The impact of the 21-gene recurrence score (Oncotype DX) on concordance of adjuvant decision making as measured by the Liverpool Systemic Therapy Adjuvant Decision Tool

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Abstract (Words = 249)

Purpose

The 21-gene recurrence score (Oncotype DX) (RS) informs systemic therapy decision making in ER-positive HER2-negative early breast cancer (BC). To date no study has described the more nuanced discussions that take place around systemic therapy decision making or the impact of the RS on concordance in such decision making. Here we utilized a novel decision making tool to assess the impact of the RS on decision making as well as concordance of treatment recommendations.

Patients and Methods

The clinicopathological information (CPI) of 50 BCs without and with the RS were presented to a panel of breast oncologists. The Liverpool Adjuvant Systemic Therapy Decision Tool (LASTDT) was developed and used to categorize treatment recommendations for each case. Outcome measures included the impact of the RS on decisiveness, ~~and~~ concordance in decision making and its impact on treatment recommendations.

Results

Availability of the RS increased definitive decision making from 8% (4/50) to 56% (28/50) [χ^2=79.35, p<0.001] and altered the LASTDT category in 68% (34/50) of cases (p<0.001), 74% of which were to forgo chemotherapy. With knowledge of the RS, ~~universal~~ concordance rose from 14% to 64% [K=0.328: K=0.729].

Conclusions

The RS improves certainty of decision making as well as concordance amongst oncologists. This provides evidence that the availability of the RS can improve consistency of decision making amongst oncologists and thus helps to ensure patients are managed consistently. This is particularly important

when patients are managed in a loco-regional, multidisciplinary team manner where heterogeneous decisions can lead to disparity in care.

Introduction (words = 2650)

The widespread use of adjuvant polychemotherapy in the treatment of early breast cancer has improved survival [1]. However, any benefits need to be weighed against both short and long term toxicities, as well as the impact on quality of life. As such there remains a population of women with ER-positive, HER2-negative, node-negative BC where treatment recommendations with regard to chemotherapy remain unclear.

The 21-gene recurrence score (RS) assay (Oncotype DX assay; Genomic Health, Redwood City, CA), is a genomic classifier which has been validated as a prognosticator [2] and a predictor of the likelihood of chemotherapy benefit in ER positive, HER2 negative early invasive breast cancer [3]. The 21-gene RS has been validated by multiple studies including The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial [2] and the NSABP trial B20 trial [1,3]. These data revealed that most of the benefit of adjuvant chemotherapy was restricted to tumours with a high RS who had a 28% absolute decrease in 10-year distant recurrence rate, as compared to minimal, if any, benefit in tumours with a low RS [3]. A clinically important benefit rate could not be excluded in the intermediate RS group estimate [3]. More recently, TAILORx has demonstrated that in this intermediate RS group there is no additional benefit is in the addition of chemotherapy to endocrine therapy [4].

Internationally it has been shown that the RS impacts significantly on decision making and alters treatment away from chemotherapy and endocrine therapy to endocrine therapy alone in a significant number of cases (Table S1) [5-10]. In a retrospective, non-MDT based, study a 63% reduction in chemotherapy usage in patients with intermediate risk early breast cancer was demonstrated [11]. In addition, a meta-analysis across 15 different countries showed that RS has a significant impact on decision making with an alteration in treatment recommendation in 30% of cases and a 16% reduction in the use of adjuvant chemotherapy [6].

Four studies have explored the use of the RS in the MDT environment, three of which found that the RS altered treatment decisions and the majority of those away from chemotherapy [12-15]. Of note, Spellman et al [15] suggests that the RS score may, in fact, complicate the discussion in a multidisciplinary team (MDT) setting given the difference of opinion amongst specialists regarding the RS score, its reliability and utility.

Whilst two studies concluded that the RS improved clinician confidence in decision making [14,15], no studies to date have investigated the impact of the RS on concordance of decision making amongst oncologists. Furthermore, none of the studies attempted to reflect the more nuanced decision making scenarios that exist in early ER+ BC regarding chemotherapy particularly in the intermediate RS group [12-15].

The aim of the present study, was to evaluate systemic therapy decision making by a group of oncologists and the influence of 21-gene RS, as well as concordance of decision making between them when using the clinicopathological information available within a routine MDT, and the effect on decision making when this information was presented with and without the RS. Furthermore, to reflect the real life uncertainty that exists with regard to systemic therapy decision in ER-positive, HER2-negative BC, the Liverpool Systemic Therapy Adjuvant Decision Tool was designed and utilized to record decisions.

