Lack of Standardization in the Processing and Reporting of Post-Neoadjuvant Breast Cancer Specimens

A Survey of Canadian Pathologists and Pathology Assistants

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Context.—The use of neoadjuvant therapy in the management of early-stage invasive breast cancer is increasing. Residual Cancer Burden and other similar tools use pathologic characteristics of post-neoadjuvant therapy breast tumors to determine long-term outcome. However, there are no standardized guidelines for the pathologic evaluation of these specimens in the routine clinical setting.

Objective.—To assess current practices among Canadian pathologists and pathology assistants with regard to the processing and reporting of post-neoadjuvant therapy breast specimens.

Design.—An electronic survey was distributed to pathologists and pathology assistants across Canada.

Results.—Sixty-three responses were obtained. A total of 48% (15 of 31) of surveyed pathologists reported familiarity with the Residual Cancer Burden tool. A total of 40% (25 of 63) of respondents reported a lack of routine use of specimen photography, and 35% (22 of 63) reported a lack of routine use of grossing diagrams. There was significant variation with respect to tumor bed sampling; the most common method was to submit 1 block per centimeter of tumor (20 of 63; 32%). There was also significant variation in the method of measuring residual tumor; the most common method was to measure the largest cross-section of residual tumor (16 of 32; 50%).

Conclusions.—There is a need for standardization of the evaluation of post-neoadjuvant therapy breast specimens in the routine clinical setting in Canada. We recommend the routine use of specimen mapping, submitting the largest cross section of tumor bed in toto, reporting tumor size as per American Joint Committee on Cancer and Residual Cancer Burden guidelines, and routinely including measurements of residual tumor cellularity and in situ disease in the final pathology report as per Residual Cancer Burden guidelines.

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Neoadjuvant therapy (NAT) is becoming increasingly common in the first-line management of early-stage breast cancer. Although it was initially intended to improve the resectability of locally advanced tumors, NAT has proven indispensable in its ability to facilitate breast-conserving procedures and allow for potential curability of early invasive disease with aggressive biology.1,2 Important-ly, it has also allowed for the evaluation of tumor response to systemic treatment in the form of pathologic complete response (pCR), which has emerged as a validated end point in the development and approval of novel therapies in the clinical trial setting.3,4 Many classification systems have been developed for the prognostication of breast cancer in cases where pCR is not achieved.5–7 Residual Cancer Burden (RCB) is a clinically validated, reproducible, and easy-to-use web-based tool that incorporates the size of the residual tumor bed, average cancer cellularity, proportion of in situ carcinoma, number of positive lymph nodes, and the size of the largest lymph node metastasis into the calculation of prognostic risk.6,8–10 The RCB score has been shown to be prognostic beyond 10 years and in all phenotypic subgroups of breast cancer.6 Whereas pCR identifies patients at the lowest risk of relapse, RCB provides prognostic information for patients who continue to have residual disease after neoadjuvant therapy, identifying those who are at a higher risk of disease recurrence.10

An international working group convened by the Breast International Group–North American Breast Cancer Group...
(BIG-NABCG) has published recommendations for the standardization of post-neoadjuvant breast processing and reporting for the clinical trial setting. In addition to the standardization of the definition of pCR, recommendations regarding the pretreatment assessment, sampling, documenting, microscopic reporting, and evaluation of lymph nodes in the post-NAT setting were made.\textsuperscript{11,12}

Although guidelines for standard processing and reporting exist in the clinical trial setting, their uptake has been limited in the routine clinical practice setting in Canada, where treatment decisions are increasingly reliant on the accurate evaluation of post-NAT breast specimens.

The purpose of the present study is to characterize the current practices of pathologists and pathology assistants in Canada with respect to the processing, evaluation, and reporting of post-NAT breast cancer specimens.

**MATERIALS AND METHODS**

Using SurveyMonkey, a multiple-choice electronic questionnaire was designed to assess the processing and reporting of post-NAT breast specimens within the year prior to survey administration among pathologists and pathology assistants in diverse practice settings across Canada. A list of 413 emails was obtained from the Canadian Association of Pathologists–Association Canadienne Des Pathologistes member mailing list. An additional 43 emails were procured from the lead investigator’s contact list of pathologists with interest in breast pathology. Responses were collected from March 20, 2018, to May 8, 2018.

