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The association between methods of biopsy and survival following breast cancer

A hospital registry based cohort study

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Abstract

Percutaneous biopsy in breast cancer has been associated with an increased risk of malignant cell seeding. However, the importance of these observations remains obscure due to lack of corroborating evidence from clinical studies. We determined whether method of biopsy is associated with breast cancer survival. This hospital registry-based cohort study included 3416 non-metastatic breast cancer patients diagnosed from 1993 to 2011 in a tertiary setting. Factors associated with biopsy methods were assessed. Multivariable Cox regression analysis was used to determine the independent prognostic impact of method of biopsy. Overall, 990 patients were diagnosed by core needle biopsy (CNB), 1364 by fine needle aspiration cytology (FNAC), and 1062 by excision biopsy. Excision biopsy was significantly associated with more favorable tumor characteristics. Radiotherapy modified the prognostic impact of biopsy method ($P_{interaction} < .001$). Following multivariable analysis, excision biopsy was consistently associated with lower risk of mortality compared to FNAC in women receiving adjuvant radiotherapy (adjusted hazard ratio: 0.81, 95%CI: 0.66–0.99), but not in those who did not receive adjuvant radiotherapy (adjusted hazard ratio: 0.87, 95%CI: 0.65–1.17). While the risk of mortality was not different between patients undergoing FNAC and CNB when radiotherapy is administered, in the absence of radiotherapy, CNB was associated with higher risk of mortality than FNAC (adjusted hazard ratio: 1.57, 95%CI: 1.16–2.12). Given that our results contradict with findings of previous clinical studies assessing the prognostic impact of method of biopsy in women with breast cancer, further studies are warranted.

Abbreviations: CNB = core needle biopsy, ER = estrogen receptor, FNAC = fine needle aspiration cytology, HER2 = human epidermal receptor 2, OS = overall survival, PR = progesterone receptor, RS = relative survival, UMMC = University Malaya Medical Centre, UMSC = University Malaya Specialist Centre.

Keywords: breast cancer, core needle biopsy, excision, fine-needle aspiration cytology, overall survival

1. Introduction

Clinical practice guidelines propose use of percutaneous needle biopsy, either via fine needle aspiration cytology (FNAC) or core needle biopsy (CNB), to establish the diagnosis of breast cancer rather than through excision biopsy.[1,2] Theoretically, percutaneous biopsies may lead to displacement of malignant breast cells into the adjacent soft tissue and skin as the needle is withdrawn from the tumor.[3] This is corroborated by studies demonstrating that the risk of epithelial cell seeding along the needle tract following percutaneous biopsy may be substantial.[4–7] A study assessing the risk of needle tract seeding following CNB of the breast through cytological examination of the core needle wash material had shown that the incidence of positive cytology may be

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as high as 65% (134/207).[8] These findings however need to be considered in light of findings of Diaz et al, who reported an inverse association between tumor cell displacement and the interval between biopsy and breast surgery.[4] As this interval grew, less tumor seeding was observed in the biopsy track suggesting that the displaced malignant cells may not be viable[5] and could have been destroyed by the immune system.[9] While evidence on impact of needle biopsy on sentinel lymph node metastases in breast cancer is contradictory,[10–14] there is an indication that needle biopsies may also promote hematogenous spillage of malignant cells.[15]

Although these findings, when taken together suggest that percutaneous biopsies may hypothetically lead to detrimental outcomes in women with breast cancer, corroborating evidence from clinical studies is clearly lacking. Apart from a number of case studies reporting breast cancer recurrence in the needle track,[16] cohort studies investigating whether needle biopsy is associated with local recurrence or overall survival following breast cancer have not found any association.[9,13,17–20]

FNAC and CNB both have a small false negative rate, hence, if there is any radiological or clinical suspicion of malignancy, excision biopsy, which has almost 100% accuracy, should be carried out.[21] In addition, the decision on whether to proceed with an FNAC or CNB depends on the clinical scenario and available pathological services.[22] FNAC requires the expertise of a trained cytopathologist while CNB and excision biopsy can be interpreted by any histopathologist. In addition, there appears to be a prevalent belief among patients that a needle biopsy will lead to the spread of cancer.[23,24] Clinicians may carry out excision biopsy when the breast lump is small, that is, when percutaneous biopsy may be difficult.