Materials and Methods

Patients

Breast cancer cases that were discussed at MDTs between November 2012 and November 2014 in two acute NHS hospital trusts (Royal Liverpool and Broadgreen University Hospitals NHS Trust and St Helens and Knowsley Teaching Hospitals NHS Trust) and where a decision was made to request the RS were identified.

Expert Panel Review

Clinicopathological information (CPI) for these cases was collected, including age, pathological size, grade, ER positivity as defined by the Allred score, HER2 status, Ki67, the presence or absence of vascular invasion, nodal status and margins. These anonymized data were summarized for each patient twice once without the RS and once with the RS. The cases were then blindly reviewed in the study MDT in a random order by a panel of five consultant oncologists specializing in breast cancer. In each instance, each member of the panel used the Liverpool Adjuvant Systemic Therapy Decision Tool (LASTDT) to make a treatment recommendation prior to the availability of the RS (pre-RS) and after the availability of the RS (post-RS) (figure 1).

The Liverpool Adjuvant Systemic Therapy Decision Tool (LASTDT)

The LASTDT was designed to reflect decision making in the context of an MDT with regard to ER-positive, HER2-negative breast cancer and consists of four categories: (1) endocrine therapy alone (Erec); (2) chemotherapy therapy recommended (Crec); (3) chemotherapy discussion with preference towards recommendation of chemotherapy (Cdis) and (4) chemotherapy discussion with a preference towards recommendation of endocrine therapy alone (Edis).

The study was registered as an audit with the Clatterbridge Cancer Centre (Audit No 123).

Study Outcomes

The primary aim of the study was to ascertain amongst a panel of oncologists the impact of the RS on treatment decision making including decisiveness as defined Erec or Crec. The secondary outcomes included the degree to which treatment decision making was stratified by RS and the degree of concordance in decision. All outcomes were measured using the LASTDT.

Statistical Analysis

Summation Score

Once the treatment recommendation had been made for each case by each oncologist before and after the RS the decision, decisions based on the LASTDT were used to produce a summation score of consultant decision-making (figure 2). The summation score is cumulative and results in a scale from -10 (all consultants agree on ERec) to 10 (all consultants agree on CRec). All values less than 0 would be towards not having chemotherapy but at least one consultant would recommend seeing the patient (EDis). If the score is more than 0 it means that at least a discussion would occur regarding chemotherapy in addition to endocrine therapy (CDis).

Statistical Methods

Continuous variables are presented with their median and interquartile range (IQR), while categorical variables are described as frequency of counts and percentages. Profile plots were produced as a graphical representation of changes in summation score between the pre- and post-RS decisions and scatter plots with Spearman correlation coefficient uses to measure the association between the RS and summation scores. Differences in treatment decisions as a result of knowledge of the ~~to~~ RS were assessed using McNeamar and Fleiss' Kappa with 95% confidence intervals (CIs) used for assessing the degree of agreement across the oncologists for both pre and post RS treatment decisions. Statistical analyses were performed with RStudio version 1.0.143, SPSS version 23 and Microsoft Excel 2010.

Results

Clinico-pathological characteristics and recurrence score data

Between November 2012 and November 2014 fifty patients ER- positive, HER2-negative BC were identified where the RS was requested following discussion within the MDT meeting. CPI of these cases are summarized in Table 1. The median age of the cohort was 56 (range 31-76; IQR 51.25-63), and median size of tumour 30mm (range 7-70mm; IQR 19.25-32.75) (Figure S2). Ki67 was available in all cases with a mean Ki67 of 29% (range 7-70%). With regard to the ~~in~~ the axillary lymph nodes 22% (11/50) and 6%(3/50) had micrometastasis and macrometastasis respectively (table 1,figure S3a). The median RS result was 16.5 (range 2-55; IQR 12-21) distributed as follows: 42% (21/50) low, 48% (24/50) intermediate, and 10% (5/50) high.

Impact of recurrence score on treatment recommendation and decisiveness of decision-making

Using the LASTDT to categorize decision making and with the CPI alone the following recommendations were made: Erec 6% (3/50), Crec 2% (1/50), Edis 50% (25/50), Cdis 42% (21/50). When the RS was added to the same CPI~~. In~~ the following recommendations were made Erec 46% (23/50), Crec 10% (5/50), Edis 26% (13/ 50) and Cdis 18% (9/50).