Comparisons of grossing and reporting practices by occupation (pathologist versus pathology assistant), practice setting (academic versus nonacademic), and years of practice (up to 5 years versus greater than 5 years) were conducted using Pearson \( \chi^2 \) tests of independence with significance level set at \( P < .05 \).

**RESULTS**

Demographic features of the survey respondents are provided in Table 1. A total of 63 survey responses were obtained; of those, 32 respondents were from pathologists and 31 were from pathology assistants. There was representation from 8 of 10 provinces. Most survey respondents reported working in an academic hospital or a large community hospital (58 of 63; 92%). Most survey respondents had been in practice for more than 5 years (60 of 63; 92%).

Most pathologists surveyed did not have postresidency training in breast pathology (19 of 32; 59%). With respect to volume of post-NAT breast cases encountered, most pathologists encountered 5 or fewer cases per month (27 of 32; 84%). In contrast, most of the pathology assistants reported working in an academic hospital or a large community hospital (58 of 63; 92%). Most survey respondents had been in practice for more than 5 years (60 of 63; 95%).

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A \( \chi^2 \) test of independence revealed that academic centers were more likely to encounter more than 5 post-NAT breast cancer cases per month than nonacademic centers (52% of academic centers, corresponding to 15 of 29 respondents, versus 24% of nonacademic centers, corresponding to 8 of 33 respondents; \( P = .03 \)).

**Preoperative Tumor Localization**

Survey results regarding preoperative tumor localization in the post-NAT setting are presented in Table 2. For lumpectomy specimens, most respondents (46 of 63; 73%) indicated that biopsy clip localization was often performed at their institutions. In cases where the specimen contained multifocal tumor, 31 respondents (49%) reported that all foci were localized preoperatively, 21 (33%) reported that only the largest focus was localized preoperatively, and 11 (17%) reported that the decision was dependent on other factors, including the relative proximity of the foci, whether the foci were palpable, or the preference of the surgeon.

### Table 1. Demographics of Survey Participants

|                      | Pathologists, No. (%) | Pathology Assistants, No. (%) | Total, No. (%) |
|----------------------|-----------------------|------------------------------|---------------|
| Institution type     |                       |                              |               |
| Academic             | 31 (45)               | 31 (48)                      | 62 (35)       |
| Large community      | 15 (48)               | 14 (45)                      | 29 (47)       |
| Small community      | 1 (3)                 | 2 (6)                        | 3 (5)         |
| Private lab          | 1 (3)                 | 0                            | 1 (1)         |
| Province             |                       |                              |               |
| Alberta              | 9 (28)                | 7 (23)                       | 16 (25)       |
| British Columbia     | 3 (9)                 | 1 (3)                        | 4 (6)         |
| New Brunswick        | 0                     | 1 (3)                        | 1 (2)         |
| Newfoundland         | 1 (3)                 | 0                            | 1 (2)         |
| Nova Scotia          | 2 (6)                 | 0                            | 2 (3)         |
| Ontario              | 13 (41)               | 20 (65)                      | 33 (52)       |
| Quebec               | 1 (3)                 | 2 (6)                        | 3 (5)         |
| Saskatchewan         | 3 (9)                 | 0                            | 3 (5)         |
| Length of practice   |                       |                              |               |
| 1–3 y                | 1 (3)                 | 2 (6)                        | 3 (5)         |
| 4–10 y               | 11 (34)               | 13 (42)                      | 24 (38)       |
| >10 y                | 20 (63)               | 16 (52)                      | 36 (57)       |
| Level of training    |                       |                              |               |
| Residency            | 19 (59)               |                              |               |
| Fellowship in surgical pathology | 5 (16)       |                              |               |
| Fellowship in breast pathology | 8 (25)    |                              |               |
| Post-neoadjuvant breast cases per month |                       |                              |               |
| <1 case              | 14 (44)               | 2 (6)                        | 16 (25)       |
| 1–5 cases            | 13 (41)               | 11 (35)                      | 24 (38)       |
| >5 cases             | 5 (16)                | 18 (58)                      | 23 (37)       |