We determined whether method of biopsy (FNAC, CNB, excision biopsy) was associated with survival following breast cancer in women presenting with non-metastatic breast cancer.

2. Methods

2.1. Study population

The study setting is in a single university hospital with a private and public wing under the leadership of a single breast surgeon, and utilizing the same pathology laboratory. FNAC is dependent on the skill of the cytopathologist and was the main method used in the hospital in earlier years when there was an excellent cytopathologist in the centre. Core needle biopsy was done freehand when large enough and under ultrasound guidance when small. Excision biopsy was done when the lesion was anatomically unsuitable for core biopsy, or when the patient refused needle biopsy, or if needle biopsy result was equivocal/benign but radiologically/clinically appear malignant.

Data for this study was obtained from the University Malaya Breast Cancer Registry, a prospective hospital-based registry of breast cancer patients newly diagnosed in University Malaya Medical Centre (UMMC), a public academic hospital, and University Malaya Specialist Centre (UMSC), the private wing of the same hospital. The registry was approved by the Institutional Review Board (Ref. No. 733.23). Further details of the registry have been described elsewhere.[25] As the study relies on non-identifiable registry-based data, the need to obtain informed consent was waived.

All methods were carried out in accordance to relevant guidelines and regulations.

2.2. Patients selection and study variables

Patients newly diagnosed with stage I to stage III breast cancer between January 1993 and December 2011 with available information on method of biopsy were identified from the registry and included in the analysis. We excluded patients with de novo metastatic disease, bilateral breast cancer, those who received neoadjuvant chemotherapy, and those who underwent breast conserving surgery without adjuvant radiotherapy. Of the 3416 patients who were included, 990 (29%) were diagnosed by CNB, 1364 (40%) by FNAC, and 1062 (31%) by excision biopsy.

Data on patient's demography included age at diagnosis, ethnicity (Chinese, Malay, Indian, or other races) and type of center (public wing [UMMC] or private wing [UMSC]). Variables for tumor characteristics included pathologically determined tumor size (mm), number of involved axillary lymph nodes, and tumor grade (good, moderate, poor).

Treatment data included type of surgery (mastectomy, breast-conserving surgery), adjuvant radiotherapy (yes, no), chemotherapy (yes, no) and hormone therapy (yes, no). Data on targeted therapy was limited and therefore not included.

2.3. Follow-up and outcome assessment

Data on all-cause mortality was verified through linkage with the mortality database of the National Registration Department using patients' unique identity card number. While reporting of death is mandated by law in Malaysia, information on cause of death was largely unavailable in patients diagnosed prior to mid-2000s. Follow-up time was calculated from date of breast cancer diagnosis until date of death, or censored at end of follow-up (February 2016). In this hospital-based registry, data on cancer recurrence was incomplete.

2.4. Statistical analysis

Demographics, clinical characteristics and treatment patterns between patients subjected to the three biopsy methods were compared using Chi-square (categorical) and Kruskal Wallis test (continuous). Multinomial logistic regression was performed to identify factors independently associated with type of biopsy, with FNAC as the main outcome.

As adjuvant radiotherapy administration may destroy malignant cells that have been displaced along the biopsy tract, we tested for effect modification by radiotherapy status. Interaction terms of radiotherapy status (yes, no) and biopsy type were included in a multivariable Cox regression model, and the fit was compared with the Cox model containing only the main effect using a likelihood ratio test.

Kaplan–Meier analysis was used to compare overall survival (OS) estimates between the biopsy methods. To approximate cancer-specific survival, we estimated relative survival (RS), which is a widely used measure of cancer survival as it does not rely on accurate cause of death coding.[26,27] Relative survival is the ratio of OS observed in breast cancer patients to the survival that would have been expected had they been subjected only to the mortality rates of the general female population (background mortality), matched for age, calendar year and ethnicity. Expected survival was derived from the Malaysian life tables.

