

Original article

Quality of pathology reporting is crucial for cancer care and registration: A baseline assessment for breast cancers diagnosed in Belgium in 2008



H. De Schutter ^{a,*}, N. Van Damme ^a, C. Colpaert ^b, C. Galant ^c, K. Lambein ^d, A. Cornelis ^e, P. Neven ^f, E. Van Eycken ^a

^a Belgian Cancer Registry, Koningsstraat 215 box 7, 1210, Brussels, Belgium

^b Department of Pathology, GZA Hospitals and Antwerp University Hospital, Wilrijkstraat 10, 2650, Antwerpen, Belgium

^c Department of Pathology, University Hospital Saint-Luc, Avenue Hippocrate 10, 1200, Brussels, Belgium

^d Department of Pathology, University Hospital Ghent, De Pintelaan 185, 9000, Gent, Belgium

^e Department of Pathology, Regional Hospital Heilig Hart Tienen, Kliniekstraat 45, 3300, Tienen, Belgium

^f Department of Gynaecology, University Hospitals Leuven, Herestraat 49, 3000, Leuven, Belgium

ARTICLE INFO

Article history:

Received 1 July 2014

Received in revised form

4 December 2014

Accepted 8 December 2014

Available online 5 January 2015

Keywords:

Pathology report

Breast cancer

Registration

Quality

Variability

ABSTRACT

Objectives: Given the crucial role of pathology reporting in the management of breast cancers, we aimed to investigate the quality and variability of breast cancer pathology reporting in Belgium.

Materials and methods: Detailed information on non-molecular and molecular parameters was retrieved from the pathology protocols available at the Belgian Cancer Registry for 10,007 breast cancers diagnosed in Belgium in 2008.

Results: Substantial underreporting was shown for several clinically relevant non-molecular parameters, such as lymphovascular invasion. High-volume laboratories performed only slightly better than others, and analyses at the individual laboratory level showed clear inter-laboratory variability in reporting for all volume categories. Information on ER/PR and HER2 IHC was mentioned in respectively 91.7% and 90.8% of evaluative cases. HER2 ISH data were available for 78.5% of the cases judged to be 2+ for HER2 IHC. For cases with different specimens analysed, discordance between these specimens was highest for HER2, followed by PR. For HER2, results obtained from different laboratories were even less concordant. In addition, inter-laboratory differences were noted in the used ER/PR scoring systems, the proportion of ER+/PR+ cases, and the relation between histological grade and ER/PR positivity. Data on Ki67 were only available for 43.8% of the investigated cases, and showed inconsistent use of cut-off values.

Conclusion: Breast pathology reporting in Belgium in 2008 was suboptimal and showed considerable inter-laboratory variability. Synoptic reporting has been proposed as a facilitator towards increased reporting quality and harmonization, but the lack of aligned informatics remains a major hurdle in its concrete implementation.

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Abbreviations: BCR, Belgian Cancer Registry; CAP, College of American Pathologists; IHC, immunohistochemistry; ISH, in situ hybridization; ASCO, American Society of Clinical Oncology; IDA, invasive ductal adenocarcinoma; NAT, neo-adjuvant systemic treatment.

* Corresponding author. Tel.: +32 2 250 10 17; fax: +32 2 250 10 11.

E-mail addresses: harlinde.deschutter@kankerregister.org (H. De Schutter), cecile.colpaert@gza.be (C. Colpaert), christine.galant@uclouvain.be (C. Galant), kathleen.lambein@ugent.be (K. Lambein), ANATOMO@rztienen.be (A. Cornelis), patrick.neven@uzleuven.be (P. Neven).

<http://dx.doi.org/10.1016/j.breast.2014.12.004>

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Introduction

Each year, approximately 10,000 new breast cancers are diagnosed in Belgium, rendering it the most frequently occurring cancer in females [1]. The Belgian Cancer Registry (BCR) is population-based and includes data on all newly diagnosed malignant cases since 2004. It is estimated to be more than 95% complete. Part of the dataflow to the BCR consists of a network with the pathologists, including the delivery of structured files containing the pathology reports. Besides cancer epidemiology descriptives, the BCR is

increasingly involved in the evaluation of quality of care for cancer patients at the population level. Several collaborations with its scientific partners have resulted in publications confirming that the quality of pathology reporting must be considered as an integral part of quality of cancer care [2–8]. In the current evolution towards individualized cancer treatments, a thorough description of both non-molecular and molecular parameters by the pathologist will guide the clinician in choosing the most adequate treatment for each individual patient.

International guidelines on breast cancer pathology have been made available at the American (College of American Pathologists (CAP)) level in 2000 and at the European level in 2005 [9,10]. Concerning non-molecular tumour characteristics, these guidelines mentioned which elements should be reported by the breast cancer pathologists. Concerning hormone receptors, they referred to the necessity of testing if clinically relevant, but did not explicitly state which cut-offs should be used. Recommendations on immunohistochemical (IHC) and in situ hybridization (ISH) testing for human epidermal growth factor receptor 2 (HER2) were included in the European guidelines of 2005 [10] and published by the American Society of Clinical Oncology (ASCO)/CAP in 2007 [11], with an update in 2013 [12]. Guidelines for immunohistochemical testing of oestrogen and progesterone receptor (ER/PR), including the recommendation of considering $\geq 1\%$ staining as positive, were published by ASCO/CAP in 2010 [13]. Specific Belgian guidelines for HER2 testing have been developed in 2007 [14] and a proposal for standardization of the breast pathology report has been made in 2010 [15].