### Table 2. Preoperative Tumor Localization

|                      | Pathologists, No. (%) | Pathology Assistants, No. (%) | Total, No. (%) |
|----------------------|-----------------------|------------------------------|---------------|
| Type of procedure    |                       |                              |               |
| Biopsy clip          | 23/32 (72)            | 23/31 (74)                   | 46/63 (73)    |
| Carbon tattoo        | 5/32 (16)             | 0                            | 5/36 (8)      |
| Seed localization    | 11/32 (34)            | 13/31 (42)                   | 24/63 (38)    |
| Wire localization    | 30/32 (94)            | 28/31 (90)                   | 58/63 (92)    |
| Other                | 1/32 (3)              | 0                            | 1/36 (2)      |
| None                 | 11/32 (34)            | 2/31 (6)                     | 13/63 (21)    |
| Localization of multifocal tumor |           |                              |               |
| All foci             | 14 (44)               | 17 (55)                      | 31 (49)       |
| Largest tumor        | 11 (34)               | 10 (32)                      | 21 (33)       |
| Other                | 7 (22)                | 4 (13)                       | 11 (17)       |
Lymph Node Localization

Survey results regarding lymph node localization are presented in Table 3. Of the 32 pathologists surveyed, 18 (56%) reported that lymph nodes that were biopsied pre-NAT were never marked with biopsy clips at their respective institutions. With respect to preoperative localization of the biopsied lymph nodes, most pathologists surveyed (23 of 32; 72%) reported that localization with seed, wire, or other methods was not commonly performed at their respective institutions.

| No. (%) | Use of clips to mark biopsied lymph nodes in the preoperative setting |
|---------|---------------------------------------------------------------|
|         | Always                  | 5 (16)                          |
|         | Yes, only when positive | 5 (16)                          |
|         | Yes, other indications  | 3 (10)                          |
|         | Never                   | 18 (58)                         |

| No. (%) | Preoperative localization of biopsied lymph nodes |
|---------|--------------------------------------------------|
|         | Yes—seed localization                            | 3 (9)                          |
|         | Yes—wire localization                            | 1 (3)                          |
|         | Yes—other indications                            | 5 (16)                         |
|         | No                                                | 23 (72)                        |

Lymph Node Assessment

Survey results regarding sentinel lymph node biopsy and intraoperative consultation in the post-NAT setting are presented in Table 4. There was a wide variation in the use of sentinel lymph node biopsy in the post-NAT setting at the institutions represented by the surveyed pathologists. Of 32 respondents, 11 (34%) reported that sentinel lymph node biopsy was performed for all cases in the post-NAT setting, 5 (16%) reported that it was performed for cases with positive lymph nodes pre-NAT, 6 (19%) reported that it was performed for cases with negative lymph nodes pre-NAT, and 7 (22%) reported that it was not performed at their institution. With respect to the use of intraoperative consultation for the evaluation of sentinel lymph nodes in the post-NAT setting, most respondents (25 of 30; 83%) reported that intraoperative consultations were not routinely requested.

| No. (%) | Use of sentinel lymph node biopsy |
|---------|----------------------------------|
|         | Yes—for all cases                | 11 (34)                         |
|         | Yes—for positive lymph nodes pre-NAT | 5 (16)                         |
|         | Yes—for negative lymph nodes pre-NAT | 6 (19)                         |
|         | Yes—other indications            | 3 (9)                          |
|         | No                                | 7 (22)                         |

| No. (%) | Intraoperative consultation for sentinel lymph node evaluation |
|---------|---------------------------------------------------------------|
|         | Yes—for positive lymph nodes pre-NAT                          | 1 (3)                          |
|         | Yes—for negative lymph nodes pre-NAT                          | 2 (7)                          |
|         | Yes—other indications                                         | 2 (7)                          |
|         | No                                                             | 25 (83)                        |

Abbreviation: NAT, neoadjuvant therapy.

