grade, size and age were highly significant in determining chemotherapy use (Table 8). In this cohort, time interval of treatment was also found to impact on decision-making ($p = 0.045$), with patients managed following the introduction of Oncotype DX into clinical practice being far less likely to receive chemotherapy than those patients managed in the era pre-Oncotype DX availability (OR 0.09, $p = 0.008$), despite a lack of formal tumour genomic assessment.

4.6. Follow up and disease recurrence

The median follow up in this series is 47 months (8–97). Over the study period, 12 (2.5%) patients experienced disease progression, relapse or a second cancer. Two patients progressed to develop visceral metastases, and one patient unfortunately succumbed to metastatic disease of bone, brain and viscera. Five patients (1%) developed metastases limited to bone. Three patients

Table 5
Factors influencing chemotherapy prescribing overall.

Factor	Significance	OR
Interval*	<0.001	
Oncotype available on trial only	0.049	0.49
Oncotype not publicly reimbursed	0.022	0.37
Oncotype routinely used	<0.001	0.20
Grade‡	<0.001	
Grade 2	<0.001	5.37
Grade 3	<0.001	7.40
Size	0.029	1.03
Age	<0.001	0.91

* Compared to interval prior to availability of Oncotype DX.
‡ Compared to grade I.

Table 6
Factors influencing chemotherapy prescribing following the introduction of Oncotype DX testing.

Factor	Significance	OR
Interval†	0.04	
Oncotype not publicly reimbursed	0.15	0.32
Oncotype routinely used	0.017	0.41
Grade‡	0.24	
Grade 2	0.15	2.17
Grade 3	0.78	1.22
Size	0.59	1.01
Age	0.04	0.96
Oncotype score	<0.001	1.33

† Compared to period of trial recruitment.
‡ Compared to grade I.

Please cite this article in press as: McVeigh T.P. et al., The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.08.002

Table 7
Factors influencing use of chemotherapy in intermediate-risk patient.

Factor	Significance	OR
TAILORx participation	0.13	0.47
Grade‡	0.016	
Grade 2	0.004	13.84
Grade 3	0.018	12.09
Size	0.44	0.98
Age	0.05	0.94
Oncotype score	0.002	1.28

‡ Compared to grade I.

Table 8
Factors influencing chemotherapy use in patients in whom Oncotype Dx was not used.

Factor	Significance	OR
Interval*	0.045	
Oncotype available on trial only	0.069	0.45
Oncotype not publicly reimbursed	0.121	0.42
Oncotype routinely used	0.008	0.09
Grade‡	0.001	
Grade 2	0.002	9.20
Grade 3	<0.0001	17.72
Size	0.03	1.06
Age	<0.0001	0.84

* Compared to interval prior to availability of Oncotype DX.
‡ Compared to grade I.

developed recurrent disease despite having received full dose chemotherapy. One patient had a recurrence score of 36 and developed visceral metastases despite receiving full dose chemotherapy. The five patients in whom bone metastases were diagnosed had received hormonal agents only. A further four patients developed contralateral breast disease. One patient was diagnosed with a contralateral breast cancer of different morphology, while three patients developed contralateral breast disease of similar morphology.

5. Discussion

It is well reported that variations in gene expression patterns can influence breast cancer phenotype, and clustering of gene expression patterns can be used to these tumours into distinct molecular subgroups [3]. It is recognised that each tumour has a unique gene expression profile, and there may be diversity in tumour biology and disease progression even between tumours of the same molecular subtype [21]. These variations can greatly influence intrinsic tumour behaviour, and, therefore, response to treatment and patient outcome.

Traditionally, the need for chemotherapy was decided based on tumour clinico-pathological prognostic indicators, with factors such as age [22], tumour size, nodal status, grade and receptor expression profiles taken into consideration as predictors of recurrence risk [23,24]. Generally, tumours <2 cm of grade 1 would not be managed on endocrine therapy alone. Those patients however, if recruited to TAILORx, underwent genomic profiling and were randomised to treatment groups according to protocol. Some traditional prognostic factors may reflect timing of cancer detection as opposed to tumour biology [25], and may therefore miss some of the patients that would accrue most survival benefit from systemic therapy, leading to potentially inappropriate under-treatment [8]. Furthermore, these traditional prognostic indicators lack specificity, resulting in over-treatment of patients with potentially harmful adjuncts of negligible benefit beyond local curative resection, radiation and systemic endocrine therapy [12].

