CES - HESG

Workshop 2006

Londres - 4-6 janvier 2006

Cost-effectiveness analysis of strategies for HER2-2/Neu testing of breast cancer patients in France

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ABSTRACT

Objectives: To conduct a cost-effectiveness analysis comparing diagnostic strategies for determining the HER2 status of invasive breast carcinomas, as indication for Trastuzumab treatment at metastatic relapse. **Methods:** A decision tree compared five strategies distinguished by (i) the use of immunohistochemical (IHC) and/or Fluorescent In Situ Hybridization (FISH) techniques, (ii) the test schedule (at initial diagnosis or metastatic relapse). Most cost and effectiveness data came from a French multicentric study of 2,045 patients from 8 hospitals. We were not able to select final criteria for Trastuzumab effectiveness since published data rely on IHC techniques not used in France (i.e. HercepTest). We therefore selected two intermediate criteria for inappropriate treatment at relapse, i.e. patients with: HER2 amplified tumors not receiving Trastuzumab (C1), HER2 non-amplified tumors improperly treated with Trastuzumab (C2). Sensitivity analyses were then performed to assess the robustness of the results to: (i) discount rate, (ii) cost of FISH, (iii) tissue fixation technique. **Results:** The strategy using IHC at diagnosis was dominated by the four other strategies. Among these, the only efficient strategy for both criteria was IHC used alone at metastatic relapse; strategies using FISH, or IHC followed by FISH on IHC2+ cases were efficient for (C1), while IHC followed by FISH on IHC2+ and 3+ cases was efficient for (C2). **Conclusion:** Determining HER2 status at diagnosis incurs substantial incremental costs, which do not appear to be justified as far as the effectiveness of adjuvant or neoadjuvant Trastuzumab is not established. No other strategie can be excluded at first.

Keywords: Cost-effectiveness analyses; breast cancer; determining HER2/neu status

Acknowledgements: This work was funded by the French Ministry of Health as part of a project entitled Programme de Soutien aux Innovations Diagnostiques et Thérapeutiques Coûteuses (STIC, Support Program for Costly Diagnostic and Therapeutic Innovations).
The authors thank Sandrine Berge-Montamat and Olivier Trédan for their contributions.

1. INTRODUCTION

In France, breast carcinoma is the most frequently occurring cancer in women. The French network of cancer registries (FRANCIM) estimates that the annual rate of incidence, standardized to the world population, averaged 88.9 per 100,000 women for the year 2000 (17). Between 25% and 30% of patients affected by infiltrating breast cancer exhibit an amplification of the c-erb2 gene, which induces abnormally elevated rates of HER2 protein. This overexpression is associated with a poor prognosis, as it indicates a more aggressive disease, with a rapid progression that results into shorter life expectancy (18; 19).

Treatment with Trastuzumab, a monoclonal antibody specifically targeting HER2 (Herceptin ®; Genentech, San Francisco, CA), is indicated for metastatic patients at first recurrence of disease when HER2 is overexpressed. The US Food and Drug Administration (FDA) approved Trastuzumab in 1998 on the basis of a randomized clinical trial (study H0648g) published in 2001 by Slamon et al. (20). No other randomized clinical trial has as yet been performed to evaluate the clinical effectiveness and tolerance of Trastuzumab in combination with chemotherapy in patients with metastatic recurrence and HER2 overexpression.

Two diagnostic techniques have been recognized as valuable tools for determining HER2 status: immunohistochemistry (IHC), and molecular hybridization, with FISH (Fluorescent In Situ Hybridization) being the most frequent technique used. IHC is simple to perform, quick, inexpensive and accessible to most laboratories. It can be performed on paraffin-embedded tissue sections, whatever type of fixative is used to preserve the tumor at the time of sample collection (Bouin's fluid or formalin). However, the lack of a standardized IHC methodology leads to a number of inconsistencies when the assays are repeated. FISH is a more reliable and reproducible technique than IHC, but it is complicated, long and expensive, and it cannot be performed when the tissues have been fixed in, or placed in contact with, Bouin's fluid.

Following the European Marketing Authorization guidelines, Trastuzumab is indicated for the treatment of patients in first metastatic relapse with an IHC score of 3+. However the gold standard method for assessing HER2 status is still a matter of debate (5). IHC, the most frequent technique used so far, is less correlated with clinical response to Trastuzumab than FISH, which may lead to incorrect diagnosis: either false-positives, which expose patients with HER2-non amplified tumors to the secondary effects of Trastuzumab (cardiotoxicity, risks of allergy, etc) while affording no therapeutic benefit, or false-negatives, which deprive patients with HER2-amplified tumors from the benefits of Trastuzumab. The use of the FISH technique on all patients showing metastatic recurrence, or to clarify an ambiguous status as determined by IHC could contribute to improved diagnostic strategies (4).

In an attempt to answer the question of how to test for HER2 status, Elkin et al. (8) recently proposed a cost-effectiveness analysis that took into account 7 different disease management strategies, of which 5 involved the assessment of HER2 status using the IHC and/or FISH methods at the time of metastatic relapse. It was assumed that IHC was performed using the HercepTest (DAKO, Carpinteria, CA). Their conclusion was that strategies using FISH, either alone or as confirmation of IHC scores of 2+ and 3+, are efficient when compared to strategies using IHC alone, or FISH on cases with IHC scores of 2+. Nonetheless, these results cannot apply to the situation in France, given the diversity of IHC methods used. The HercepTest kit is not used in France and the standardized national protocol laid down by the French *Groupe d'Etude des Facteurs Pronostiques par Immunohistochimie dans les Cancers du Sein* (GEFPICS, Group for the Evaluation of Immunohistochemical Prognostic Factors in Breast Cancer) recommends the use of DA485 polyclonal antibody (DAKO) or CB11 monoclonal antibody (Tebu/Novocastra, Ventana, Biogenenex, etc). Moreover, in the study by Elkin et al., HER2 levels are always tested at metastatic relapse, which corresponds to current clinical practice. However the tumor blocks embedded in paraffin at the time of initial diagnosis may have been destroyed or no longer be available at the time of metastasis. The French legislation only requires that private clinical pathology laboratories store fixed tumor sections over a 10-year period (by decree of 03/11/1968). It might therefore be worth considering testing HER2 levels at the time of initial diagnosis. This approach was recently considered at ASCO (4) and might be adopted if therapeutic trials confirm the benefit of administering Trastuzumab as an adjuvant therapy.