Grossing Practices

Survey results regarding grossing practices of post-NAT breast cancer specimens are presented in Table 5. Of the 32 pathologists surveyed, 18 (56%) reported never grossing these specimens, and 10 (31%) reported sometimes grossing these specimens. Approximately one-third of pathologists described themselves as only somewhat comfortable (10 of 32; 31%) or not comfortable (2 of 32; 6%) with grossing post-NAT breast cases. Most pathology assistants described themselves as very comfortable (24 of 31; 77%) with grossing post-NAT breast cases. Nearly all respondents reported regularly following and reporting ischemic time (62 of 63; 98%) and fixation time (58 of 63; 92%) as

| No. (%) | Grossing by pathologists |
|---------|--------------------------|
|         | Always                   | 32 (100)                       |
|         | Sometimes                | 10 (31)                        |
|         | Never                    | 18 (56)                        |

| No. (%) | Level of comfort with grossing |
|---------|--------------------------------|
|         | Very comfortable             | 20 (63)                        |
|         | Somewhat comfortable         | 10 (31)                        |
|         | Not comfortable              | 2 (6)                          |

| No. (%) | Reporting of ischemic time |
|---------|-----------------------------|
|         | Yes                         | 31 (97)                        |
|         | No                          | 1 (3)                          |

| No. (%) | Reporting of fixation time |
|---------|----------------------------|
|         | Yes                         | 28 (88)                        |
|         | No                          | 4 (13)                         |

| No. (%) | Reviewing of radiologic information |
|---------|-------------------------------------|
|         | Always                              | 25 (78)                        |
|         | Sometimes                           | 4 (13)                         |
|         | Never                               | 3 (9)                          |

| No. (%) | Ordering of x-ray on specimen |
|---------|-------------------------------|
|         | Yes, routinely                  | 4 (13)                         |
|         | Yes, in occasional cases        | 24 (75)                        |
|         | No                              | 4 (13)                         |

| No. (%) | Routine use of photography |
|---------|-----------------------------|
|         | Yes, all cases              | 16 (50)                        |
|         | Yes, select cases           | 0 (0)                          |
|         | No                           | 16 (50)                        |

| No. (%) | Routine use of grossing diagrams |
|---------|----------------------------------|
|         | Yes, all cases                   | 19 (59)                        |
|         | Yes, select cases                | 11 (34)                        |
|         | No                               | 2 (6)                          |

| No. (%) | Sampling of tumor bed |
|---------|-----------------------|
|         | In toto               | 10 (31)                        |
|         | Largest cross section in toto | 8 (25)                        |
|         | One block per 1 cm of tumor | 11 (34)                        |
|         | Other                 | 3 (9)                          |

| No. (%) | Routine use of photography |
|---------|-----------------------------|
|         | Yes, all cases              | 19 (59)                        |
|         | Yes, select cases           | 11 (34)                        |
|         | No                           | 2 (6)                          |

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|---------|-----------------------|
|         | In toto               | 10 (31)                        |
|         | Largest cross section in toto | 8 (25)                        |
|         | One block per 1 cm of tumor | 11 (34)                        |
|         | Other                 | 3 (9)                          |
recommended by the College of American Pathologists. Most pathologists (25 of 32; 78%) and pathology assistants (28 of 31; 90%) reported always reviewing radiologic information relevant to post-NAT cases. With respect to the localization of the tumor or biopsy clip within the specimen, most pathologists (24 of 32; 75%) and pathology assistants (22 of 31; 71%) surveyed reported occasionally ordering an x-ray of the specimen.

With respect to photographing the sliced specimen, only half of the surveyed pathologists (16 of 32; 50%) did so routinely. In contrast, most pathology assistants (22 of 31; 71%) reported routinely photographing the sliced specimen. Grossing diagrams, either in the form of specimen photographs or schematic representations of breast specimens, are often used to illustrate the location of the sections taken (Figure 1). Most pathologists (19 of 32; 59%) reported always using a grossing diagram, and 34% (11 of 32) reported doing so only on select cases. Similarly, most pathology assistants (22 of 31; 71%) reported always using a grossing diagram, and 29% (9 of 31) reported doing so only on select cases.