Although both national and international guidelines are assumed to be known to Belgian pathologists, it remains unclear whether these have been implemented in daily practice. An estimation of the actual

quality of breast pathology reports regarding non-molecular and molecular predictive and prognostic characteristics at the Belgian population level has previously not been reported.

This study first evaluated the availability of pathology reports at the BCR for the incidence year 2008. For non-molecular parameters, the quality of the breast pathology reports delivered to the BCR was assessed for all studied parameters at the population level and by volume of the laboratory, completed with analyses on inter-laboratory variability in reporting for a selection of parameters. Reporting on molecular parameters was studied at the population level in terms of availability of information on ER, PR, HER2 (IHC and ISH) and Ki67, used scoring systems for ER and PR, cut-off values for Ki67 and concordance between specimens for ER, PR and HER2. Some surrogate quality indicators for molecular testing such as the proportion of ER negative/PR positive cases were calculated both at the overall and at the inter-laboratory level.

The study was set up as a collaboration between the BCR and the Belgian Working Group for Breast Pathology (BWGBP).

Materials and methods

All newly diagnosed invasive breast cancers in females (Belgium, 2008) were selected from the database of the BCR. Following exclusion of atypical morphologies such as phyllodes tumours, 10,007 breast cancers corresponding to 9764 different patients were considered for further analysis. To retrieve detailed information from all available pathology reports, an extended dataset with a total of 151 variables was developed. The following variables were included: (a) non-molecular information on the primary invasive tumour (i.e. largest tumour in case of

Table 1
Overall reporting of non-molecular parameters.

Non-molecular parameter	% Available information			
	All cases	High volume ^a	Middle volume ^a	Low volume ^a
<i>All cases</i>	<i>n = 10,007</i>	<i>n = 2793</i>	<i>n = 3342</i>	<i>n = 2454</i>
Histological grade	95.3%	97.0%	95.2%	93.9%
<i>Primary invasive tumour^b</i>	<i>n = 7827</i>	<i>n = 2187</i>	<i>n = 2548</i>	<i>n = 1971</i>
Tumour extent (uni/multifocal)	98.4%	98.3%	98.7%	98.7%
Number of invasive foci	77.7%	85.7%	70.1%	77.3%
Maximal diameter of invasive tumour ^c	95.5%	95.4%	96.3%	96.0%
Presence/absence of lymphovascular invasion ^c	61.7%	66.9%	63.9%	54.2%
Resection margins first resection	88.9%	92.7%	86.1%	89.7%
Resection margins additional resection ^d	87.0%	86.8%	88.2%	85.7%
Presence of in situ component	75.4%	79.5%	75.4%	70.5%
<i>Associated DCIS^b</i>	<i>n = 4375</i>	<i>n = 1324</i>	<i>n = 1393</i>	<i>n = 994</i>
Nuclear grade of DCIS	76.9%	80.5%	79.6%	67.6%
Total diameter invasive carcinoma + DCIS	32.6%	41.4%	32.4%	22.9%
Resection margin DCIS	51.1%	60.7%	48.7%	43.3%
<i>Sentinel node procedure</i>	<i>n = 3332</i>	<i>n = 1080</i>	<i>n = 1386</i>	<i>n = 866</i>
Number of sentinel nodes examined	98.4%	99.4%	97.4%	98.7%
Presence of isolated tumour cells ^c	51.8%	50.5%	57.1%	43.3%
Number of positive sentinel nodes ^c	99.2%	99.5%	98.9%	99.3%
<i>Positive sentinel nodes</i>	<i>n = 923</i>	<i>n = 266</i>	<i>n = 338</i>	<i>n = 191</i>
Maximal diameter of largest metastasis in sentinel node ^c	47.1%	44.0%	52.1%	47.1%
Extracapsular spread of sentinel node metastasis ^c	59.8%	63.0%	62.0%	56.5%
<i>Axillary lymph node dissection</i>	<i>n = 5539</i>	<i>n = 1402</i>	<i>n = 1927</i>	<i>n = 1361</i>
Number of lymph nodes examined	98.7%	99.1%	98.6%	98.7%
Number of positive axillary lymph nodes ^c	99.3%	99.2%	99.3%	99.5%
<i>Positive axillary lymph nodes</i>	<i>n = 2266</i>	<i>n = 571</i>	<i>n = 801</i>	<i>n = 567</i>
Maximal diameter of largest metastasis in axillary clearance ^c	29.7%	41.5%	28.2%	24.5%
Extracapsular spread – axillary clearance ^c	74.7%	76.7%	77.1%	76.5%

The italics in the first column indicate the different categories of non-molecular parameters for which reporting was assessed. The numbers in italics in 2nd to 5th column refer to the number of reports available for assessment of pathology reporting for parameters of the concerned category, by laboratory volume (all cases, high volume, middle volume, low volume).

^a For the volume analyses, only the cases that could be assigned to one laboratory were taken into account (see methodology section).

^b Limited to cases for which at least one complete report of a resection specimen was available.

^c Parameters additionally explored at the individual laboratory level.