Our study proposes a cost-effectiveness analysis adapted to the situation in France, including the techniques and fixatives used and the possibility that the paraffin-embedded tumor samples might be inaccessible at metastatic recurrence. This analysis examines the medico-economic section of a multicentric study that has been carried out, as a result of the national program referred to above, in eight volunteering hospitals: six university teaching hospitals from the Rhone-Alps region [1] and two cancer centers[2]. These last two hospitals are reference centers for HER2 testing, because (1) they treat large numbers of invasive breast carcinoma patients, (2) they have calibrated the IHC method to the FISH technique following the GEFPICS guidelines, and (3) they regularly subject IHC procedures to quality controls laid down by the *Association Française d'Assurance Qualité en Anatomie Pathologique* (AFAQAP, French Association for Quality Assurance in Pathology) (24). Over a period of two years, the eight centers involved in the study prospectively assessed the HER2 status of infiltrating breast cancers using IHC at initial diagnosis following the GEFPICS / AFAQAP

guidelines. As planned, all cases with IHC scores of 2+ and 3+ and 10% of cases scoring 0 or 1+ were subjected to control analysis using FISH. The two reference centers where the FISH technique was available performed the controls. In total, the multicentric study enrolled 2,045 patients and 171 paraffin-embedded tumor sections were simultaneously screened using both IHC and FISH techniques. Our analysis is based on the simulated follow-up from initial diagnosis of a hypothetical cohort of patients with infiltrating breast cancer, according to the different strategies used for HER2 testing. Unlike Elkin et al. (8), who assessed effectiveness using QALYs (quality-adjusted life years), we decided to use intermediate criteria. In their study, Elkin et al. used the results of the only phase III clinical trial available (20), in which the IHC technique was performed using the HercepTest. As pointed out above, French laboratories use a different method, so these results cannot be extrapolated to the French population. Despite this fact, we shall compare our results with those of Elkin et al. (8).

2. METHODS

2.1. The Decision-Analysis Model

We devised a decision tree to compare 5 different strategies for the determination of HER2 status. Each strategy was as follows:

(S1) IHC at first metastatic relapse whenever it was possible to locate the archival tumor material or to collect a new histological sample; this is the method most commonly used in France; (S2) systematic IHC staining at diagnosis during the management of the primary tumor; (S3) FISH, as a substitute for IHC, at first metastatic relapse (depending on the type of fixative used); (S4) FISH, in addition to IHC, to clarify the status of IHC 2+ patients at first metastatic relapse (depending on the type of fixative used); (S5) FISH, in addition to IHC, to clarify the status of IHC 2+ and 3+ patients at first metastatic relapse (depending on the type of fixative used). This model was created using DATA 4.0 software (TreeAge Software, Williamstown, Mass). For each strategy, a simulation model was devised to represent the development over time of a cohort of 10,000 French patients, from initial diagnosis of infiltrating breast cancer to potential metastatic recurrence. The maximum duration of the simulation was 20 years from initial diagnosis. As an example, the structure of the decision tree representing the (S1) strategy is shown in Figure 1 below. Two types of events are distinguished, depending on whether they relate to the morbi-mortality of the cohort or to the implementation of HER2 tests. [Figure 1]

2.2. Evaluation Criteria

2.2.1. Effectiveness

Only one phase III randomized trial has been conducted so far (20) to assess the clinical effectiveness and the tolerance of Trastuzumab combined with chemotherapy in metastatic patients whose tumors exhibit HER2 overexpression. The IHC techniques used to select patients in this trial (Herceptest) are different from those recommended by the French GEFPICS/ AFAQAP guidelines. Since the clinical results from these studies cannot be extrapolated to the French situation we chose two intermediate criteria selected as follows:

Criterion 1. HER2 amplified tumor and no Trastuzumab treatment at first metastatic recurrence. Two different factors may lead to this situation: (i) false-negatives, or (ii) HER2 testing found to be impossible. *Criterion 2*. HER2 non-amplified tumor and improper Trastuzumab treatment at first metastatic relapse as a consequence of inadequate testing (false-positives).

2.2.2. Costs

In view of effectiveness criteria, only direct medical costs (expressed in euros, 2002 prices) likely to be influenced by the strategies under evaluation were taken into consideration. Few economic studies relating to IHC and FISH have been found in the literature (10; 12; 13; 23) but, again, the variability of standard practices and unit costs make these difficult to transpose to other settings. Hence, we carried out a cost analysis within the framework of the multicentric study referred to above.

2.3. Data and assumptions

The data required to evaluate the 5 strategies are mainly derived from the multicentric study, from which we created an initial database (DB1), and from the literature. However, since this multicentric study only applied to the determination of HER2 status at initial diagnosis, other data sources had to be used, as specified later on.