There was wide variation in the way tumor and tumor bed were sampled among the pathologists and pathology assistants surveyed. Of the 32 pathologists surveyed, 10 pathologists (31%) reported that they submit the tumor or tumor bed in toto, 8 (25%) submit the largest cross section in toto, and 11 (34%) submit 1 block per 1 cm of tumor. A minority of pathologists (3 of 32; 9%) reported that the sampling of tumor bed was case dependent. Of the 31 pathology assistants surveyed, 9 (29%) reported they submit the tumor or tumor bed in toto, 3 (10%) submit the largest cross section in toto, and 9 (29%) submit 1 block per 1 cm of tumor. The remainder of the pathology assistant respondents reported that the sampling of tumor or tumor bed was dependent on other factors, such as the size of the tumor.

A $\chi^2$ test of independence showed no significant difference in the grossing practices of pathologists and pathology assistants. Grossing practices were also independent of practice setting and years of practice.

**Reporting Practices**

Survey results regarding the reporting of post-NAT breast cancer specimens are presented in Table 6. Approximately one-third of the surveyed pathologists described themselves as either only somewhat comfortable (10 of 32; 31%) or not comfortable (1 of 32; 3%) with assessing and reporting these cases. In addition, of the 31 pathologists that responded to the query, 16 (52%) were either not familiar or at most somewhat familiar with the RCB system. More than half the surveyed pathologists (16 of 31; 52%) did not have any formal training in the reporting of post-NAT breast cases, either through residency, through fellowship, or through a formal course.

Most pathologists surveyed (21 of 32; 66%) reported that they use a synoptic report in all post-NAT breast cases, regardless of the presence of residual invasive disease.
When queried on how they would report the size of residual tumor after NAT, there was marked variation, with 50% (16 of 32) of respondents considering the size to be the 2 dimensions of the largest cross section of residual tumor including intervening tumor bed (size A in Figure 2, A), 28% (9 of 32) considering the size to be the extent of the largest contiguous focus of residual tumor (size B in Figure 2, A), and the remainder of respondents either using a combination of both options or not reporting the residual tumor size at all. There was also marked variation in the reporting of

**Table 6. Reporting Practices**

| Description                                                                 | No. (%) |
|-----------------------------------------------------------------------------|---------|
| Level of comfort with reporting post-NAT breast specimens                   | 32      |
| Very comfortable                                                           | 21 (66) |
| Somewhat comfortable                                                        | 10 (31) |
| Not comfortable                                                             | 1 (3)   |
| Familiarity with RCB                                                        | 31      |
| Very familiar (have reported it in clinical practice routinely)             | 5 (16)  |
| Familiar (have reported it in selected cases)                               | 10 (32) |
| Somewhat familiar (have read or heard about RCB but have never used it in clinical practice) | 11 (35) |
| Not familiar                                                                | 5 (16)  |
| Highest level of training in reporting post-NAT breast specimens            | 31      |
| Training in RCB through a formal course                                      | 6 (19)  |
| Training during fellowship                                                  | 2 (6)   |
| Training during residency                                                   | 7 (23)  |
| No formal training                                                          | 16 (52) |
| Use of synoptic report for post-NAT breast cancer                           | 32      |
| Yes—all cases                                                               | 21 (66) |
| Yes—if cases with residual invasive or in situ carcinoma                    | 9 (28)  |
| No                                                                          | 2 (6)   |
| Determination of size of residual tumor                                     | 32      |
| As the extent of the largest cross section of residual tumor                | 16 (50) |
| As the extent of the largest contiguous focus of residual tumor            | 9 (28)  |
| As both the extent of the largest cross section of residual tumor and the extent of the largest contiguous focus of residual tumor | 4 (13)  |
| Other                                                                       | 2 (6)   |
| Do not report size of residual tumor                                        | 1 (3)   |
| Determination of size of largest lymph node metastasis                      | 32      |
| As the extent of the entire residual metastasis including intervening tumor bed | 11 (34) |
| As the extent of the largest contiguous focus of residual metastasis       | 17 (53) |
| As both the extent of the entire residual metastasis including tumor bed and the extent of the largest contiguous focus of residual metastasis | 3 (9)  |
| Do not report size of residual tumor in lymph nodes                          | 1 (3)   |
| Reporting of average tumor cellularity                                      | 32      |
| Always                                                                      | 18 (56) |
| Sometimes                                                                   | 7 (22)  |
| Never                                                                       | 7 (22)  |
| Reporting of percentage of residual disease that is CIS                     | 32      |
| Always                                                                      | 19 (59) |
| Sometimes                                                                   | 7 (22)  |
| Never                                                                       | 6 (19)  |
| Reporting of lymphovascular invasion in breast parenchyma                   | 32      |
| Always                                                                      | 30 (94) |
| Sometimes                                                                   | 2 (6)   |
| Never                                                                       | 0       |
| Definition of pCR                                                           | 32      |
| No residual invasive or in situ carcinoma or lymphovascular invasion in breast or in lymph node | 16 (50) |
| No residual invasive carcinoma or lymphovascular invasion in breast or in lymph node | 11 (34) |
| No residual invasive carcinoma in breast or lymph node. Focal lymphovascular invasion permitted for pCR | 3 (9)  |
| Unsure                                                                      | 2 (6)   |