A crude Cox regression model was built to estimate the relative risk of all-cause mortality among breast cancer patients subjected

to the three different biopsy methods, with FNAC as the reference. Stepwise adjustment of the initial model for patient characteristics, tumor characteristics and cancer therapy was undertaken.

We also tested for effect modification by tumor size given that excision biopsy may be more likely to be performed on patients with small tumors. Sensitivity analysis was conducted to assess the prognostic impact of method of biopsy within patients with early stage breast cancer (T1 N0–1 M0 tumors).

A *P*-value of <.05 and 95% confidence interval (CI) for odds ratio (OR) or hazard ratio (HR) that does not include 1.0 were considered statistically significant. Analyses were performed using SPSS version 22 (IBM Corp, Armonk, NY) and STATA, version 12.0 (Stata, College Station, TX).

3. Results

Median age at diagnosis was 52 years, with less than one third of patients aged 60 years and above. Median tumor size at diagnosis was 25 mm. Nearly 60% of patients had no nodal involvement at initial presentation. Compared to patients who had FNAC, those who underwent CNB or excision biopsy tend to have been diagnosed more recently. We did not observe any difference in the types of biopsy between patients managed in the public and private wings. Patients who received needle biopsies (CNB [median age: 54 years] and FNAC [median age: 53 years]) were significantly older at diagnosis compared to their counterparts subjected to excision biopsy (median age: 48 years). Chinese patients were significantly less likely to have been subjected to FNAC but more often underwent excision biopsy compared to Malay and Indian patients (Table 1). Notably, a significantly higher proportion of patients diagnosed by excision biopsy had more favorable tumor characteristics compared to patients subjected to needle biopsies, including smaller tumors, less regional lymph node involvement, well differentiated tumors, and ER expressions. In a multinomial logistic regression analysis, excision biopsy remained independently associated with recent calendar year of diagnosis, younger age, Chinese ethnicity, smaller tumors, less nodal involvement, and ER expression, when compared with FNAC (Table 1). Core needle biopsy was independently associated with more recent year of diagnosis, low grade tumor and ER expression compared to FNAC.

Patients who had excision biopsy were significantly less likely to undergo mastectomy compared to patients diagnosed by needle biopsies (Table 2). Adjuvant chemotherapy and radiotherapy administration were also lower following excision biopsy compared to FNAC. Both mastectomy and adjuvant radiotherapy remain less likely to be associated with excision biopsy

Table 1

Patient and tumor characteristics by method of biopsy in 3416 patients with stage I to stage III breast cancer.

					Adjusted odds ratio* (95% CI)	
	Overall (N = 3416) n, %	Core needle (n = 990) n, %	Excision (n = 1062) n, %	Fine needle aspiration cytology (n = 1364) n, %	Core needle biopsy	Excision biopsy
Year of diagnosis (calendar year)					1.20 (1.16–1.23)†	1.03 (1.00–1.06)†
Age at diagnosis (years)						
<40	380 (11.1%)	68 (17.9%)	207 (54.5%)	105 (27.6%)	0.96 (0.68–1.36)	2.78 (2.12–3.66)†
40–59	2087 (61.1%)	594 (28.5%)	664 (31.8%)	829 (39.7%)	1	1
≥60	949 (27.8%)	328 (34.6%)	191 (20.1%)	430 (45.3%)	0.88 (0.72–1.07)	0.49 (0.40–0.61)†
Ethnicity						
Chinese	2381 (69.7%)	685 (28.8%)	784 (32.9%)	912 (38.3%)	1	1
Malay	571 (16.7%)	171 (29.9%)	159 (27.8%)	241 (42.2%)	0.96 (0.75–1.23)	0.75 (0.58–0.96)†
Indian	440 (12.9%)	131 (29.8%)	106 (24.1%)	203 (46.1%)	0.92 (0.70–1.20)	0.71 (0.54–0.93)†
Others	24 (0.7%)	3 (12.5%)	13 (54.2%)	8 (33.3%)	0.64 (0.15–2.65)	2.59 (0.95–7.07)
Tumor size (mm)‡						
Median (IQR)	25 (22)	28 (20)	20 (15)	30 (20)	1.00 (1.00–1.01)	0.99 (0.98–0.99)†
Involved axillary nodes						
0	1913 (56.7%)	524 (27.4%)	707 (37.0%)	682 (35.7%)	1	1
1–3	795 (23.6%)	247 (31.1%)	203 (25.5%)	345 (43.4%)	1.06 (0.85–1.32)	0.64 (0.52–0.80)†
4–9	388 (11.5%)	111 (28.6%)	84 (21.6%)	193 (49.7%)	0.90 (0.68–1.20)	0.51 (0.38–0.69)†
≥10	276 (8.2%)	101 (36.6%)	42 (15.2%)	133 (48.2%)	1.09 (0.79–1.49)	0.47 (0.32–0.69)†
Unknown	44	7	26	11		
Grade						
Good	316 (11.2%)	99 (31.3%)	122 (38.6%)	95 (30.1%)	1.46 (1.05–2.04)†	1.35 (0.98–1.87)
Moderate	1456 (51.8%)	440 (30.2%)	420 (28.8%)	596 (40.9%)	1	1
Poor	1039 (37.0%)	293 (28.2%)	268 (25.8%)	478 (46.0%)	0.85 (0.69–1.06)	0.91 (0.73–1.14)
Unknown	605	158	252	195		
Estrogen receptor status						
Negative	1275 (39.4%)	333 (26.1%)	356 (27.9%)	586 (46.0%)	0.73 (0.56–0.94)†	0.75 (0.59–0.96)†
Positive	1961 (60.6%)	635 (32.4%)	627 (32.0%)	699 (35.6%)	1	1
Unknown	180	22	79	79		