2.3.1. Probabilities of model events

2.3.1.1. Morbi-mortality

Metastatic relapse rate within 10 years

To obtain the most accurate estimate of the incidence of metastatic relapse over the 10-year period following initial diagnosis, we used data from published works, including meta-analyses (6, 7, 14) adapted by Bachelot et al. to take into account the clinical practice guidelines in use in France (2). We obtained tumor recurrence rates over the 10-year period following initial diagnosis for subgroups of patients defined by tumor size, SBR (Scarff,

Bloom, Richardson) histo-prognostic grade and lymph node invasion, stratified for the presence or absence of hormone receptors, and age. The percentage of patients in each subgroup was calculated using a new database (DB2) available at one of the hospitals involved in the multicentric study, the Centre Léon Bérard (CLB). This database referred to all new patients undergoing surgery between January 1996 and January 2003 (n=1,815).

Metastatic relapse rate after 10 years

According to Fisher et al. (11), about 13% of metastatic relapses seen at twenty years occurred after the first 10 years. For our analysis, we hypothesized that the metastatic relapse rates after 10 years were proportional to the rates within 10 years.

Mortality from other causes

Mortality data were obtained from the *Institut National d'Etudes Démographiques* (INED, French Institute of Population Studies). In order to include in our model age-specific mortality rates from other causes, we stratified the population into 4 age classes: (a) under 60 years, (b) between 60 and 69 years, (c) between 70 and 80 years, and (d) over 80 years. Mortality rates were estimated on the one hand within the 10 years following diagnosis and, on the other hand, between 10 and 20 years after initial diagnosis. The DEALE method was used to convert mortality rates into probabilities (3).

2.3.1.2. Determination of HER2 status

Type of fixative

We conducted a postal survey among the clinical pathology laboratories of the Rhone-Alps region in order to estimate the distribution of fixatives used in 2002 to preserve breast tumor tissues, i.e. Bouin's fluid and formalin. It is important to remember that Bouin's fluid is still commonly used in France, although it is being progressively replaced by formalin (24), and that the FISH test can only be performed on formalin-fixed tissues free from all traces of Bouin's fluid.

HER2 testing

From the CLB database (DB2), we identified patients with first metastatic recurrence who had been managed according to the (S1) strategy. We used this population to evaluate the frequency of HER2 tests that were either (1) impossible (tumor blocks destroyed and inaccessible metastases), (2) possible and performed (either on the initial tumor block or on a metastatic sample, with or without having to retrieve archival tumor tissue), or (3) not performed due to premature death or to inappropriate HER2 testing. The probabilities of all related events were calculated on the basis of these frequencies for all strategies assessed.

Quality of the techniques

In terms of the quality of the technique, FISH has been recognized as the gold standard for HER2 testing as it enables the most accurate predictions of clinical responses to Trastuzumab treatment (13; 22), despite the fact that, in 2.9% to 8.3% of the cases, HER2 protein was reported to be overexpressed in the absence of gene amplification (1; 16). As far as IHC is concerned, results reported in the literature are heterogeneous since the methods use different commercialized antibodies, with different technical conditions (dilutions, pre-heating treatment, fixative etc), and scores (absence of standardized cut-off values for positive scores) (4; 5). Because of this, the sensitivity and specificity of IHC as used in France (according to the French guidelines elaborated by the GEFPICS/ AFAQAP), were estimated using the multicentric analysis referred to above (DB1). On the basis of the European Marketing Authorization guidelines for Trastuzumab, IHC2+ cases were considered to be negative. As a result, true positives were IHC3+ and FISH positive cases, and true negatives IHC2+ or 0/1+ and FISH negative cases (fig. 1). Any reader interested in acquiring more details can refer to the full report, available from the authors (unpublished data, 2003).

Results of the HER2 tests

The distribution of IHC scores (0/1+ *versus* 2+ *versus* 3+) at the time of metastatic relapse was calculated using the (DB2) database. As regards the FISH technique, the distribution between patients with and without HER2-amplified tumor at the time of metastatic relapse was inferred from the distribution of the previously established IHC scores and the results obtained from the (DB1) database showing concordance between IHC and FISH.

2.3.2. Cost data

The cost data used in the simulation were primarily derived from the multicentric study (DB1). This enabled us to estimate the average cost per patient of retrieving archival tumor blocks and performing IHC and FISH analyses. Several questionnaires were produced, some being sent to hospitals, the others to the manufacturers, in order to collect data on both physical quantities and unit costs. Five cost categories were isolated: personnel, reagents, consumables, equipment and maintenance. The working time of each staff category (physicians, laboratory technicians, medical assistants) was observed and recorded by the hospitals. Data regarding reagents, consumables, equipment and maintenance were provided by both the hospitals and the manufacturers. For example, quantities of consumables were derived from the hospital questionnaires and unit prices from the industry questionnaires. Of note, the unit prices quoted by the manufacturers are catalogue prices, not the negotiated

prices that are actually charged, which remain confidential. The life expectancy, as well as the market prices of the equipments used, were gathered from the manufacturers. We also took into account the need to repeat the tests (either IHC or FISH) when artifacts or interpretation difficulties were encountered. The investigators estimated that approximately 10% of the cases were repeated. Moreover, the average cost per patient of performing a metastatic biopsy was estimated using the 2002 rates for corresponding interventions (pleuroscopy, liver biopsy or bone puncture etc.).

2.4. Discount rate

Costs and effectiveness measures were calculated without discount, then discounted at 3% and 5% to account for the distribution over time of the recurring metastases, as observed from the (DB2) database.

3. RESULTS

3.1. Parameters of the model

3.1.1. Clinical characteristics of the hypothetical cohort

As mentioned above, the clinical characteristics of the hypothetical cohort at the time of initial diagnosis were obtained from an exhaustive sample of 1,815 breast cancer patients undergoing surgery at the CLB between January 1996 and January 2003 (DB2) (cf. § 2.3.1.1). The results are shown in Table 1 below. [Table 1]

3.1.2. Probabilities

We also recall that the probabilities used in the model are derived from both the literature and (DB1) and (DB2) databases (cf. section 2.3.). These are presented in Table 2 below. [Table 2] Of note, HER2 testing was never reported impossible in the (DB2) database. The corresponding probability was therefore estimated as 0. As a result, the effectiveness criterion 1 is restricted to the number of false negatives.