Abbreviations: CIS, carcinoma in situ; NAT, neoadjuvant therapy; pCR, pathologic complete response; RCB, residual cancer burden.
the size of the largest lymph node metastases in the post-
NAT setting. Just more than half of the respondents (17 of 32; 53%) considered it to be the extent of the largest
contiguous focus of residual metastatic disease (size B in
Figure 2, B), 34% considered it to be the span of the entire
residual metastasis including intervening tumor bed (size A
in Figure 2, B), and the remainder of respondents considered
it as a combination of both options or would not report the
size of residual metastatic disease at all.

Only 56% of respondents (18 of 32) reported that they
always evaluate and report average tumor cellularity for
post-NAT cases. Similarly, only 59% of respondents (19 of
32) reported that they always report the percentage of
carcinoma in situ in the residual tumor. However nearly all
(30 of 32; 94%) respondents routinely report the presence or
absence of lymphovascular invasion (LVI) in breast paren-
chyma in the post-NAT setting.

Marked variation was also noted among the surveyed
pathologists in their understanding of the definition of pCR.
A total of 50% (16 of 32) indicated that it represented no
residual invasive carcinoma, carcinoma in situ, or LVI in the
breast or lymph nodes; 34% (11 of 32) indicated that it
represented no residual invasive carcinoma or LVI in the
breast or lymph nodes; 9% (3 of 32) indicated that it
represented no residual invasive carcinoma in the breast or
lymph nodes, allowing for focal LVI; and 6% (2 of 32)
indicated that they were unsure of the definition of pCR.

A $\chi^2$ test of independence showed no significant
difference in the reporting practices of pathologists in the
academic or nonacademic setting. Reporting practices were
also independent of years of practice.

Repeating Breast Biomarkers

Survey results regarding the repeating of estrogen
receptor (ER), progesterone receptor (PR), and human
epidermal growth factor receptor 2 (HER2) biomarker
assessment in the post-NAT setting are presented in Table
7. Of the surveyed pathologists, 13 (41%) indicated that they
repeat breast biomarkers in all cases, 9 (28%) indicated that
they would do by clinician request only, 3 (9%) indicated that
they would do so only based on select pathologic features and 4 (13%) indicated that they would do so based on clinician request and select pathologic features. The pathologic features most likely to prompt the re-testing of biomarkers were the presence of residual invasive carcinoma with a different morphology than in the pre-NAT biopsy (23 of 27; 85%), followed by negative ER on initial biopsy (16 of 27; 59%) and negative or equivocal HER2 on initial biopsy (16 of 27; 59%).

**DISCUSSION**

The pathologic evaluation of post-NAT breast specimens is complex. It depends on many factors, including appropriate grossing practices, adequate tumor sampling, and identification of clinically relevant microscopic features of residual disease. In this survey, we document the wide variability in the recent practice of grossing and reporting post-NAT breast cancer specimens among pathologists and pathology assistants across Canada.

