Received: 27 June 2017 | Revised: 30 July 2017 | Accepted: 23 August 2017

DOI: 10.1111/ajco.12783

ORIGINAL ARTICLE

WILEY

Attitudes of patients with metastatic cancer towards research biopsies

Danielle H. Robinson[1] | **Leonid Churilov**[2] | **Nancy U. Lin**[3,4] | **Elgene Lim**[5,6,7] | **Davinia Seah**[6,7,8]

[1]Austin Health, Heidelberg, Victoria, Australia

[2]The Florey Institute of Neuroscience and Mental Health, VIC, Australia

[3]Dana-Farber Cancer Institute, Boston, MA, USA

[4]Harvard Medical School, Boston, MA, USA

[5]Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

[6]University of New South Wales, Kensington, NSW, Australia

[7]St Vincent's Health, Darlinghurst, NSW, Australia

[8]University of Notre Dame Australia, Darlinghurst, NSW, Australia

Correspondence
Davinia Seah, Sacred Heart Hospice, St Vincent's Health, 170 Darlinghurst Road, Darlinghurst, NSW 2010, Australia.
Email: davinia.seah@svha.org.au

E. Lim and D. Seah contributed equally to this article.

Abstract

Aim: To evaluate the attitudes of patients with different cancers towards research biopsies outside a clinical trial.

Methods: Patients with metastatic cancer completed a questionnaire that assessed patients' willingness to consider research biopsies. Research biopsies were divided into two groups: biopsies performed as stand-alone procedures (research purposes only biopsy, RPOB) or performed during a clinically indicated biopsy (additional pass biopsy, APB). Factors analyzed included biopsy timing, biopsy site, sociodemographic information and information about prior trial participation. Univariate and multivariable analyses were conducted using random-effects logistic regression.

Results: One hundred and sixty-five patients with cancer (40 melanoma, 37 colorectal, 32 breast, 30 lung, 26 prostate) completed the questionnaire. Patients with melanoma demonstrated the greatest willingness to consider a research biopsy compared to patients with other cancer types ($P < 0.05$). Patients' ethnicity, time since previous biopsies, time since metastatic diagnosis, and previous trial enrolment were all statistically significant for willingness to consider a research biopsy on univariate analysis. When adjusting for statistically significant variables on univariate analysis, the odds of patients considering APBs were 14.6 times greater than RPOBs ($P < 0.0001$). Patients were also more willing to consider having blood or skin taken for research purposes ($P < 0.0001$) compared to liver and bone biopsies.

Conclusions: Patients with cancer show a greater willingness to consider APBs compared to RPOBs, and biopsies performed at less invasive body sites. There are differences in the attitudes of patients with different cancers towards research biopsies. Further research addressing motivations and barriers to research biopsies should be considered to increase the availability of this important resource.

KEYWORDS

biopsy, metastatic, neoplasms, patient participation, patient preference

1 | INTRODUCTION

Patient tissue samples are critical building blocks for translational research. In addition to immunohistochemical phenotyping, we now have tools to perform genomic, transcriptomic and other analyses on these tissues. Tumor-based biomarkers are increasingly used to determine a patient's eligibility into clinical trials.[1] Although clinically indicated tumor biopsies are obtained with the intent of influencing patient management, biopsies for research purposes do not offer the promise of any direct clinical benefit to the patient,[2] and the procedure itself is associated with some degree of risk.[3,4] Research biopsies may be obtained as stand-alone procedures (research purposes only biopsy, RPOB), or involve additional passes of the biopsy needle during a clinically indicated tissue biopsy (additional pass biopsy, APB).

The majority of research biopsies are performed in association with clinical trials, and most often in the setting of advanced cancer. Although most are optional, some trials mandate research biopsies.[5–11] Studies have demonstrated that patients find mandatory research biopsies to be a deterrent in clinical trial participation.[5,7,12] About 50–60% of patients are willing to undergo a research biopsy outside the context of clinical trials,[13–16] particularly if the research tissue is obtained at the same time as a clinically indicated

biopsy.[14,15,17] The majority of these studies have been conducted in patients with breast cancer, who have been shown to be more willing to undergo optional biopsies and participate in clinical trials compared with the general oncology community.[6]

We conducted a survey to compare the attitudes of Australian patients with different cancers towards undergoing research biopsies and the factors that influence this. We assessed whether patients would consider undergoing RPOBs and/or APBs at various anatomical sites outside of an interventional clinical trial, and whether patients would consent to research use of tumor tissue in excess of diagnostic requirements obtained during surgery. Finally, we identified the factors influencing patients' attitudes towards consenting to RPOBs and APBs.