3.1.3. Costs

The average costs per patient of using the IHC and FISH methods are presented in Table 3. [Table 3]

The average cost of retrieving a tumor section from the archive was 14 euros (2002 prices). The cost of performing a metastatic biopsy was calculated to be 893 euros (2002 prices).

3.2. Expected costs and effectiveness of the strategies in the primary analysis.

(S2), (S3), (S4) and (S5) strategies were compared with (S1) in a differential analysis. The total cost of using the (S1) strategy in a cohort of 10,000 patients reaches 106,400 $_{2002}$ €. However, this strategy leads to a certain number of inappropriate disease management decisions being made at the time of metastatic occurrence: of 10,000 patients at diagnosis, 73

patients with HER2 amplification were not given Trastuzumab treatment, and 26 patients with no HER2 amplification were wrongly given Trastuzumab treatment.

3.2.1. Costs and numbers of patients correctly managed according to criterion 1 (patients with HER2 amplification receiving Trastuzumab treatment)

The results are shown in Table 4 and Figure 2. [Table 4][Figure 2]

Non-dominated strategies or, in other words, strategies considered efficient according to the first criterion of effectiveness, were (S1), (S4) and (S3). We recall that the objective according to this criterion was to minimize the loss of chances, namely the number of patients who, under the (S1) strategy, would appear as false negatives and would not therefore receive Trastuzumab.

3.2.2. Costs and numbers of patients correctly managed according to criterion 2 (patients without HER2 amplification and not treated by Trastuzumab)

The results are shown in Table 4 and Figure 3 [Figure 3]

Strategies considered efficient according to the second criterion of effectiveness were (S1) and (S5). We recall that the objective according to this criterion was to minimize the risk of incorrect treatment by Trastuzumab of patients who, under the (S1) strategy, would appear as false positives and would wrongly receive Trastuzumab.

3.2.3. Synthesis

The (S2) strategy brought no added element of effectiveness, whatever the criteria, and was dominated in both cases. Given the current state of knowledge, this lead us to ban the use of IHC at initial diagnosis in all patients. (S1), which consisted of using IHC alone in cases of metastatic relapse, was the only efficient strategy according to the two criteria above.

Nevertheless, the (S4) strategy, which consisted of using IHC, then FISH, in cases of metastatic relapse for 2+ cases only, was more effective than (S1) according to the first criterion, without being any less effective according to the second, with an incremental cost which might be considered minimal (in comparison to others). (S3), which consisted of using only FISH whenever possible in the event of metastatic relapse, was the most effective strategy according to the first criterion, but also the most expensive (if we exclude (S2)), with an incremental 269,600 2002€ per 10,000 patients at diagnosis. (S5), which consisted of using IHC followed by FISH on 2+ and 3+ cases in the event of metastatic relapse, was the most effective strategy according to the second criterion, while at the same time being far less expensive than (S3) (75,600 versus 269,600 $_{2002}$€). Thus, in case of budgetary constraints which would tend to exclude (S3) but to permit (S5), (S5) could become a preferred option,

since it is as effective as (S4) according to the first criterion and more effective according to the second.

3.3. Sensitivity analyses

In view of the fact that metastatic relapse may occur at different times in the future, cost and effectiveness results may be sensitive to the choice of a discount rate. Moreover, the expected cost of those strategies that use the FISH test depends on the cost of the test itself, which is high at this stage of development of the technique. Finally, as the FISH test can only be applied when the tissues have been fixed in formalin, cost and effectiveness results will vary with the proportion of samples fixed in formalin (the others being fixed in Bouin's fluid).

As these three parameters may vary, three sensitivity analyses were performed to investigate the impact of variations on the results.

3.3.1. Sensitivity to the choice of discount rate

Cost and effectiveness data were simultaneously discounted by 3% and 5% (Table 5). [Table 5].Overall, the results were only slightly modified by the choice of the discount rate, whether applied to the costs or to the measurements of effectiveness. Consequently, the choice of the discount rate was of very little importance, which, a posteriori, justified the presentation of the primary analysis without discounting. This is not particularly surprising, because most metastatic spreads occur in the first years following initial diagnosis (49% of tumor recurrence within the first two years (DB2)). The cost of the (S2) strategy increased slightly with the discount rate. This result, though it may not make sense at first, can be explained as follows: (1) extra expenses represent the incremental cost of (S2) over (S1), (2) all the costs associated with (S2) are incurred at the beginning of the disease (because all the tests are performed at initial diagnosis) and are therefore independent from the discount rate, and (3) the costs corresponding to (S1) are spread over time and consequently decrease as the discount rate increases.

3.3.2. Sensitivity to the costs of the FISH test

The price of the reagents alone (estimated 283 $_{2002}$€) accounted for 61% of the cost of the FISH test (Table 3). However, this cost was calculated on the basis of catalogue prices, whereas negotiated prices might be substantially lower (up to 60% less). Following this hypothesis, the cost of the FISH test would be reduced by over 40%, falling from 283 $_{2002}$€ to 162 $_{2002}$€. The corresponding results are listed in Table 6 below. [Table 6]

No variations in cost or in effectiveness affected the (S2) strategy, which excluded the use of the FISH test. The incremental cost of (S3), (S4) or (S5) strategies over (S1) decreased by at

least 40% (between 43% and 50%), while effectiveness remained unchanged with reference to both criteria. The cost-effectiveness ratios were decreased accordingly.