The Oncotype DX 21-gene assay represents the first clinically validated multi-gene assay that can quantify the likelihood of breast cancer recurrence [8]. The recurrence score generated in this test has been consistently shown to directly impact decision-making in breast cancer management [25,26]. Treatment decisions among medical oncologists for early breast cancer are variable even with the use of gene assays [27,28]. A pooled analysis by Carlson and Roth [12] found the proportion of patients with low-risk recurrence scores receiving chemotherapy to range between 0 and 16% across fourteen series (pooled mean 5.8%). In our series, 14% ($n = 16$) of patients in this category received chemotherapy. It is worth noting that all 16 of these patients were enrolled in the TAILORx trial. These patients all had recurrence scores greater than 11, necessitating their inclusion in the trial arm. They were then randomised to receive chemotherapy. Patients not enrolled to TAILORx were spared chemotherapy in all cases of a low-risk recurrence score. All patients with a high-risk recurrence score ($n = 16$, 100%) received chemotherapy whether or not they were enrolled to a clinical trial. In other series this proportion ranged between 72% and 100% (pooled mean 83.4%) [12]. Patients found to have an intermediate-risk recurrence score (18–30) received chemotherapy in 65% cases. Patients were more likely to receive chemotherapy if they were not enrolled to TAILORx ($n = 40$ (70%)-versus-25 (58%)). This proportion is higher than that reported in other series (range 23.9–65% [12]). When considering factors influencing chemotherapy prescribing in this group alone (Table 7), the absolute Oncotype score was significant in influencing use of chemotherapy (OR 1.28 per unit increase). TAILORx participation was not shown to be an independent predictor of chemotherapy use when considering other factors such as Oncotype score, age at diagnosis and tumour size and grade. Grade was found to retain strong significance in this group, with tumours of grade 2 and grade 3 associated with a 13.8- and 12.1-fold increased used of chemotherapy compared to

Please cite this article in press as: McVeigh T.P. et al., The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.08.002

tumours of low grade even when all other factors were considered ($p = 0.016$). This reflects a reversion back to traditional prognostic indicators in the decision-making process when faced with an indeterminate score.

The most striking finding of this series was the observed stepwise reduction in chemotherapy use. Considering time intervals alone, this is unexpected, given that the cost of systemic therapy has decreased drastically over the study period and yet is being utilised less frequently. The application of Oncotype DX has previously been shown to influence decision-making in chemotherapy-prescribing [29]. In this series, we have shown the introduction of the 21-gene assay into the clinical arena to have an influence on decision-making among disciplinary teams independent of its direct use. The concept that not all patients might benefit from chemotherapy by virtue of favourable tumour genomics has translated into reduced application of systemic therapy even in those patients in whom formal genomic appraisal was not available. Traditional prognostic factors are now only relied on in the case of an indeterminate result. Validation of the Oncotype DX by level one evidence [30] has led to a change in physician attitudes towards risk stratification and adjuvant chemotherapy use.

6. Conclusion

The application of Oncotype DX has been successfully integrated into the treatment paradigm of patients with early stage ER+, node-negative breast cancer in our institution. Patients at lowest risk of disease recurrence on the basis of the test have been spared chemotherapy, while those found to be likely to receive most survival benefit from chemotherapy have all received systemic treatment. Traditional prognostic factors remain important in decision-making in patients of indeterminate scores. The introduction of Oncotype DX testing into clinical practice in our institution has led to reduction in the application of systemic therapy independent of its actual use. Long-term data regarding patient outcome are awaited but certainly short- and medium-term results are favourable. This illustrates the importance of continued adaptation of the clinical team to new evidence in decision-making of breast cancer management.

Conflict of interest statement

None declared.