CI = confidence interval.

* Derived using multinomial logistic regression model with fine needle aspiration cytology as outcome. The model was adjusted for year of diagnosis (continuous), type of center (public, private), age, ethnicity, tumor grade, tumor size (continuous), number of involved axillary lymph nodes, estrogen receptor status, progesterone receptor status, and HER2 status. Only factors significantly associated with method of biopsy are shown in the table.

† Statistically significant.

‡ Unknown in 6 patients.

Table 2

Cancer treatment pattern by method of biopsy in 3416 patients with stage I to stage III breast cancer.

					Adjusted odds ratio* (95% CI)	
	Overall (N = 3416) n, %	Core needle (n = 990) n, %	Excision (n = 1062) n, %	Fine needle aspiration cytology (n = 1364) n, %	Core needle biopsy	Excision biopsy
Type of surgery						
Mastectomy	2621 (76.8%)	809 (30.9%)	702 (26.8%)	1110 (42.4%)	1.00 (0.75–1.34)	0.57 (0.43–0.74)†
Breast-conserving surgery	792 (23.2%)	181 (22.9%)	358 (45.2%)	253 (31.9%)	1	1
Unknown	3	0	2	1		
Radiotherapy						
No	1212 (37.0%)	355 (29.3%)	406 (33.5%)	451 (37.2%)	1	1
Yes	2065 (63.0%)	576 (27.9%)	622 (30.1%)	867 (42.0%)	0.87 (0.68–1.12)	0.66 (0.52–0.85)†
Unknown	139	59	34	46		
Chemotherapy						
No	1137 (33.8%)	341 (30.0%)	398 (35.0%)	398 (35.0%)	1	1
Yes	2228 (66.2%)	623 (28.0%)	654 (29.4%)	951 (42.7%)	0.84 (0.67–1.06)	1.02 (0.81–1.28)
Unknown	51	26	10	15		
Hormone therapy						
No	1011 (31.5%)	285 (28.2%)	295 (29.2%)	431 (42.6%)	1	1
Yes	2194 (68.5%)	635 (28.9%)	714 (32.5%)	845 (38.5%)	0.89 (0.64–1.24)	1.03 (0.76–1.41)
Unknown	211	70	53	88		

CI = confidence interval.

* Derived using multinomial logistic regression model with fine needle aspiration cytology as outcome. The model was adjusted for year of diagnosis (continuous), type of centre (public, private), age, ethnicity, tumor grade, tumor size (continuous), number of involved axillary lymph nodes, estrogen receptor status, progesterone receptor status, HER2 status, type of surgery (mastectomy, breast conserving surgery), radiotherapy (no radiotherapy, radiotherapy), chemotherapy (no chemotherapy, chemotherapy) and hormone therapy (no hormone therapy, hormone therapy).