2 | METHODS

This study was conducted in accordance with the Austin Health Human Research Ethics Committee in Victoria, Australia.

2.1 | Participants

We conducted a cross-sectional self-administered paper questionnaire of oncology outpatients at the Austin Hospital from August 2014 to May 2015. Eligibility criteria included a diagnosis of metastatic breast, colorectal, lung, melanoma or prostate cancers, above 18 years of age, and the ability to understand written English. There were no exclusion criteria. Patients were approached prior to, or after their oncology outpatient clinic appointments, and included new patients and follow-up patients returning to the outpatient clinic. The study investigators explained the purpose of the study to the patients verbally (DR or DS), and a plain language statement was given out. Patients provided verbal consent to participating in this study. The anonymous questionnaire took approximately 10–15 min to complete; some patients completed the questionnaire at home and returned it via mail or in person. There was no financial compensation provided.

2.2 | Questionnaire design and outcome measures

The questionnaire was adapted from a previous study that assessed attitudes of patients with metastatic breast cancer towards research biopsies that was performed by DS in Boston, MA, USA.[14] As this research was designed for the Australian context, and additionally sought to compare attitudes of patients with different cancer types, adaptations included additional questions regarding donation of excess tissue from surgery, which does not require an additional procedure on the patient, but requires patient consent as it may have implications on their personal information. The questionnaire was also modified to factor in Australian demographics (e.g. different ethnic populations).

2.3 | Statistical methods

The primary analysis compared patients' attitudes towards undergoing an RPOB or APB at various different anatomical locations. This was analyzed as a dichotomous variable, collapsing the categories "definitely" or "probably" versus "maybe," "probably not" or "definitely not." Biopsy sites such as skin, bone, liver and blood tests were considered. Secondary outcome measures included the patient willingness to consider donation of excess tumor tissue taken at the time of surgery, and the factors influencing the patients' attitudes towards APBs, RPOBs and donation of tumor tissue for research following surgery. Demographic information collected included age, ethnicity, gender, education, marital status, prior clinical trial participation and the number of prior biopsies. When patients were asked about prior biopsies, it was not specified whether the biopsy was performed under general or local anaesthetic.

As each participant responded to different hypothetical scenarios, the response provided by a given participant for any individual scenario is not independent from the responses provided by the same participant to other scenarios. To adequately model such dependencies, individual responses were treated as repeated measures of the participant's willingness to undergo a research biopsy with the cancer type. Sociodemographic factors and cancer type were treated as patient level characteristics. Random effect logistic regression modeling with individual participants treated as a random effect was used to investigate the association between various characteristics and a patient's willingness to consider a research biopsy. The corresponding effects were reported as unadjusted or adjusted odds ratios (ORs) with 95% confidence intervals (CI). Individual factors were first included in univariate analysis. Variables that demonstrated statistically significant association were subsequently included in a multivariable analysis. P values <0.05 were considered to be statistically significant. Statistical analyses were conducted using Stata IC V13 software (Stata Corp., College Station, TX, USA).

3 | RESULTS

A total of 203 patients were approached and 165 patients (40 melanoma, 37 colorectal, 32 breast, 30 lung and 25 prostate cancer) completed the questionnaires, comprising 81 males (49%) and 65 females (40%; Table 1). The mean age was 62 years, the median time from diagnosis of cancer was 29 months, and the median time from diagnosis with metastatic disease was 19 months.

3.1 | Additional pass biopsy versus research purposes only biopsy

The unadjusted odds of patients agreeing to consider an APB were 4.5 times higher compared to RPOBs (Table 2; OR 4.52, $P < 0.0001$; 95% CI, 3.32–6.14). In the adjusted analysis, the odds of patients considering an APB was 14.6 times higher compared to a RPOB (Table 2; OR 14.62, $P < 0.0001$; 95% CI, 7.91–27.01).

3.2 | Sociodemographic factors

Although none of the sociodemographic factors appeared to be statistically significant in the adjusted analysis, ethnicity and previous clinical trial participation appeared statistical significant in the unadjusted