Evaluation of post-NAT breast specimens begins with the identification of the pretreatment marker of tumor placed in the breast and lymph nodes at the time of biopsy. In the post-NAT setting, residual tumor and tumor bed may only be grossly identifiable as an area of irregular fibrous tissue (Figure 3).14 Pretreatment marking of tumor allows for easier identification of residual disease during gross examination and tissue sampling. Most participants in our survey (70%) indicated that pretreatment tumor marking with biopsy clips in the breast was often performed at their institutions. There was greater variation in the practices of tumor localization when the initial cancer was multifocal. Although our knowledge there are currently no practice guidelines for the marking of multifocal tumor, clinical trial protocols have recommended that each satellite lesion be marked separately.15 This practice would be of benefit in the routine clinical setting, in order to ensure that all tumor foci can be located during pathologic gross examination. Interestingly, most survey respondents indicated that the marking of lymph nodes in the pre-NAT setting was not commonly performed at their respective institutions. This is surprising, because NAT can result in the eradication of grossly evident metastatic disease in lymph nodes. Therefore, pretreatment markers would be extremely helpful in localizing previously involved nodes. Indeed, pre-NAT marker placement in affected lymph nodes has been recommended by the American Society of Breast Surgeons.3

Our survey identified that most pathologists and pathology assistants were consistent with the reviewing of relevant radiologic information (85%) and ordering imaging of the specimen when necessary (87%). However, more than one-third of survey participants (38%) reported not using photography to map sections taken from the specimen, and approximately one-third (31%) reported using grossing diagrams only in select cases. Assessment of size, focality, and distance to margin can be more challenging in the post-NAT setting. Standardization of the use of specimen mapping during grossing would result in improved accuracy in the reporting of these parameters. This is one of the practice recommendations from the BIG-NACBCG collaboration.12

Perhaps most critical to the accurate evaluation of pathologic response to treatment is the adequate sampling of the tumor and tumor bed. In their clinical trial guidelines, the international working group has recommended that 5 sections be taken from the largest cross section of tumor bed per 1 to 2 cm of tumor size, up to a maximum of 25 blocks.11 These guidelines were developed based on expert consensus and through the review of standard operating protocols of various NAT breast cancer trials. In contrast, the RCB tool requires submission of the largest cross section of tumor bed in toto, or a minimum of 5 sections from the tumor bed if the largest cross section is very large.8 Guidelines developed by the US Food and Drug Administration (FDA) require a minimum of 1 block per 1 cm of pretreatment tumor size or at least 10 blocks, whichever is greater.16 As expected, our survey results demonstrate a wide variation with respect to how tumor and tumor bed is sampled in routine clinical practice. The development of standards for the routine sampling of tumor and tumor bed in the post-NAT setting would allow for greater precision in the evaluation of pathologic response to treatment and in the designation of pathologic complete response.

In our survey, roughly half of pathologists (51%) reported themselves as either unfamiliar or only somewhat familiar with the RCB tool, with a similar proportion (53%) having had no formal training in the reporting of post-NAT breast specimens. Roughly the same proportion do not routinely report average tumor cellularity (44%) or percentage of residual in situ disease (41%). With the growing clinical utility of the RCB and other similar classification systems in determining prognosis risk, it is imperative that patholo-

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**Table 7. Breast Biomarkers**

| Pathologic features that prompt reordering of biomarkers | No. (%) |
|----------------------------------------------------------|---------|
| Residual invasive carcinoma with different morphology than invasive carcinoma pre-neoadjuvant therapy | 23/27 (85) |
| Multifocal residual invasive carcinoma                    | 11/27 (41) |
| Residual metastatic disease in lymph nodes                | 7/27 (26)  |
| Negative ER result pre-neoadjuvant therapy                | 16/27 (59) |
| Negative or equivocal HER2 result pre-neoadjuvant therapy | 16/27 (59) |

**Abbreviations:** ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
Another crucial determinant in the calculation of prognostic risk is the size of residual tumor in the breast and lymph nodes. However, residual tumor often presents as scattered islands of tumor cells in a fibrotic stroma, making its evaluation challenging (Figure 4). According to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, if multiple foci of residual tumor are identified within a fibrotic tumor bed, staging is based on the extent of the largest single focus of residual tumor, and the tumor is considered multifocal. Although there are no data correlating this method with clinical outcomes, the measurement of post-NAT tumor in this manner likely results in the significant underestimation of tumor extent.