3.3.3. Sensitivity to the proportion of samples fixed in formalin

As mentioned above, only 60% of samples included in the primary analysis were fixed in formalin, which is a pre-requisite for HER2 FISH testing. As the use of formalin is becoming more and more common, we adopted a proportion of 100% for the sensitivity analysis, which yielded the results presented in Table 7 below. [Table 7]

The performance of strategy (S2), which excluded the use of the FISH test, remained unaltered. There was an increase in costs of over 60% (between 63 and 66%) for strategies (S3), (S4) and (S5), whereas effectiveness increased by over 50% (between 55 and 66%) according to the two criteria. The strategies considered efficient were the same as in the primary analysis: (S1), (S3) and (S4) according to the first criterion of effectiveness, (S1) and (S5) according to the second. Because measurements of costs and effectiveness increased in similar proportions, the cost-effectiveness ratios of efficient strategies (in relation to (S1)) remained almost unchanged.

4. DISCUSSION

We assessed the cost-effectiveness of different strategies used to determine HER2 status in invasive breast cancer patients. Knowing the HER2 status of the patients enables to select those eligible for Trastuzumab treatment. All the strategies defined in the present study involved IHC protocols tailored to the GEFPICS/AFAQAP recommendations, and/or FISH tests. Previously published data on the clinical effectiveness of Trastuzumab treatments were of little help because they involved different IHC systems, such as the HercepTest. For this reason, we did not use the final criterion of Trastuzumab effectiveness, and we chose instead the following two intermediate criteria for evaluating the performance of diagnostic strategies: patients with HER2-amplified tumors who have not been treated, and patients with non-amplified tumors who have been wrongly treated. In the absence of applicable data from the literature, the costs of the tests used in our simulations were obtained from a multicentric medico-economic study conducted in France at 8 hospitals, which permitted to include 2,045 patients at initial diagnosis of infiltrating breast cancer. Average costs of IHC and FISH tests were calculated at 43 and 283 $_{2002}$€ respectively. In the study by Elkin et al. (8), the costs of both techniques were calculated as 85 and 381 US$, which corresponds to the amount of Medicare reimbursement. These differences are not surprising, as we know that health care costs are far higher in the United States than in France, which makes generalisability of the results of economic evaluations questionable, as emphasized in different studies (9; 15; 21).

Data on the sensitivity and specificity of the IHC test were derived from the multicentric study previously described. They were, to the best of our knowledge, the only data available for standardized IHC protocols developed by the GEFPICS/AFAQAP. The strategy chosen as comparator (S1) corresponded to the current practice in France, which consists of determining HER2 status using IHC at metastatic relapse. All other strategies were more expensive, but at least as effective judging from the two effectiveness criteria chosen. The strategy that consisted of assessing HER2 status using IHC at the time of initial diagnosis (S2), was dominated by all the others because it was more expensive without being any more effective. This held true for all the simulations, whether we referred to the primary analysis or to the sensitivity analysis. For a group of 10,000 patients at diagnosis, the costs of determining HER2 status were increased by 313,600 $_{2002}$€ in the primary analysis, which corresponds to 4 times the current cost (106,400 $_{2002}$€). Therefore, applying the test at the time of diagnosis does not improve performance because, according to our observations, it is extremely rare that the test cannot be performed at the moment of metastatic relapse (Table 2). Nonetheless, certain authors advocate determining HER2 status at diagnosis, as indicated in the recent recommendations from ASCO (4). An amplification of HER2 could in fact be correlated with faster metastatic evolution. In this case, adjuvant or neo-adjuvant treatment using Trastuzumab, which would require knowledge of the HER2 status at diagnosis, could be justified. Clinical trials are currently underway to test this hypothesis. Moreover, one can argue that retrieving the archival tumor material at the moment of metastatic relapse can take time (up to two months, according to our information), and this delay in administering Trastuzumab might weaken the effect of the treatment. All other strategies consisted of determining HER2 status at metastatic relapse. Of these, the most costly was the (S3) strategy, which consisted of substituting the FISH test for IHC whenever possible. This result was expected, because the cost of the FISH test is far higher than IHC (283 $_{2002}$€ versus 43 $_{2002}$€). Several strategies were considered efficient in the primary analysis, according to the first criterion of effectiveness based on the reduction of false negatives. They consisted of:

- performing the IHC test alone (S1),
- performing the FISH test whenever possible (that is, when the tumor had been fixed in formalin) or the IHC test otherwise (S3), with a cost-effectiveness ratio (cost per case correctly treated) of 6,127 $_{2002}$€,
- performing the IHC test, and subsequently the FISH test (depending on the type of fixative) only on 2+ cases (S4), with a cost-effectiveness ratio of 722 $_{2002}$€.

Strategies considered efficient according to the second criterion of effectiveness, based on the reduction of false positives avoided, were:

- performing the IHC test alone (S1),
- performing the IHC test, and subsequently the FISH test (depending on the type of fixative) only on 2+ and 3+ cases (S5), with a cost-effectiveness ratio of 4,725 $_{2002}$€.

Interestingly, the only efficient strategy in relation to the two criteria was the comparator. This does not, of course, provide sufficient cause for eliminating the strategies that are only efficient in terms of one of the two criteria ((S3), (S4), (S5)).