^d Only cases with an additional resection were taken into account ($n = 2440$ for all cases, 744 for high volume, 730 for middle volume and 565 for low volume laboratories).

multifocality) and its associated in situ component, sentinel node procedure, axillary lymph node dissection and (b) molecular information on immunohistochemistry results for ER, PR, Ki67 and HER2, and on ISH results for HER2. According to detailed guidelines, a team of specifically trained data managers at the BCR manually entered all pathology information, case by case, in the dataset.

In a first step, the availability of pathology information at the BCR was described in terms of delivered reports and missing information on clinical and pathological staging.

Secondly, analyses focused on the reporting of detailed non-molecular information. For each parameter concerned, the proportion of reports clearly mentioning this parameter was calculated, for all laboratories together as well as for different categories of laboratories based on the number of breast cancer protocols delivered to the BCR in 2008 (<100 cases: low volume ($n = 56$), 100–200 cases: middle volume ($n = 23$), >200 cases: high volume ($n = 7$)). For a selection of parameters with a potential influence on the therapeutic approach (listed in Table 1), availability of information at the individual laboratory level was also investigated.

Third, detailed analyses were performed regarding the molecular characteristics. At the overall level, availability of molecular information regarding ER, PR, HER2 (IHC and ISH) and Ki67 was studied. For ER and PR, the use of different scoring systems was listed. If the same molecular test was performed on more than one specimen, the concordance of the results was investigated both for

different specimens investigated in one laboratory and in different laboratories. For HER2, IHC results were compared with ISH results whenever available. For Ki67, the cut-off values used by different pathologists were explored.

Additionally measured surrogate quality indicators for molecular testing included the proportion of ER negative lobular cancers, ER positive metaplastic carcinoma, ER negative/PR positive cases and ER (or PR) positive cases by histological grade within invasive ductal carcinoma (IDA). The latter two parameters were also studied at the individual laboratory level.

For analyses at the individual laboratory level, the variability in pathology reporting was graphically presented by means of funnel plots, showing a relation between the number of informative cases delivered by the individual laboratory and the quality of the report concerning the studied parameter, with binomial control limits of 95% and 99% around the overall estimate (overall result).

For these analyses as well as for the analyses by laboratory volume, cases needed to be assigned to one laboratory if possible. For the 7640 cases that were delivered by only one laboratory, this presented no problem. For an additional 949 cases delivered by two laboratories, knowledge on common collaboration practices between these laboratories made it possible to identify the laboratory delivering the report of the resection specimen. The remaining 1418 cases were not taken into account for the analyses by individual laboratory or by laboratory type (volume).