In contrast, the RCB classification tool requires that the extent of the area involved by all islands of residual invasive cells and intervening stroma be included in the determination of residual tumor size. A similar principle is true for the evaluation of residual metastatic disease in lymph nodes. The 8th edition of the AJCC staging guidelines requires that only the largest contiguous focus of residual tumor in the lymph node without the inclusion of treatment-related fibrosis be used for pathologic N stage. However, the international consensus guidelines suggest that treatment-related fibrosis may be included in ypN determination. Our survey results again reflect the lack of a standard protocol for the evaluation of post-NAT breast specimens within the pathology community.

There has been variation in the way pCR has been defined, even in the clinical trial setting. This variation is well reflected in our survey results, with no general consensus on how pCR is defined across the different institutions represented. Half of the surveyed pathologists (50%) regarded pCR as no residual invasive or in situ carcinoma, and no LVI in the breast or lymph nodes. Approximately one-third (34%) regarded pCR as no residual invasive carcinoma or LVI in the breast or lymph nodes, allowing residual in situ carcinoma to qualify for pCR. According to an FDA-supported pooled analyses of 12 clinical trials, overall survival and event-free survival of patients with no evidence of residual invasive cancer in the breast or lymph nodes are independent of the presence or absence of residual in situ carcinoma. In theory, pCR can be defined in either manner—AJCC stage ypT0/is ypN0 or ypT0 ypN0—with the same prognostic implications. However, from a surgical perspective, the presence of carcinoma in situ has implications for the local control and completeness of excision of the disease. It is of paramount importance that the definition of pCR be agreed upon with multidisciplinary input at each institution.

Several studies have documented changes in ER, PR, and HER2 receptor expression status after NAT. A meta-analysis evaluating changes in receptor status demonstrates a receptor phenotypic drift rate of up to 12.9% for ER, 32.0% for PR, and 8.9% for HER2 following NAT. Although there are no consensus guidelines with respect to the repeat testing of ER, PR, and HER2 receptor status in the post-NAT setting, it has generally been recommended that biomarkers be retested when the pretreatment results are negative or, in the case of HER2, negative or equivocal. This is because a change in receptor status could result in altered clinical management. This principle was reflected in our survey results, with a large proportion of pathologists reporting that they would order repeat testing of biomarkers in selected instances, including a negative pretreatment hormone receptor or HER2 result or the presence of residual invasive carcinoma with a morphology different from the pretreatment biopsy. Although this practice has been recommended by the College of American Pathologists in its protocol for the reporting of breast biomarker testing results, specific guidelines for retesting in the post-NAT setting have not yet been established.

There are several limitations associated with our study. Given the overall response rate, it is possible that pathologists and pathology assistants with interest in academic work and a greater exposure to post-NAT breast specimens are overrepresented in our survey population. Thus, the overall variation in specimen handling and reporting demonstrated in our audit may be underestimated. In addition, our survey does not address the impact of pathologic reporting and the use of classification tools on the clinical management of patients who do not achieve pCR. In future studies, we plan to include oncologists in the determination of how post-NAT pathologic evaluation, in particular RCB, affects clinical decision-making in routine practice. Lastly, our survey did not address the impact of implementing new standards on clinical laboratories. In particular, although the complexity of pathologic assessment of breast specimens is increasing, there does not seem to be a compensatory increase in available resources. The impacts of the implementation of a new set of standards as well as the incorporation of this information into laboratory information systems are questions for future studies.

CONCLUSIONS

Our findings highlight the wide variation in the processing and assessment of post-NAT breast specimens in routine clinical practice in Canada. Based on our survey results and existing guidelines in the clinical trial setting, we recommend the following for the pathologic evaluation of post-NAT breast specimens in routine practice: (1) routinely use specimen mapping during grossing; (2) submit the largest cross section of tumor bed in toto or a minimum of 5 blocks of tumor bed if the largest cross section is very large; (3) in cases where tumor size would differ depending on the use of AJCC or RCB guidelines, report both measurements, using AJCC guidelines for the determination of pathologic stage; and (4) routinely include measurements of residual tumor cellularity and percentage of residual in situ disease in the final pathology report. The implementation of a standard set of guidelines such as these will allow for greater uniformity in the approach to the post-NAT breast specimen and greater equity in patient care. The College of American Pathologists may also consider the incorporation of these elements in the protocol for reporting breast specimens.

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