We selected three parameters against which to analyze sensitivity: the discount rate, the cost of the FISH test and the proportion of paraffin-embedded tumor samples fixed in formalin, as these alone will allow the FISH test to be applied. The low sensitivity of the results to the choice of discount rate justified the fact that the primary analysis was presented on the basis of undiscounted data. In the primary analysis, the major part of the cost of strategies using the FISH test came as a direct result of the cost of this test, which is far more expensive than IHC. In fact, there were two reasons for testing the effect of a reduction of this cost: the negotiated prices of reagents are lower than catalogue prices and, on the other hand, these prices should decrease as the method becomes more widely used. A reduction in the cost of the FISH test would have a mechanical impact on the cost of (S3), (S4) and (S5) strategies in which it participates, as well as on the corresponding cost-effectiveness ratios. However, efficient strategies would be unchanged. In the primary analysis, the proportion of formalin-fixed tumors reached 60%, but this percentage increases rapidly. If all the tumors were fixed in formalin, the FISH tests included in the (S3), (S4) and (S5) strategies would be feasible in all cases. An increase of around 60% in the costs and the two measurements of effectiveness of these strategies would follow, without affecting the corresponding cost-effectiveness ratios. Again, efficient strategies would remain the same as in the primary analysis. Some of our conclusions echo those of Elkin et al. (8), although a number of differences exist between the two studies. The most important one results from the choice of the effectiveness criteria: these authors compare the effectiveness of the different strategies using QALYs, on the basis of clinical data compatible with the use of the HercepTest kit for IHC testing. From the cost-effectiveness ratios expressed as costs per QALY, they identify two efficient strategies, which correspond to two of our own: to perform the FISH test at the time of metastatic relapse (corresponding to our (S3)), or to apply the IHC test at metastatic relapse, followed by the FISH test on 2+ and 3+ cases only (corresponding to (S5)). Interestingly, the first

strategy is efficient according to our first effectiveness criterion, while the second one is efficient according to our second criterion.

5. CONCLUSION

In conclusion, the determination of HER2 status at diagnosis infers significant incremental costs, which do not appear to be justified until trials testing adjuvant or neoadjuvant Trastuzumab therapy have proven its benefit. As far as the other four strategies are concerned, HER2 status is determined at the time of metastatic relapse and the strategies only differ in their application of IHC and FISH tests. None of the four deserves to be excluded outright, as each one is efficient for at least one of the two criteria of effectiveness. The question remains of whether the corresponding cost-effectiveness ratios are acceptable.

Notes

[1] Hôtel-Dieu, Hôpital de la Croix-Rousse, Hôpital Edouard Herriot and the Centre Hospitalier Lyon Sud, located in Lyon, Hôpital Bellevue in Saint-Etienne, and Hôpital Michallon in Grenoble.

[2] The Centre Léon Bérard (CLB) in Lyon and the Centre Jean Perrin in Clermont-Ferrand.

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Table 1. Characteristics of the hypothetical cohort of invasive breast cancer patients at initial diagnosis (DB2).

Characteristics	N	%
Age		
Under 60 years	943	59.4%
Between 60 and 69 years	364	23.0%
Between 70 and 79 years	220	13.9%
Over 80 years	60	3.6%
Total	*1,587*	*100%*
Hormone receptors		
Rh+	1,499	87%
Rh-	222	13%
Total	*1,721*	*100%*
SBR histo-prognostic grade		
1	433	25%
2	806	46%
3	504	29%
Total	*1,743*	*100%*
Tumor size		
≤ 1 cm	368	21%
1 cm to 2 cm	654	38%
>2 cm	723	41%
Total	*1,745*	*100%*
Lymph node invasion		
N+	856	50%
N-	840	50%
Total	*1,696*	*100%*

Table 2. Probability of events in the decision analysis model

PROBABILITIES	Base-line Estimation	
Morbi-mortality		
Metastatic relapse		
Within 10 years of diagnosis, according to prognostic factors [a], after adjuvant therapy [b]	age<60 years / age>60 years	
RH+, N-, T≤1 cm and SBR 1	0.07	/ 0.05
RH+, N-, T>1 cm and SBR1 or SBR2/3	0.13	/ 0.11
RH+, N-, T>2 cm and SBR2/3	0.16	/ 0.16
RH+, N+	0.29	/ 0.24
RH-, N-, T≤1 cm and SBR 1	0.10	/ 0.10
RH-, N-, T>1 cm and SBR1 or SBR2/3	0.13	/ 0.14
RH-, N-, T>2 cm and SBR2/3	0.21	/ 0.22
RH-, N+	0.36	/ 0.38
Mortality from causes other than breast cancer		
within 10 years of diagnosis, according to age at diagnosis		
< 60 years at diagnosis	0.02	
60-69 years at diagnosis	0.06	
70-79 years at diagnosis	0.18	
80-89 years at diagnosis	0.45	
over 10 years after diagnosis, according to age at diagnosis		
< 60 years at diagnosis	0.05	
60-69 years at diagnosis	0.18	
70-79 years at diagnosis	0.54	
80-89 years at diagnosis	0.86	
Determination of HER2 status		
Type of fixative used:		
Formalin-AFA, uncontaminated by Bouin's fluid	0.60	
HER2 testing [c]:		
HER2 tests impossible	0	
HER2 tests possible and performed on:		
Archival tumor tissue or biopsy from the metastasis	0.99	
New metastatic biopsy specifically taken for HER2	0	
New metastatic biopsy not taken specifically for HER2	0.01	
HER2 tests not performed because of:		

Early death	0.04
Not appropriate, patient under 70 years old at relapse / over 70 years old at relapse	0.03 / 0.31
Quality of the techniques:	
Comparison of IHC and FISH	
FISH- given that IHC 0/1+	0.96
FISH- given that IHC 2+	0.61
FISH- given that IHC3+	0.06
IHC sensitivity / specificity as compared to FISH (gold standard)	0.88 / 0.91
HER2 test results at metastatic relapse	
IHC:	
scores of 0 or 1+ vs 2+ vs 3+, relapse within 10 years of diagnosis	0.74 vs 0.02 vs 0.24
scores of 0 or 1+ vs 2+ vs 3+, relapse more than 10 years after diagnosis	1 vs 0.0 vs 0.0
FISH:	
amplified vs non-amplified, relapse within 10 years of diagnosis	0.26 vs 0.74
amplified vs non-amplified, relapse more than 10 years after diagnosis	0.04 vs 0.96

(a) RH = hormone receptors, N = lymph node invasion, T = tumor size, SBR = Scarff, Bloom, Richardson histo-prognostic grade ; (b) Chemotherapy for RH-, and hormone therapy +/- chemotherapy for RH+ 0 ; (c) The probabilities only concern (S1), (S3), (S4) and (S5). In (S2), all HER2 tests were performed on tumor sections from the original paraffin block.