References

[1] Heneghan HM, Prichard RS, Devaney A, et al. Evolution of breast cancer management in Ireland: a decade of change. BMC Surg 2009;9(1).
[2] Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305(6):569–75.
[3] Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001;98(19):10869–74.
[4] Perou CM, Sørile T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406(6797):747–52.
[5] Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2011;121(7):2750–67.
[6] Howe HL et al.. Women with multiple primary breast cancers diagnosed within a five year period, 1994–1998. Breast Cancer Res Treat 2005;90(3):223–32.
[7] Clarke M, Collins R, Davies C, et al. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352(9132):930–42.
[8] Oakman C, Bessi S, Zafarana E, et al. Recent advances in systemic therapy: new diagnostics and biological predictors of outcome in early breast cancer. Breast Cancer Res 2009;11(2):205.
[9] Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24(23):3726–34.
[10] Harris L, Fritsche H, Mennel R, et al. American society of clinical oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol 2007;25(33):5287–312.
[11] Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011;22(8):1736–47.
[12] Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. Breast Cancer Res Treat 2013;141(1):13–22.
[13] Cronin M, Pho M, Dutta D, et al. Measurement of gene expression in archival paraffin-embedded tissues: development and performance of a 92-gene reverse transcriptase-polymerase chain reaction assay. Am J Pathol 2004;164(1):35–42.
[14] Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. New Engl J Med 2004;351(27):2817–26.
[15] Sandberg MEC et al.. Estrogen receptor status in relation to risk of contralateral breast cancer-a population-based cohort study. PLoS ONE 2012;7(10).
[16] Sparano JA. TAILORx: Trial Assigning Individualized Options for Treatment (Rx). Clin Breast Cancer 2006;7(4):347–50.
[17] Kelly CM. Oncotype-DX® gene expression profile and chemotherapy decision-making in patients with early stage breast cancer. Irish Society of Medical Oncology guideline; 2011.
[18] Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991;19(5):403–10.
[19] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(6):1471–4.
[20] Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene recurrence score assay and adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. Breast Cancer Res Treat 2011;127(1):133–42.
[21] Sørlie T. Molecular portraits of breast cancer: tumour subtypes as distinct disease entities. Eur J Cancer 2004;40(18):2667–75.
[22] Fisher B, Jeong JH, Bryant J, et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet 2004;364(9437):858–68.

Please cite this article in press as: McVeigh T.P. et al., The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.08.002

[23] Carlson RW, Brown E, Burstein HJ, et al. NCCN Task Force report: adjuvant therapy for breast cancer. JNCCN J Natl Comp Cancer Netw 2006;4(suppl. 1):S-1–S-26.
[24] Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham prognostic index in primary breast cancer. Breast Cancer Res Treat 1992;22(3):207–19.
[25] Markopoulos C. Overview of the use of Oncotype DX((R)) as an additional treatment decision tool in early breast cancer. Expert Rev Anticancer Ther 2013;13(2):179–94.
[26] Hornberger J et al.. Clinical validity/utility, change in practice patterns, and economic implications of risk stratifiers to predict outcomes for early-stage breast cancer: a systematic review. J Natl Cancer Inst 2012;104(14):1068–79.
[27] Drukker CA, Van Den Hout HC, Sonke GS, Brain E, et al. Risk estimations and treatment decisions in early stage breast cancer: agreement among oncologists and the impact of the 70-gene signature. Eur J Cancer 2014;50(6):1045–54.
[28] Zardavas D, Ades F, Spasojevic IB, Pugliano L, et al. Controversial issues in early-stage breast cancer: a global collaborative survey, supported by the European Society for Medical Oncology (ESMO). Ann Oncol 2014;25(8):1558–62.
[29] Eiermann W, Rezai M, Kümmel S, et al. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for er-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. Ann Oncol 2013;24(3):618–24.
[30] Harbeck N, Sotlar K, Wuerstlein R, Doisneau-Sixou S. Molecular and protein markers for clinical decision making in breast cancer: today and tomorrow. Cancer Treat Rev 2014;40(3):434–44.

Please cite this article in press as: McVeigh T.P. et al., The impact of Oncotype DX testing on breast cancer management and chemotherapy prescribing patterns in a tertiary referral centre, Eur J Cancer (2014), http://dx.doi.org/10.1016/j.ejca.2014.08.002