Comparing ~~the~~ decisions with CPI alone and with the CPI plus the RS there was a decrease in the number of cases within the Edis and Cdis groups and an increase in definitive decision making from 8% (4/50) to 56% (28/50) [χ^2=79.35, p<0.001]. There was a clear move towards endocrine therapy in 50% (25/50) of cases with a move from chemotherapy to endocrine therapy (Cdis to Edis/Erec) in 26% (13/50) cases and from Edis to Erec in a further 24% (12/50). Combining CPI and RS resulted in more definitive decision making as evidenced by the increase in Crec from 2% (1/50) to 10% (5/50) and an increase in Erec 6% (3/50) to 46% (23/50) (Figure 3, S4, S5). Figures 4a, 4b and S5 illustrate the outcomes for individual patients and their treatment recommendation based on the summation score before and after the RS.

Correlation of RS and treatment recommendations

Scatter plots of RS against summation score using the LASTDT show that there is no correlation when treatment decision making is based on CPI alone (figure 5a) but that there is a strong correlation between knowledge of the RS and decision making [ρ=0.928, p<0.001] (Figure 5b).

Impact of RS on nature of oncology referral

The nature of the out-patient consultation when an MDT decision is made to recommend chemotherapy (Crec) or to discuss chemotherapy (Cdis and Edis groups) is very different in terms of information provision and discussion as compared to one ~~whcN~~ when endocrine therapy alone (Erec) is recommend. Within this study, with CPI alone, 94% (47/50) of patients would have been referred for an appointment where chemotherapy would have been discussed either with a clear recommendation (Crec) 2% (1/50) or for a discussion (Cdis and Edis) ~~-~~92% (46/50) falling within the (Cdis and Edis). However, the addition of the RS resulted in a decrease in the number of patients being referred to discuss chemotherapy 54% (27/50), with the number within Cdis and Edis decreased to only 28% (14/50). The correlation between RS and treatment recommendation was significant (Figure 5a&b) [ρ=0.928, p<0.001].

Concordance in decision making between oncologists

With CPI alone concordance amongst all participating oncologists occurred in only 14% of cases the addition of the RS this increased ~~this~~ to 64% (figure 6). The initial level of agreement across the panel [K=0.328 (95%CI 0.220-0.437)] increased by 1.2 fold (120%) after the disclosure of RS information [K=0.729 (95%CI 0.632-0.827)]. In addition, the decision-wise Kappas differed between pre and post RS assessment demonstrating an increase in definitive decision making (Table 2).

Conclusions

This study explored decision making regarding use of adjuvant chemotherapy in ER-positive, HER2-negative breast cancer with and without 21-gene recurrence score, utilising a novel tool to document decision making, the so-called Liverpool Adjuvant Systemic Therapy Decision Tool (LASTDT). The tool was designed to record decision making with regard to systemic therapy in this group and to reflect that decision making in the real world is not always a binary, given the uncertainty of the benefit of chemotherapy in ER-positive, HER2-negative node negative breast cancer. This uncertainty existed at the time of the study given the lack of data regarding the benefit of chemotherapy within the intermediate RS group [11]. LASTDT in addition to the two clear decisions of endocrine therapy alone or endocrine therapy plus chemotherapy allows for two other decisions; namely a discussion regarding adjuvant chemotherapy with a preference either towards or against a recommendation of chemotherapy following a discussion with the patient.

The published literature has previously illustrated that the availability of the RS impacts and alters adjuvant decision making regarding systemic therapy in 20% of cases [6] and more often than not this is to recommend to omitting chemotherapy rather than to recommending it [16], with a reduction in the use of chemotherapy (table S1,S2). The results reported in this study are consistent with these published data, with alteration in the recommended treatment occurring in 67% of cases, with the majority of these to omit adjuvant chemotherapy.

However, previous studies do not address the more nuanced issues around the intermediate group and do not appreciate the presence of a 'grey-area' in decision making with regard to the intermediate RS group present at the time of the study. For example, within the SAKK25/10 study the decision made by the MDT with knowledge of the RS was binary: either endocrine therapy (ET) or chemotherapy plus endocrine therapy (CT + ET) [17]. Furthermore, other studies have assumed that without a RS result,

all patients would have received chemotherapy, which does not necessarily reflect the real world clinical scenario; with no recording of the discussion at MDTs without the RS [11]. One study recorded physician's confidence in treatment recommendation before and after the RS, based on answers to "I am confident in my treatment recommendation prior to ordering Oncotype DX" [18]. In this study, availability of the RS appeared to reduce the percentage of physicians who agreed/strongly agreed from 96% (pre-assay) to 90% (post-assay), although CT recommendations decreased from 52.1% to 37.7% [18]. Similarly in a Canadian population-based cohort study a pre-test category of "unsure" (whether chemotherapy should be given) was included and this group accounted for 328 of 508 patients (65%) who had a change in recommendation [16].