TABLE 1 Patient characteristics

Characteristic	All patients (*N* = 165)	Breast cancer (*N* = 32)	Colorectal cancer (*N* = 37)	Lung cancer (*N* = 30)	Melanoma (*N* = 40)	Prostate cancer (*N* = 26)
Time since diagnosis (months)						
Median (0.25, 0.75; IQR)	28.5 (10, 74; 64)	67 (25, 118.5; 93.5)	24 (9, 49; 40)	8.5 (4, 24; 20)	29 (19, 72; 53)	48 (20, 90; 70)
Unknown	3	0	0	0	2	1
Time since metastatic diagnosis (months)						
Median (0.25, 0.75; IQR)	19 (7, 36; 29)	33 (12, 72; 60)	18 (9, 32; 23)	6 (4, 10; 6)	24 (6, 31; 25)	24 (12, 37; 25)
Unknown	50	6	10	13	10	11
Age (years)						
Mean (SD)	62.8 (12.3)	61.4 (15.3)	58.8 (11.7)	65.2 (9.8)	61.4 (11.6)	70.3 (9.5)
Median (0.25, 0.75; IQR)	64.5 (55, 71; 16)	63 (53, 76; 23)	58.5 (53, 65; 12)	66.5 (60, 71; 11)	64 (55, 69; 14)	70 (65, 74; 9)
Unknown	29	7	7	6	3	6
Sex [*n* (%)]						
Males	81 (49)	0	22 (60)	9 (30)	30 (75)	21 (81)
Females	65 (40)	28 (88)	13 (35)	15 (50)	9 (23)	0
Unknown	18 (11)	4 (12)	2 (5)	6 (20)	1 (2)	5 (19)
Highest level of education [*n* (%)]						
Never/primary	12 (7)	5 (16)	1 (3)	3 (10)	1 (2)	2 (8)
Some secondary	37 (22)	9 (28)	9 (24)	6 (20)	8 (20)	5 (19)
Completed Secondary	29 (18)	6 (19)	8 (22)	3 (10)	8 (20)	4 (15)
Trade certificate	26 (16)	2 (6)	11 (30)	4 (13)	3 (8)	6 (23)
Bachelor degree	30 (18)	6 (19)	5 (13)	4 (13)	14 (35)	1 (4)
Post-graduate degree	11 (7)	0	1 (3)	4 (13)	4 (10)	2 (8)
Unknown	20 (12)	4 (12)	2 (5)	6 (20)	2 (5)	6 (23)
Number of previous biopsies [*n* (%)]						
0	25 (15)	2 (6)	11 (30)	3 (10)	4 (10)	5 (19)
1 or 2 biopsies	92 (56)	19 (59)	17 (46)	23 (77)	17 (43)	16 (62)
3 or more biopsies	25 (15)	7 (22)	3 (8)	3 (10)	12 (30)	0
Unknown	23 (13)	4 (12)	6 (16)	1 (3)	7 (17)	5 (19)
Previous trial participation [*n* (%)]						
Yes	64 (39)	10 (31)	13 (35)	7 (23)	24 (60)	10 (38.5)
No	84 (51)	18 (56)	22 (60)	20 (67)	14 (35)	10 (38.5)
Unknown	17 (10)	4 (12)	2 (5)	3 (10)	2 (5)	6 (23)
Previous research biopsy						
Yes	21 (13)	2 (6)	6 (16)	1 (3)	11 (27)	0
No	127 (77)	26 (81)	29 (79)	26 (87)	27 (68)	20 (77)
Unknown	17 (10)	4 (12)	2 (5)	3 (10)	2 (5)	6 (23)

analysis. The time since diagnosis of metastatic cancer and the time since biopsy while of statistical significance, the effect was small.

3.3 | Research biopsies of different metastatic cancer cohorts

Patients with melanoma were between 3.4 and 8.3 times more willing to consider a research biopsy of any kind compared to the other cancer cohorts (Table 2). Although patients with melanoma were the most likely to consider having a research biopsy, the odds of patients with melanoma considering a bone biopsy or liver biopsy were lower compared to skin biopsy (Bone: OR 0.14, $P = 0.001$; 95% CI, 0.05–0.44, liver: OR 0.11, $P < 0.0001$, 95% CI, 0.04,0.34; Table 3).

All cancer cohorts, when analysed individually, demonstrated that the odds of patients considering undergoing an APB were between 8.5 and 15.1 times higher compared to an RPOB (Table 3). Patients with lung cancer had the highest odds of considering APBs.

3.4 | Research biopsies of different body sites

Overall, patients were more likely to consider research biopsies in less invasive anatomical sites compared to more invasive sites. In the

TABLE 2 Factors associated with patients' willingness to undergo a research biopsy