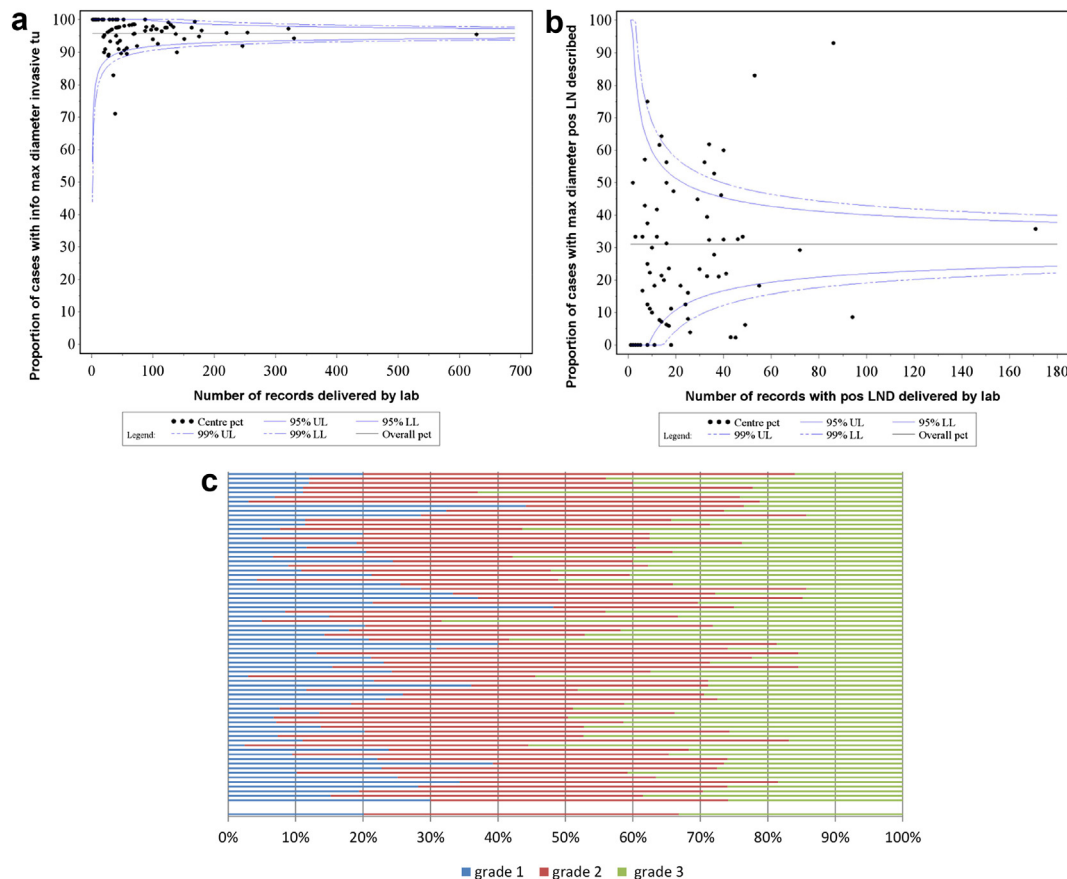


Fig. 1. Inter-laboratory variability for reporting of non-molecular parameters. a: Maximal diameter of invasive tumour ($n = 6697$ cases delivered by 83 different laboratories). max = maximal, tu = tumour, lab = laboratory, UL = upper limit, LL = lower limit, pct = percentage. b: Maximal diameter of largest metastasis in axillary lymph node dissection ($n = 1939$ cases delivered by 83 different laboratories). max = maximal, pos = positive, LN = lymph node, LND = lymph node dissection, lab = laboratory, UL = upper limit, LL = lower limit, pct = percentage. c: Distribution of histological grade by delivering laboratory ($n = 8047$ cases delivered by 73 different laboratories). Analyses were restricted to laboratories to which at least 25 cases could be assigned. The lowest line represents the general results and the upper lines represent the results by individual laboratory ranked by volume (smallest volumes at the top).

Results

Availability of pathology information at the BCR

For 7827 cases (78.2%), at least one complete report of a resection specimen was available at the BCR. For 291 cases, only a conclusion report of a resection specimen was available. For the remaining cases, we could retrieve information from a report concerning a biopsy ($n = 1461$) or cytology ($n = 125$). No report was available for 2.1% of the studied tumours.

The clinical stage was missing in 41.3% of cases, the pathological stage in 11.6% of all cases (and for 0.9% of cases with a complete report of a resection specimen).

Availability of non-molecular parameters and inter-laboratory variability

As shown in Table 1, reporting of non-molecular parameters ranged from excellent for some parameters to poor for others. Although high-volume laboratories performed slightly better than lower-volume laboratories, reporting remained low for crucial parameters such as lymphovascular invasion, DCIS margins and diameter, and diameter and extracapsular spread of lymph node metastases. Analyses of inter-laboratory differences showed little variability and few outliers for parameters with an overall good reporting such as maximal diameter of the invasive tumour. Other clinically relevant non-molecular characteristics such as maximal diameter of the largest axillary metastasis were more prone to variability in reporting between individual laboratories (Fig. 1a–b).

Information regarding histological grade was available for 9538 cases (95.3%), resulting in a distribution of 19.7% grade 1, 46.8% grade 2 and 33.6% grade 3 tumours. Remarkably, the distribution of the histological grade varied highly amongst laboratories, independent of their volume (Fig. 1c).

Availability of molecular parameters and inter-laboratory variability

Data on oestrogen and progesterone receptor expression were missing for 1135 cases (11.3%) and 1136 cases (11.4%) respectively. Restricting analyses to those cases for which at least a report of a biopsy or resection specimen was available ($n = 9579$), this proportion decreased to 8.3% for both molecular parameters.

In total, 10,773 ER immunohistochemistry (IHC) tests were described in the studied reports. Semiquantitative scoring integrating both the percentage of stained cells and staining intensity was mentioned in 76.3% of these cases. The Quick-Allred scoring system was the most frequently used (57.1%), followed by the H-score (11.1%) and the IRS score (8.1%). Similar results were obtained for PR (results not shown).

For 3157 cases, information on ER and PR IHC was available for two different specimens of the same tumour. Of this group, 331 patients were treated with neo-adjuvant systemic treatment (NAT). Proportions of discordance on hormone receptor status between the different specimens were 6.7% for ER and 17.8% for PR in the patients with NAT and 5.2% for ER and 11.6% for PR in the patients without NAT. These proportions were similar for cases studied in a single laboratory or in different laboratories.

HER2 immunohistochemistry results were very well reported in the studied protocols, with missing results for 12.3% of all cases, and for 9.2% of the cases with at least an available report of a biopsy or resection specimen ($n = 9579$). HER2 ISH results were delivered to the BCR in 25.5% of all cases, and in 78.5% of the cases judged to be 2+ for HER2 IHC.

Similar to ER and PR, information on HER2 IHC status was sometimes derived from two different specimen types ($n = 3199$).

Concordance rates reached 77.7% for cases treated without NAT ($n = 2858$), and 76.5% for cases treated with NAT. Discordant results were mainly due to cases determined to be 0 or 1+ for HER2 on one specimen and 2+ on another specimen ($n = 517$). Few cases turned from 3+ into 0 or 1+ ($n = 99$) or into 2+ ($n = 101$). Specimens studied in different laboratories ($n = 1020$) were less concordant than results obtained from the same laboratory ($n = 2169$): 71.0% vs. 79.8% for cases treated with NAT and 69.6% vs. 81.4% for cases treated without NAT.

For HER2 ISH, the presence or absence of amplification as determined for the first specimen was confirmed for the second specimen in 91.5% of all available cases ($n = 153$), independent of NAT. Again, results obtained from different laboratories were less concordant than results obtained from the same laboratory (11/79 vs. 2/73 discordant cases).

For 368 cases with concordant HER2 IHC results, without NAT and with ISH information available, HER2 IHC was compared with ISH. For 88.7% and 92.0% of the cases scored 0–1+ or 3+, respectively, the ISH test did confirm the IHC result. Of 110 cancers with HER2 IHC score 2+, 32 showed amplification by ISH (29.1%).