Within this study the LASTDT allows the 'grey area' to be recorded and it clearly demonstrates that the majority of cases prior to the availability of the RS sit within the Cdis and Edis ie a discussion with a preference to recommending or not chemotherapy. This would have entailed a detailed discussion of the risk of relapse with patient and the potential benefit of chemotherapy in reducing this risk as well as its side effects. This is not only resource intense but may lead to anxiety for patients [15]. The addition of the RS to CPI resulted in a significant reduction in the number of patients within the Cdis/Edis group, demonstrating that it provides oncologists with the reassurance to make decisive and definitive treatment recommendations: more often, this was to endocrine therapy alone. While this study did not aim to formally quantify or cost time and resource saved in the context of consultation time or benefits to patients, it is likely that the RS led to a more efficient use of oncological resource allowing more focused and definitive discussions to take place. This is likely also to have led to less uncertainty and anxiety overall in the intermediate RS group [15].

Another key impact of the availability of the RS that is demonstrated by this study is the increased concordance in decision making amongst a group of experienced oncologists. It is clearly seen that with the CPI alone concordance in decision making was not very strong, reflecting differences in views regarding the use and benefit of chemotherapy in individual cases. However, the addition of the RS

results in a dramatic change with a highly significant correlation between RS and decisions made. It is of interest that concordance in decision making reduces for those BC with a RS of 20-29, reflecting the real life uncertainty at the time in the absence of the results from the TAILORX study [4]. If these observations were to be translated and generalised into the setting of an MDT it would mean more unanimity in decision making, and more standardisation of treatment decisions regarding the use or not of chemotherapy.

Strengths of the current study include that it was carried out in a blinded fashion using real patient data with each consultant recording data independently. Weaknesses include that the study was retrospective and the impact of the decisions on actual treatment in the clinic was not measured.

In conclusion, the current study supports the previously published data in demonstrating that the availability of the RS results in a reduction in chemotherapy use. By utilising a novel decision making tool to record more nuanced decision making we have for the first time demonstrated that the RS not only enables more definitive decision making by individual oncologists but also significantly improves concordance of decision-making amongst the same a group of oncologists with all the benefits that follow from this. The LASTDT could be used and/or adapted for further impact assessment studies regarding the effects of the introduction of genomic assays/information in the management of breast cancer.

Disclosures

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References

1. Fisher B DJ, Wolmark N, DeCillis A, Emir B, Wickerham DL, Bryant J, Dimitrov NV, Abramson N, Atkins JN, Shibata H, Deschenes L, Margolese RG. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 1997;89:1672-82.
2. Paik S SS, Tang G et al. A Multigene Assay to predict recurrence of Tamoxifen-treated, node-negative breast cancer. NEJM 2004;351:2817-26.
3. Paik S TG, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor positive breast cancer. JCO 2006;24:3726-34.
4. Sparano JA, Gray RJ, Makower DF et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. NEJM 2018; 379:111-121
5. Augustovski F SN, Caporale J et al. Decision-making impact on adjuvant chemotherapy allocation in early node-negative breast cancer with 21-gene assay: systematic review and meta-analysis. Breast Cancer Research 2015;152:611-25
6. Augustovski F SN, Caporale J et al. Response to real-life decision-making impact of Oncotype DX. Breast Cancer Research and Treatment 2015;154:211
7. Conlin AK SA. Use of the Oncotype DXTM 21-gene assay to guide adjuvant decision making in Early-Stage Breast Cancer. Molecular diagnosis and therapy 2012;11:355-60
8. Gligorov J PX, Jacot W et al. Prospective clinical utility study of the use of the 21-gene assay in adjuvant clinical decision making in women with estrogen receptor positive early invasive breast cancer: results from the SWITCH study. Oncologist 2015;20:873-9
9. Holt S BG, Humphreys I et al. A decision impact, decision conflict and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pN1mi, ER-positive, breast cancer in the UK. British Journal of Cancer 2013;108:2250-8.
10. Rutter CE YX, Mancini BR et al. Influence of a 21-gene recurrence score assay on chemotherapy delivery in breast cancer. Clinical Breast Cancer 2016;16:59-62

11. Loncaster J, Armstrong A, Howell S, et al. Impact of Oncotype DX breast Recurrence Score testing on adjuvant chemotherapy use in early breast cancer: Real world experience in Greater Manchester, UK. Eur J Surg Oncol 2017;43:931-7

12. Cheung PS TA, Leung RC et al. Initial experience with the Oncotype DX assay in decision-making for adjuvant therapy of early oestrogen receptor positive breast cancer in Hong Kong. Hong Kong Medical Journal 2014;20:401-6.