Table 3. Estimated costs of methods for assessing HER2 status (average cost per patient in $_{2002}$ €)

Cost center	**IHC**	**FISH**
Personnel	19.31	16.15
Reagents	15.73	174.20
Consumables	1.30	0.30
Equipment	1.99	47.50
Maintenance	0.55	19.05
Total	*38.88*	*257.02*
Retained value [(a)]	**43**	**283**

(a) figure obtained by adding in unavoidable losses, at an estimated 10% of cases.

Table 4. Incremental costs and incremental numbers of patients correctly managed according to criterion 1 (HER2 amplified and treated with Trastuzumab) and to criterion 2 (HER2 non-amplified and no Trastuzumab) among a cohort of 10,000 patients at diagnosis, as compared to (S1).

Strategy	**Cost $_{2002}$ €**	**Effectiveness**			
		According to criterion 1		**According to criterion 2**	
		Number of patients correctly managed (false-negatives avoided)	**ICER ($_{2002}$€ per correctly managed case)**	**Number of patients correctly managed (false-positives avoided)**	**ICER ($_{2002}$€ per correctly managed case)**
(S1)	0	0	Comparator	0	Comparator
(S2)	313,600	0	Dominated	0	Dominated
(S3)	269,600	44	6,127	16	Dominated
(S4)	6,500	9	722	0	Dominated
(S5)	75,600	9	Dominated	16	4,725

Table 5. Incremental costs and incremental numbers of patients correctly managed among a cohort of 10,000 patients at diagnosis, as compared to (S1). Results undiscounted and discounted at 3% and 5%.

Strategy	**Cost (x 10^4 $_{2002}$ €)**			**Number of patients correctly managed**					
				False negatives avoided (criterion 1)			**False positives avoided (criterion 2)**		
	0%	3%	5%	0%	3%	5%	0%	3%	5%
(S1)	0	0	0	0	0	0	0	0	0
(S2)	31.36	32.42	33.00	0	0	0	0	0	0
(S3)	26.96	24.26	22.82	44	39	37	16	14	14
(S4)	0.65	0.60	0.57	9	8	8	0	0	0
(S5)	7.56	6.98	6.65	9	8	8	16	14	14

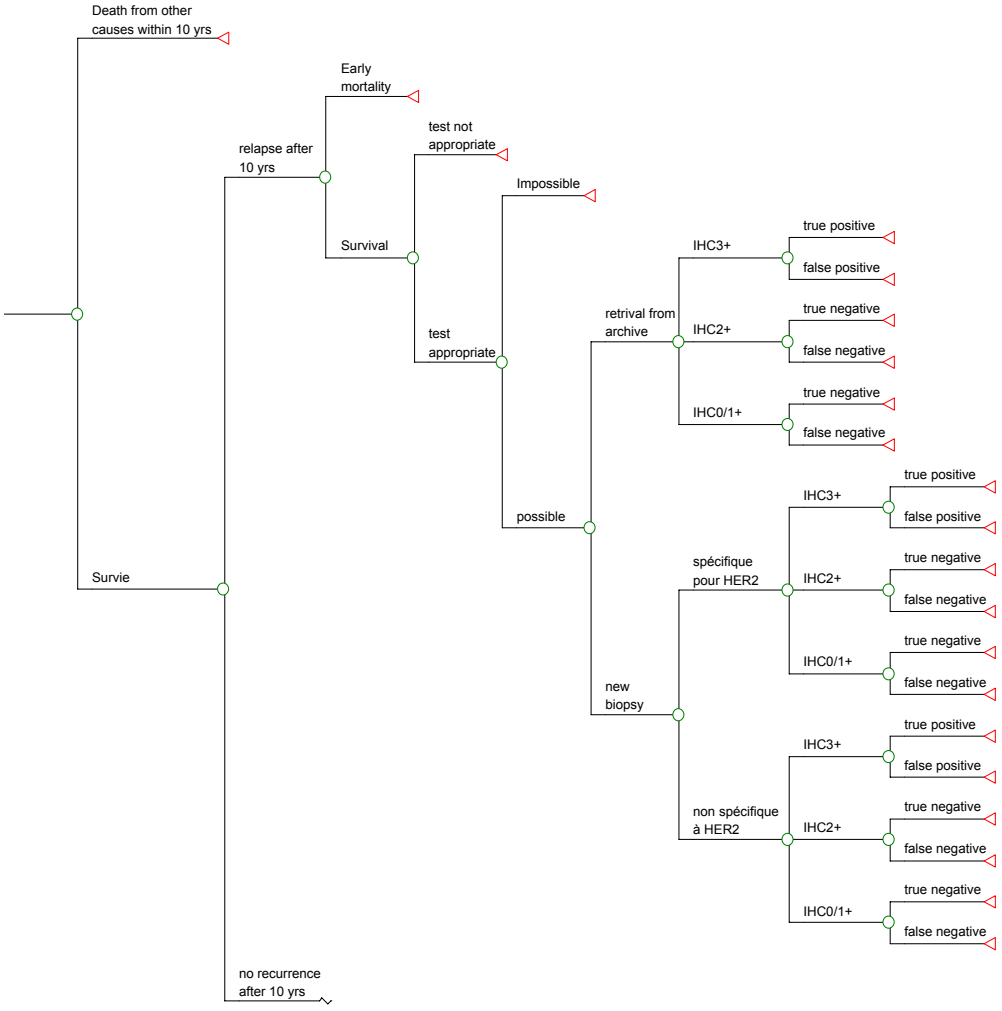
Table 6. Incremental costs and incremental numbers of patients correctly managed among a cohort of 10,000 patients, as compared to (S1). Reducing the price of FISH (from 283 $_{2002}$€ to 162 $_{2002}$€).