† Statistically significant.

compared to FNAC in multivariable analysis. There were no significant differences in treatment patterns between women undergoing CNB and FNAC.

Likelihood ratio test revealed that radiotherapy status modified the prognostic impact of biopsy method; $P < .001$. As such, all survival analyses were stratified by radiotherapy status (received radiotherapy, no radiotherapy). Tumor size however was not an effect modifier (P for likelihood ratio test = .235).

Among 2065 (60.5%) patients who received radiotherapy, the highest OS and RS were observed among patients subjected to excision biopsy, followed by CNB, and FNAC (Supplementary Figure 1, http://links.lww.com/MD/D736, Table 3). Multivariable Cox regression analysis adjusted for demographic, tumor, and treatment characteristics showed that excision biopsy remained significantly associated with 20% lower risk of mortality compared to FNAC (adjustedHR: 0.81, 95%CI: 0.66–0.99) (Table 3). There was no significant difference in mortality between patients undergoing CNB and FNAC (Table 3).

All patients who did not receive adjuvant radiotherapy comprised women who had mastectomy. In these 1212

Table 3

Association between method of biopsy and all-cause mortality in 2065 breast cancer patients receiving adjuvant radiotherapy.

Overall	Total	Fine needle aspiration cytology	Core needle biopsy	Excision biopsy
Number of patients (%)	2065	867 (42.0%)	576 (27.9%)	622 (30.1%)
Number of death (%)	622	319 (51.3%)	149 (24.0%)	154 (24.8%)
5-year overall survival		81.2% (78.7–83.7%)	84.8% (81.9–87.7%)	89.4% (87.0–91.8%)
5-year relative survival		84.7% (81.8–87.2%)	89.1% (85.8–91.8%)	91.9% (89.1–94.1%)
Hazard ratio model A (95% CI)*		1	0.87 (0.71–1.06)	0.60 (0.50–0.73)†
Hazard ratio model B (95% CI)‡		1	0.94 (0.76–1.15)	0.62 (0.51–0.75)†
Hazard ratio model C (95% CI)§		1	0.97 (0.79–1.20)	0.82 (0.66–1.01)
Hazard ratio model D (95% CI)¶		1	0.95 (0.77–1.16)	0.81 (0.66–0.99)†
T1, N0–1, M0 tumors	**Total**	**Fine needle aspiration cytology**	**Core needle biopsy**	**Excision biopsy**
Number of patients (%)	702	232 (33.0%)	188 (26.8%)	282 (40.2%)
Number of deaths (%)	122	59 (48.4%)	22 (18.0%)	41 (33.6%)
5-year overall survival		90.1% (86.4–93.8%)	93.9% (90.4–97.4%)	94.3% (91.6–97.0%)
Hazard ratio model D (95% CI)¶		1	0.82 (0.47–1.46)	0.59 (0.37–0.93)†

CI = confidence interval.

* Unadjusted hazard ratio derived using Cox regression analysis.

† Statistically significant.

‡ Adjusted hazard ratio (adjHR) derived using Cox regression analysis, adjusted for year of diagnosis, type of centre (public, private), age, and ethnicity.

§ Model was adjusted for variables in model B plus tumor size (mm), number of regional lymph nodes positive, tumor grade, estrogen receptor status, progesterone receptor status, and HER2 status.

¶ Model was adjusted for variables in model C plus type of surgery (mastectomy, breast-conserving surgery), chemotherapy (no chemotherapy, chemotherapy), and hormone therapy (no hormone therapy, hormone therapy).

Table 4

Association between method of biopsy and all-cause mortality in 1212 breast cancer patients not receiving adjuvant radiotherapy[*].