13. Dreyfus C BM, Gligorov J et al. Impact of the 21-gene assay in decision-making during multidisciplinary breast meeting: A French experience. Gynecol Obstet Fertil 2015;43:780-5

14. Eiermann W KR, Kuhn T 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. Annals of Oncology 2013;24:618-24

15. Spellman E SN, Eggly S et al. Conveying genomic recurrence risk estimates to patients with early stage breast cancer: oncologist perspectives. Psychooncology 2013;22:2110-6

16. Levine MN, Julian JA, Bedard PL, Eisen A, Trudeau ME, Higgins B, Bordeleau L, Pritchard KI. Prospective evaluation of the 21-Gene recurrence score assay for breast cancer decision-making in Ontario. JCO. 2015;34:1065–72.

17. Pestalozzi BC, Tausch C, Dedes KJ et al. Adjuvant treatment recommendations for patients with ER-positive/HER2 negative early breast cancer by Swiss tumour boards using the 21-gene recurrence score (SAKK 26/10). BMC Cancer. 2017: 17(1):265

18. Leung RC, Yau TCC, Chan MCM et al. The impact of the Oncotype DX breast cancer assay on treatment decisions for women with estrogen receptor positive, node negative breast carcinoma in Hong Kong. Clin Breast Cancer. 2016:16(5):372-378

19. Lo SS, Mumby PB, Norton J et al. Prospective multicentre study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. JCO. 2010:28(10):1671-6

20. Albanell J, Gonzalez A, Ruiz-Borrego M et al. Prospective trans-GIECAM study of the impact of the 21-gene recurrence score assay and traditional clinicopathological factors of adjuvant clinical decision making in women with early breast cancer. Ann Oncol. 2011:23(3):625-31

21. Stemmer SM, Klang SH, Ben-Baruch N et al. The impact of the 21-gene recurrence score assay on clinical decision-making in node-positive (upto 3 positive nodes) estrogen receptor positive breast cancer patients. Breast Cancer Res Treat. 2013. 140:83–92

22. Yamauchi H, Nakagawa C, Takei H et al. Prospective study of the effect of the 21-gene assay on the adjuvant clinical decision-making in Japanese women with estrogen receptor-positive, node negative and node-positive breast cancer. Clin Breast Cancer. 2014:14(3):191-7.

23. Lee MH, Han W, Lee JE et al. The clinical impact of the 21-gene recurrence scone on treatment decisions for patients with hormone receptor-positive early breast cancer in Korea. Cancer Res Treat. 2015:47(2):208-14

24. Ozmen V, Atasoy A, Gokmen E et al. Impact of Oncotype DX Recurrence Score on Treatment Decisions: Results of a prospective multicentre study in Turkey. Cureus. 2016: 8(3): e522.

25. Hall PS, Smith A, Hulme C et al. Value of information analysis of multiparameter tests for chemotherapy in early breast cancer: The OPTIMA prelim trial. Value Health. 2017:20(10):1311-1318.

26. Mittmann N, Earle CC, Cheng SY et al. Population-based study to determine the health system costs of unsing the 21-gene assay. J Clin Oncol. 2018:20;36(3):238-243

27. Lux MP, Nabieva N, Hildebrandt T, et al. Budget impact analysis of gene expression tests to aid therapy decisions for breast cancer patients in Germany. Breast. 2018: 37:89-98

28. Katz G, Romano O, Foa C et al. Economic impact if gene expression profiling in patients with early-stage breast cancer in France. PLoS One. 2015:10(6):e0128880

29. Bargalló-Rocha JE, Lara-Medina F, Perez-Sanchez V et al. Cost-effectiveness of the 21-gene breast cancer assay in Mexico. Adv Ther. 2015:32(3):239-53

30. Hannouf MB, Xie B, Brackstone M et al. Cost-effectivemess of a 21-gene recurrence score assay versus Canadian clinical practice in women with early-stage estrogen or progesterone receptor positive, axillary lymph node negative breast cancer patients. BMC Cancer. 2012:12:447