Data on Ki67 IHC were only available for 4386 (43.8%) of the investigated cases. In total, 4760 test results for Ki67 were described in the investigated reports. A clear interpretation for these results was provided by the pathologist in 1099 cases. Results for Ki67 were stated positive in 439 reports, of which 23 cases showed a Ki67 percentage of less than 14%. Similarly, 541 cases were called negative, of which 104 had a Ki67 percentage of $\geq 15\%$. The remaining cases were found to be equivocal by the pathologist, and showed a Ki67 percentage of between 4 and 50%.

Estimates of quality of molecular testing can be made by measurements of surrogate quality indicators. This is the case for ER-negativity in a lobular cancer, which was reported in 3.3% of the lobular cancers, and for ER-positivity in a metaplastic carcinoma, which was noted in 5 out of 38 metaplastic carcinomas in our database. Similarly, 163 cases were stated ER negative but PR positive, corresponding to 1.9% of the cases for which information on ER and PR status was available. This percentage of ER–/PR+ cases was higher for some individual laboratories, as depicted in Fig. 2.

Another surrogate quality indicator could be the proportion of hormone receptor positive results within a specific histological

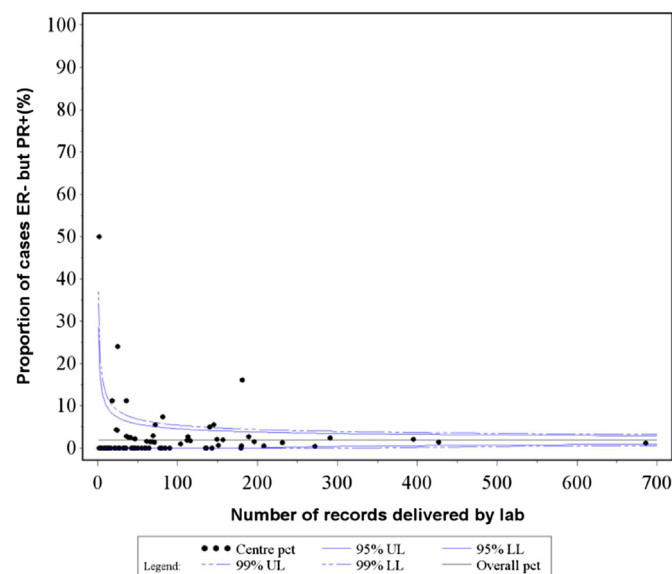


Fig. 2. ER–/PR+ results ($n = 7406$ cases delivered by 82 different laboratories).

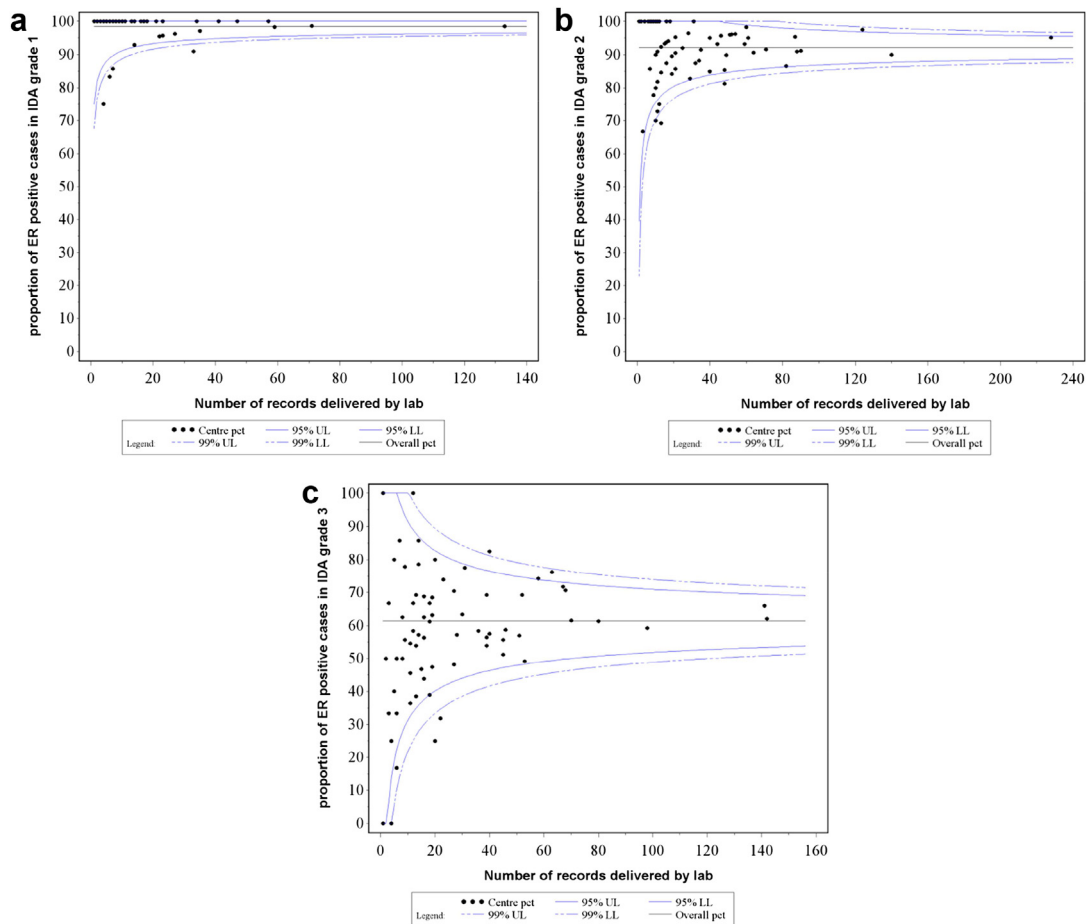


Fig. 3. Invasive ductal adenocarcinoma (IDA): relation between histological grade and ER status and inter-laboratory variability. a: Proportion of ER positive cases within grade 1 IDA ($n = 1025$ cases delivered by 76 laboratories). b: Proportion of ER positive cases within grade 2 IDA ($n = 2449$ cases delivered by 80 laboratories). c: Proportion of ER positive cases within grade 3 IDA ($n = 2032$ cases delivered by 79 laboratories).