Overall	Total	Fine needle aspiration cytology	Core needle biopsy	Excision biopsy
Number of patients (%)	1212	451 (37.2%)	355 (29.3%)	406 (33.5%)
Number of death (%)	323	144 (44.6%)	92 (28.5%)	87 (26.9%)
5-year overall survival		82.7% (79.2–86.2%)	82.7% (78.8–86.6%)	90.3% (87.4–93.2%)
5-year relative survival		89.8% (85.8–93.1%)	90.0% (85.2–93.9%)	94.2% (90.8–96.8%)
Hazard ratio model A (95% CI)[†]		1	1.12 (0.86–1.47)	0.60 (0.47–0.78)[‡]
Hazard ratio model B (95% CI)[§]		1	1.51 (1.14–2.00)[‡]	0.68 (0.51–0.89)[‡]
Hazard ratio model C (95% CI)[¶]		1	1.64 (1.21–2.22)[‡]	0.88 (0.66–1.19)
Hazard ratio model D (95% CI)[‖]		1	1.57 (1.16–2.12)[‡]	0.87 (0.65–1.17)
T1, N0–1, M0 tumors	**Total**	**Fine needle aspiration cytology**	**Core needle biopsy**	**Excision biopsy**
Number of patients (%)	507	149 (29.4%)	149 (29.4%)	209 (41.2%)
Number of deaths (%)	76	21 (27.6%)	17 (22.4%)	38 (50.0%)
5-year overall survival		93.9% (90.0–97.8%)	94.9% (91.2–98.6%)	92.3% (88.6–96.0%)
Hazard ratio model D (95% CI)[¶]		1 (ref)	1.38 (0.67–2.85)	1.31 (0.73–2.37)

CI = confidence interval.

[*] Comprising patients who had mastectomy.

[†] Unadjusted hazard ratio derived using Cox regression analysis.

[‡] Statistically significant.

[§] Adjusted hazard ratio (adjHR) derived using Cox regression analysis, adjusted for year of diagnosis, type of centre (public, private), age and ethnicity.

[¶] Model was adjusted for variables in model B plus tumor size (mm), number of regional lymph nodes positive, tumor grade, estrogen receptor status, progesterone receptor status and HER2 status.

[‖] Model was adjusted for variables in model C plus type of surgery (mastectomy, breast-conserving surgery), chemotherapy (no chemotherapy, chemotherapy) and hormone therapy (no hormone therapy, hormone therapy).

(35.5%) patients, the 5-year OS and 5-year RS were significantly higher among patients undergoing excision biopsy compared to patients receiving percutaneous biopsies (Supplementary Figure 2, http://links.lww.com/MD/D737, Table 4). Although the risk of mortality following excision biopsy was lower than FNAC in the multivariable analysis (HR: 0.87, 95%CI: 0.65–1.17), this association was not statistically significant. Nevertheless, patients subjected to CNB were significantly associated with higher risk of mortality compared to their counterparts receiving FNAC (adjustedHR: 1.57, 95%CI: 1.16–2.12).

In a sensitivity analysis of 1209 (35.4%) breast cancer patients with T1,N0–1,M0 tumors, out of which 702 received radiotherapy, excision biopsy remained significantly associated with lower risk of mortality compared to FNAC; adjustedHR: 0.59 (95%CI: 0.37–0.93) (Table 3). In the subset of 507 early breast cancer patients whose management did not include adjuvant radiotherapy, no significant differences in risk of mortality were observed between the different biopsy methods, although CNB was still associated with a non-significant 40% increased risk of mortality compared to FNAC (Table 4).

4. Discussion

While our findings suggest that method of biopsy may be associated with risk of mortality following breast cancer, this observation has not been previously reported.

Needle biopsies have emerged as the preferred procedure of choice in diagnosing breast lesions following the endorsement of a multidisciplinary international consensus conference in 2005.[28,29] Nevertheless, almost a third of breast cancer patients in the present study were diagnosed through excision biopsy. We also found a modest increase in excision biopsy utilization in the recent calendar years compared to FNAC. Similarly, studies in the United States (US) have shown that utilization of excision biopsy remained high,[30,31] although there was a trend favoring increased use of needle biopsies in recent times.[2] Apart from younger age at diagnosis and smaller tumor size, we found that Chinese ethnicity was independently associated with excision biopsy. This may be culturally driven, as Chinese women have been reported to fear needle biopsy due to concerns that it may trigger distant metastasis,[23] akin to myths in certain communities in the US where it is thought that exposure of the tumor to air will accentuate cancer spread.[24] While we found that type of hospital (public vs private) was not associated with the method of biopsy in breast cancer, we did not have data on individual surgeon-related factors, which may also influence the type of biopsy.[2]