Strategy	Cost (x 10^4 $_{2002}$€)		Number of patients correctly managed: False negatives avoided (criterion 1)		False positives avoided (criterion 2)	
	Primary	Sensitivity	Primary	Sensitivity	Primary	Sensitivity
(S1)	0	0	0	0	0	0
(S2)	31.36	31.36	0	0	0	0
(S3)	26.96	13.37	44	44	16	16
(S4)	0.65	0.37	9	9	0	0
(S5)	7.56	4.33	9	9	16	16

Table 7. Incremental costs and incremental numbers of patients correctly managed among a cohort of 10,000 patients, as compared to (S1). Increasing the proportion of formalin-fixed tissues (from 60% to 100%).

Strategy	Incremental cost (x 10^4 $_{2002}$€)		Number of patients correctly managed: False negatives avoided (criterion 1)		False positives avoided (criterion 2)	
	Primary	Sensitivity	Primary	Sensitivity	Primary	Sensitivity
(S1)	0	0	0	0	0	0
(S2)	31.36	31.36	0	0	0	0
(S3)	26.96	44.92	44	73	16	26
(S4)	0.65	1.06	9	14	0	0
(S5)	7.56	12.56	9	14	16	26

Figure 1. Decision tree for the (S1) strategy, over a period of 10 years after diagnosis (a).



(a) FISH is the reference test, and IHC scores of 2+ are considered negative (cf. §2.3.1.2.). After 10 years the tree structure is identical, only the probabilities of events will change.

Figure 2. Incremental costs and incremental numbers of patients correctly managed according to criterion 1 (HER2 amplified and treated with Trastuzumab) among a cohort of 10,000 patients at diagnosis, as compared to (S1).

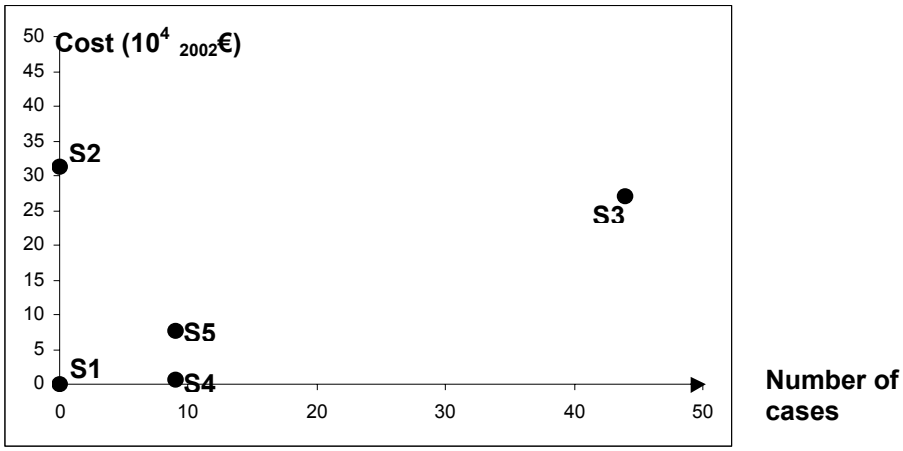
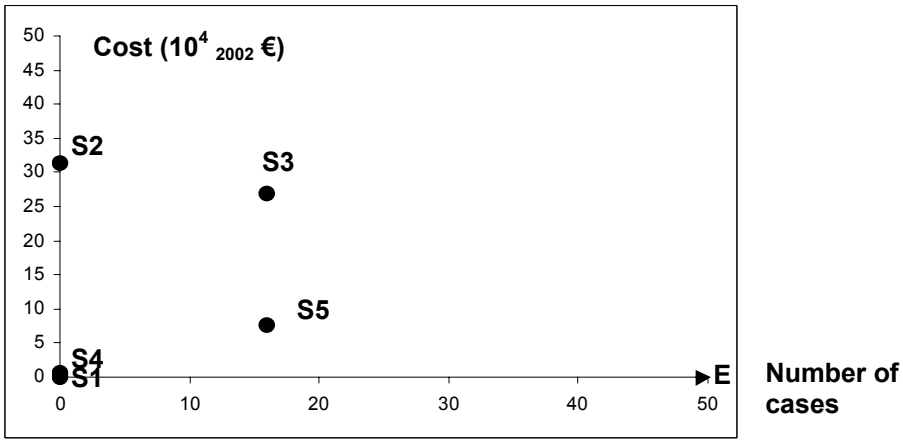


Figure 3. Incremental costs and incremental numbers of patients correctly managed according to criterion 2 (HER2 non-amplified and not treated with Trastuzumab) among a cohort of 10,000 patients at diagnosis, as compared to (S1).



Captions to figures 2 and 3

(S1) At relapse: IHC (comparator); **(S2)** At diagnosis: IHC; **(S3)** At relapse: FISH if formalin-fixed, otherwise IHC; **(S4)** At relapse: IHC, followed by FISH on 2+ cases if formalin-fixed; **(S5)** At relapse: IHC followed by FISH on 2+ and 3+ cases if formalin-fixed