subtype, according to the histological grade. For invasive ductal carcinomas, it is known that the proportion of ER/PR positive cases is inversely related with histological grade [16]. As shown in Fig. 3, considerable inter-laboratory variability was noted in IDA for ER positivity within each grade. Results for PR were similar, except for the lower percentage of positivity than for ER, which was observed for each histological grade (results not shown).

Discussion

As a clear insight in the extent and type of the disease guides the clinicians in their treatment decisions, the pathology assessment of a breast cancer specimen is a pivotal element of the care process. Given the unique population-based availability of pathology reports concerning all newly diagnosed breast cancers at the BCR, the present study aimed to investigate the quality and variability of breast cancer pathology reporting in Belgium for the year 2008 as a baseline assessment.

As shown in Table 1, the non-molecular parameters were reported as expected from similar publications, with a quasi-consistent reporting of characteristics such as histological grade, tumour size and number of examined and metastatically involved lymph nodes, and a poor reporting for lymphovascular invasion, DCIS margins and diameter, isolated tumour cells in the sentinel node, the maximal diameter of the largest (sentinel) node metastasis and the presence of extracapsular spread in the metastatically involved (sentinel) nodes [17–19]. Large-volume laboratories

performed only slightly better in their reporting, and substantial room for improvement was noted for several clinically relevant parameters. Reporting of these characteristics was already recommended by international guidelines published before 2008, however [9,10]. Moreover, for most of these, clinical relevance has been demonstrated, although inconsistently [20–27]. Additional variance within the assigned volume categories was examined by means of funnel plots at the individual laboratory level. The observed individual laboratory proportions (Fig. 1a–b) often were neither reaching 100 nor 0%, suggesting a variability in reporting between pathologists of the same laboratory. It is also possible that some laboratories only mentioned non-molecular parameters (e.g. lymphovascular invasion) when present.

The distribution of the histological grade also differed widely amongst the different laboratories (Fig. 1c), and only few laboratories approached the standard distribution of 20% grade 1, 30% grade 2 and 50% grade 3. Again, larger volume laboratories did not outperform their smaller counterparts. Possibly, contrary to recommendations, the Nottingham combined histological grade was not consistently used in the investigated time period. In addition, the lack of firm conclusions of some pathologists might play a role, resulting in cases being described as “moderately to poorly” differentiated.

As expected from the European recommendations of 2005 [10], data on ER and PR were widely available and the Quick-Allred system was the most frequently used semiquantitative scoring system. Availability of information on HER2 IHC was also high, in

line with the ASCO/CAP guidelines on HER2 that were available from 2007 onwards [11]. Missing data on HER2 ISH most probably resulted from referral of cases by one laboratory to another laboratory with ISH experience. In that case, the latter laboratory did not necessarily report these results to the BCR. The poor availability of Ki67 results is not surprising either, as in 2007, ASCO considered data still insufficient to recommend measurement of Ki67 [28].

Discordance rates for molecular results of two different specimens of the same tumour were similar to other published rates [29–31]. Tumour heterogeneity, sampling error, fixation artefacts, the use of NAT, different tissue handling and immunohistochemistry protocols such as choice of antibodies may all contribute to these discordances [29,30,32]. The lower concordance for PR than for ER was expected, and can be explained by the fact that ER expression is more homogeneous in tumour cells than PR [33]. Lowest concordance rates were noted for HER2 (especially ISH), and were even more pronounced for results obtained in different laboratories. Presumably, technically related issues play a bigger role than intra-tumour heterogeneity in the variability of HER2 results, certainly for ISH. In addition, quality assurance measures as described in the ASCO/CAP HER2 guidelines were probably not yet widely implemented in 2008 [11,12]. Nevertheless, the agreement between the IHC- and ISH-determined amplification status for the cases with concordant HER2 IHC results, was in line with previous publications [34].

Besides its poor reporting, substantial variability was noted in the interpretation of Ki67 IHC results, resulting from the inconsistent use of cut-off values. Although more evidence has been published supportive of the prognostic and predictive potential of this nuclear proliferation marker [35], the lack of standardized protocols to score for Ki67 remains a major hurdle. As a consequence, substantial inter-laboratory variability has been reported [36].

The surrogate quality indicators (ER– negative lobular cancers, ER+ metaplastic carcinoma, ER–/PR+ results, ER/PR+ cases by histological grade) also showed inter-laboratory variability, suggesting room for improvement in the quality of molecular marker assessments and histological grading. Poor scores on these quality indicators should alert the pathologist to eventually perform additional stains or to do a re-assessment of the immunohistochemistry results. It cannot be excluded that in certain cases, this was done without notifying the BCR on the final results.