To the best of our knowledge, the present study is the first to show that breast cancer patients diagnosed through needle biopsies have significantly lower survival (both overall and disease-specific survival) compared to women subjected to excision biopsy. Although the survival gain associated with excision biopsy was not statistically significant in the subgroup of women who had mastectomy without adjuvant radiotherapy, we are unsure if this was due to lack of power as the observed effect size (HR: 0.87, 95%CI: 0.65–1.17) was not very different from the effect size in women receiving radiotherapy (HR: 0.81, 95% CI: 0.66–0.99). Within breast cancer patients managed with radiotherapy, excision biopsy appeared to be consistently associated with a survival advantage compared to percutaneous needle biopsy, both in the main and sensitivity analyses. These findings are conceivable as the entire tumor is removed with wide margins during excision biopsy and not penetrated as in the case of needle biopsy, possibly reducing the risk of malignant cell seeding. As radiotherapy administration is capable of destroying locally displaced malignant cells,[16] the observation that patients who had needle biopsies were still associated with a higher risk of mortality despite receiving radiotherapy points toward an underlying pathophysiology, which probably involves hematogenous seeding.[15,32] Contrary to our present findings, a previous study showed that CNB was associated with significantly higher OS compared to excision biopsy in breast cancer patients who

underwent breast conserving surgery and radiotherapy. Nevertheless, it has to be noted that apart from a very low number of deaths in the above-mentioned study, data on potential confounders were limited and no multivariable analysis was undertaken.[9]

Our findings in women without radiotherapy are intriguing. The higher risk of mortality associated with CNB compared to FNAC in this subgroup (adjustedHR: 1.57, 95%CI: 1.16–2.12), appears to suggest that there is a higher risk of tumor seeding associated with use of large bore needles such as in CNB when compared to FNAC. An important consideration is that, in the present study, patients who did not receive radiotherapy comprised those who underwent mastectomy whom would have had their biopsy tracks as well as axillary nodes excised. This again implies that the survival disadvantage associated with CNB may be better explained by the hematogenous dissemination of displaced malignant cells. A previous study reported significantly higher rates of distant metastasis in CNB patients compared to FNAC patients.[33] Contrary to the present findings however, a study in 1525 breast cancer patients with T1 tumors had recently shown that CNB was associated with higher OS than FNAC, which however attenuated following adjustment for age and tumor characteristics (adjustedHR: 0.94, 95%CI: 0.69–1.30).[13] No difference in breast cancer specific or recurrence free survival was observed between CNB and FNAC. Taken together with our own observation that the HR for CNB attenuated following sensitivity analysis within patients with T1,N0–1,M0 tumors, it is felt that more studies comparing clinical outcomes between CNB and FNAC are needed before solid conclusions can be made.

Given the observational nature of the present study and lack of data on local and distant recurrence, we remain cautious in making any strong inferences that may impact current clinical practice. Complete data on clinical indications for the type of biopsy was lacking and may have affected study findings. Furthermore, data on time intervals between biopsy, surgery, systemic therapy, and/or radiotherapy were not available to allow assessment of the effect of time from diagnosis to extirpation of tumor and survival. While data on cause of death in the present study were incomplete, we had computed RS, which provides an estimate of net survival attributed to breast cancer given that it captures both the direct and indirect contribution of cancer diagnosis on survival.[27] We also had a large number of patients with extensive clinical data and adequate number of events that enabled testing for effect modification, adequate confounder adjustment, and sensitivity analysis, hence improving the validity of our findings.

Given that our results contradict with findings of previous clinical studies assessing the prognostic impact of method of biopsy in women with breast cancer, further investigations are warranted. This is particularly of importance when considering that surgeons worldwide are advised to move away from excision biopsy to avoid unnecessarily putting breast cancer patients through "more surgery" and to decrease costs and morbidity.[28,29]

Author contributions

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