In conclusion, results show substantial underreporting and inter-laboratory variability for both non-molecular and molecular parameters considered to be of clinical relevance. Larger-volume laboratories performed only slightly better than others. Several explanations could be put forward to explain this underreporting. Although we might assume that pathologists were aware of international guidelines, no specific Belgian guidelines were available in 2008, except for HER2 testing [14]. For Ki67, ASCO even stated that evidence was too limited to recommend Ki67 scoring [28]. In addition, it is possible that information on certain parameters was available to the treating physician by direct communication with the pathologist, but did not reach the BCR.

Nevertheless, even for overall well reported parameters, some room for improvement is noted in the results of 2008. Meanwhile, Belgian pathologists have been made aware of the importance of good pathology reporting by oral and paper communications. ASCO/CAP checklists on pathology reporting have continuously been updated, and ASCO/CAP guidelines on ER/PR assessment as well as an update on HER2 assessment have been published [12,13]. In alignment with international initiatives, a Belgian proposal has been made for standardization of the pathology report and implementation of synoptic reporting [15,37–39] (see Appendix A).

Although synoptic reporting is considered very useful in assuring a complete and uniform pathology report, it is still inconsistently used in Belgian laboratories. Similar to the experience in other countries, the lack of adapted and aligned informatics seems to be the major hurdle in the concrete implementation of synoptic reporting [37,38].

However, such a reporting system would be of benefit for additional partners besides pathologists, ranging from patients to clinicians and cancer registrars. Indeed, as population-based research is gaining importance in oncology, especially in molecular marker studies, a correct and complete registry on detailed tumour aspects seems indispensable. Whether passive distribution of guidelines will succeed in achieving this goal remains questionable, and additional measures such as quality auditing and feedback may be warranted. Similar efforts in other countries have led to more than satisfying improvements [17,18,39]. Next to pathology reporting, such a quality assurance system should also focus on the prevalence of spurious results at the individual laboratory level. Any more than average occurrence of such results should at least lead to a revision of the concerned cases and could potentially entail adaptations in laboratory procedures.

Conclusion

The current study shows that pathology reporting for breast cancers diagnosed in 2008 in Belgium was suboptimal for several clinically relevant molecular and non-molecular parameters. Large-volume laboratories performed only slightly better than others, and substantial inter-laboratory variability was noted.

Although we anticipate that some progress has been made since 2008, more efforts are needed to improve the quality of pathology reporting for breast cancer in Belgium. While synoptic reporting of pathology data could be an important tool in achieving that goal, the lack of aligned informatics remains a major hurdle in its concrete implementation.

Ethical approval

Ethical approval was not required for this study.

Financial support

Financial support was provided by RIZIV-INAMI (<http://www.riziv.fgov.be/homenl.htm>; <http://www.inami.fgov.be/homefr.htm>). This organization did not have any role in the design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Acknowledgement

The team of data managers at the Belgian Cancer Registry for their work in retrieving detailed information from the pathology protocols.

Dr. Geert Silversmit, senior statistician at the Belgian Cancer Registry, for his statistical support.

Appendix A. Synoptic report proposed to Belgian pathologists at the Belgian Week of Pathology, October 5th 2013

Synoptic report for invasive breast carcinoma with/without neo-adjuvant therapy.

Time to fixation:	Fixation time:	Tissue frozen: ☐ yes ☐ no
Reporting elements in bold are required; elements in <i>italics</i> are recommended.		
Post neo-adjuvant treatment (NAT):	☐ yes ☐ no	
<i>If yes, some additional reporting elements marked with undulating frame are recommended/required</i>		
Type of breast resection specimen: (more than one specimen can be described in one report)		
☐ excision biopsy ☐ with localisation procedure ☐ without localisation procedure ☐ additional local excision(s) after previous excision ☐ mastectomy ☐ mastectomy after previous wide excision		
Side:	☐ right ☐ left ☐ NS	
Weight of specimen:	gram	
Number of foci of invasive carcinoma:		
☐ no residual focus of invasive carcinoma		
☐ localised:	☐ 1 invasive tumour ☐ one area of DCIS with multiple (micro)invasive foci	
☐ multiple: n=		

Cave: several foci of residual carcinoma after NAT clearly belonging to one tumour bed should not be considered as multiple foci.

For all invasive tumour foci record localization, diameter of invasive tumour, diameter of whole tumour (invasive+DCIS), margins for invasive carcinoma, margins for DCIS, histological type of invasive carcinoma, histological grade of invasive carcinoma and nuclear grade of DCIS, hormone receptors and HER2 status, see next pages.

Alternatively, record these features for the largest and the less differentiated invasive tumour focus only and record the features of the other invasive tumour foci in the comments section at the end of the report.

Localisation of tumour:	
☐ nipple ☐ upper-inner quadrant ☐ upper-outer quadrant ☐ axillary tail ☐ breast NOS	☐ central portion ☐ lower-inner quadrant ☐ lower-outer quadrant ☐ overlapping lesion of breast
Size of tumour bed:	mm x mm ☐ cannot be assessed
Maximal diameter of (micro)invasive tumour:	mm
DCIS:	☐ present ☐ absent
<i>If present: whole size of tumour (invasive + DCIS): mm</i> <i>This size differs from invasive tumour diameter only if DCIS extends >1 mm beyond invasive tumour.</i>	
<i>Estimated % of tumour bed that contains invasive carcinoma %</i> <i>Estimated % of tumour bed that contains DCIS: %</i>	

Resection margins for the tumour bed:

- ☐ **uninvolved:**
- ☐ **distance from closest margin:** mm
 - ☐ **specify margin:** ☐ superior/cranial ☐ inferior/caudal ☐ lateral
 ☐ medial ☐ anterior ☐ posterior ☐ orientation unknown
- ☐ **involved:**
- ☐ **specify margin:** ☐ superior/cranial ☐ inferior/caudal ☐ lateral
 ☐ medial ☐ anterior ☐ posterior ☐ orientation unknown
- ☐ **cannot be assessed**

Resection margins for invasive carcinoma:	
☐ uninvolved: ☐ distance from closest margin: mm ☐ specify margin: ☐ superior/cranial ☐ inferior/caudal ☐ lateral ☐ medial ☐ anterior ☐ posterior ☐ orientation unknown ☐ involved (ink on cancer cells): ☐ specify margin: ☐ superior/cranial ☐ inferior/caudal ☐ lateral ☐ medial ☐ anterior ☐ posterior ☐ orientation unknown ☐ approximate extent of margin involvement (CAP 2012) ☐ focal: 1 focal area of invasive carcinoma at the margin <4 mm ☐ minimal/moderate: 2 or more foci of carcinoma at the margin ☐ extensive: carcinoma present at the margin over a broad front (>5 mm) ☐ cannot be assessed	
Resection margins for DCIS (if present):	
☐ uninvolved: ☐ distance from closest margin: mm ☐ specify margin: ☐ superior/cranial ☐ inferior/caudal ☐ lateral ☐ medial ☐ anterior ☐ posterior ☐ orientation unknown ☐ involved (ink on cancer cells): ☐ specify margin: ☐ superior/cranial ☐ inferior/caudal ☐ lateral ☐ medial ☐ anterior ☐ posterior ☐ orientation unknown ☐ approximate extent of margin involvement (CAP 2012) ☐ focal (DCIS at the margin in a <0.1 cm area in 1 block) ☐ minimal/moderate (between focal and extensive) ☐ extensive (DCIS at the margin in an area ≥1.5 cm or in 5 or more low-power fields and/or in 8 or more blocks) ☐ cannot be assessed	
Histological type of invasive carcinoma (WHO 2012):	-

Histological grade (Nottingham):	
☐ only microinvasion (not graded) ☐ grade 1 ☐ grade 2 ☐ grade 3 ☐ score cannot be assessed	
Glandular/tubular differentiation:	
☐ 1 (>75% tubules) ☐ 2 (10 to 75% tubules) ☐ 3 (<10% tubules)	
Nuclear pleomorphism:	Mitotic rate:
☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3 <i>(depends on microscopic field diameter!)</i> Absolute MAI: mitoses/10 HPF Diameter of microscopic field: mm
Percentage of necrosis in invasive carcinoma:	%
Fibrotic reaction:	☐ present ☐ absent
Nuclear grade of associated DCIS if present (ECWGBSP):	
☐ grade 1 (low) ☐ grade 2 (intermediate) ☐ grade 3 (high)	
Histological type of DCIS (Eusoma): -	
Comments:	

Other elements of extent of tumour:	
Extent of invasion: ☐ chest wall invasion not beyond pectoralis muscle ☐ chest wall invasion beyond pectoralis muscle (T4a) ☐ skin invasion without ulceration ☐ skin invasion with ulceration (T4b) ☐ skin satellite nodules (T4b) Paget disease of the nipple associated with the invasive carcinoma: ☐ yes ☐ no Associated LCIS: ☐ yes ☐ no	
Lymphovascular invasion:	☐ present ☐ not seen
Lymph nodes (LN) sampling: (more than one specimen can be described in one report)	
☐ no LN ☐ sentinel LN(s) ☐ axillary dissection ☐ other lymph nodes: specify:	
Number (#) of sentinel LN examined:	n=
# sentinel LNs with macrometastasis: # sentinel LNs with micrometastasis: # sentinel LNs with isolated tumour cells:	
Number (#) of non-sentinel LN examined:	n=
# non-sentinel LNs with macrometastasis: # non-sentinel LNs with micrometastasis: # non-sentinel LNs with isolated tumour cells:	
Size of largest metastatic deposit if present:	mm
Number of LN with extranodal extension:	n=
# of LN metastases with evidence of treatment response:	n=
# of LN with treatment response, without metastasis:	n=
Pathologic staging:	
Descriptors: ☐ m-multiple ☐ r-recurrent ☐ y-post tx pT , pN / (sn) pN , pM (only if present)	
Predictive factors for invasive carcinoma:	
ER	☐ not done ☐ pending ☐ ≥1% = positive ☐ <1% = negative Quick score (Allred): PS + IS = TS
PR	☐ not done ☐ pending ☐ ≥1% = positive ☐ <1% = negative Quick score (Allred): PS + IS = TS
HER2 IHC score (CAP criteria)	☐ not done ☐ pending ☐ 0 ☐ 1+ ☐ 2+ ☐ 3+
HER2 ISH	☐ not done ☐ pending ☐ no amplification ☐ amplification ☐ equivocal ☐ not interpretable HER2/CEP17 = / =
Ki-67:	% immunoreactive nuclei
Comments:	

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