	Unadjusted		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Biopsy timing				
Additional pass biopsy (reference: research purposes only biopsy)	4.52 (3.32, 6.14)	$P < 0.0001$	14.62 (7.91, 27.01)	$P < 0.0001$
Biopsy site				
Unspecified location (reference: skin)	0.53 (0.33, 0.86)	$P = 0.011$	0.43 (0.21, 0.91)	$P = 0.027$
Blood (reference: skin)	13.38 (7.20, 24.86)	$P < 0.0001$	26.02 (9.10-74.47)	$P < 0.0001$
Bone (reference: skin)	0.24 (0.14, 0.39)	$P < 0.0001$	0.10 (0.04, 0.21)	$P < 0.0001$
Liver (reference: skin)	0.26 (0.16, 0.43)	$P < 0.0001$	0.09 (0.04, 0.20)	$P < 0.0001$
Sociodemographics[a]				
Ethnicity[b] (reference: Caucasian)	5.14 (1.57, 16.88)	$P = 0.007$	5.93 (0.74, 47.76)	$P = 0.095$
Time since diagnosis of metastatic cancer[c] (per year)	1.22 (1.02, 1.46)	$P = 0.032$	1.26 (0.77, 2.06)	$P = 0.355$
Time since biopsy of any kind[c] (per year)	1.19 (1.02, 1.38)	$P = 0.024$	1.04 (0.72, 1.50)	$P = 0.827$
Previous clinical trial participation (ref: yes)	3.84 (1.74, 8.48)	$P = 0.001$	4.13 (0.80, 21.28)	$P = 0.090$
Age (per year)	0.99 (0.95, 1.02)	$P = 0.386$		
Time since diagnosis of cancer (per year)	1.05 (0.99, 1.11)	$P = 0.073$		
Sex (reference: male)	1.67 (0.75, 3.70)	$P = 0.21$		
Education (reference: secondary education)				
No education/primary education	0.48 (0.10, 2.32)	$P = 0.36$		
Tertiary education, trade	1.39 (0.61, 3.15)	$P = 0.43$		
Employment status (reference: employed)	1.26 (0.50, 3.15)	$P = 0.622$		
Previous biopsy of any kind (reference: yes)	0.99 (0.35, 2.78)	$P = 0.981$		
Number of previous biopsies (reference: no previous biopsies)				
1 or 2 previous biopsies	1.18 (0.40, 3.52)	$P = 0.761$		
3 or more previous biopsies	1.43 (0.36, 5.61)	$P = 0.611$		
Experience of previous biopsies (reference: as expected)				
Much worse or a little worse than expected	0.36 (0.09, 1.38)	$P = 0.136$		
Much better or a little better than expected	0.55 (0.18, 1.67)	$P = 0.291$		
Previous research biopsy (reference: yes)	2.75 (0.84, 9.03)	$P = 0.096$		
Cancer type				
Colorectal cancer (reference: melanoma)	0.12 (0.04, 0.34)	$P < 0.0001$	Not included in the adjusted analysis due to high co-linearity in the model, but included as a second level random effect. Variability in the outcome due to cancer type is negligible.	
Breast cancer (reference: melanoma)	0.15 (0.05, 0.43)	$P = 0.001$		
Lung cancer (reference: melanoma)	0.18 (0.06, 0.56)	$P = 0.003$		
Prostate cancer (reference: melanoma)	0.29 (0.09, 0.97)	$P = 0.045$		

[a]Only sociodemographic variables that were statistically significant in unadjusted (univariate) analysis were included in adjusted (multivariable) analysis.
[b]Ethnic categories include Caucasian *vs* Other (Asian, African, Middle Eastern, Aboriginal or Torres Strait Islander, other and undisclosed).
[c]Years is a continuous variable.

unadjusted analysis, the odds of patients willing to have blood taken for research purposes were 13 times higher (OR 13.38; $P < 0.0001$; 95% CI, 7.2–24.9) compared to skin biopsies. Patients were also more likely (OR 26.02; $P < 0.0001$; 95% CI, 9.1–74.5) to consider having blood taken for research compared to skin biopsies in the adjusted analysis. The odds of a patient being willing to consider a bone and liver biopsy were lower than for skin biopsy (bone: unadjusted OR 0.24, $P < 0.0001$, 95% CI, 0.14–0.39; adjusted OR 0.10, $P < 0.0001$, 95% CI, 0.04–0.21; liver: unadjusted OR 0.26, $P < 0.0001$, 95% CI, 0.16–0.43; adjusted OR 0.09, $P < 0.0001$, 95% CI, 0.04–0.20).

3.5 | Donation of excess tumor tissue

The majority of patients would consider donating excess tissue obtained during surgery for research (82%; 95% CI, 76–88%). Most patients were willing to have their personal medical records linked to

TABLE 3 Analysis of biopsy timing and site for the individual cancer cohorts

	OR (95% CI), *P* values
Biopsy timing: Additional pass (reference: research purposes only biopsy)	
Colorectal cancer	8.47 (3.86, 18.55), $P < 0.0001$
Melanoma	9.06 (4.01, 20.48), $P < 0.0001$
Breast cancer	13.26 (5.05, 34.8), $P < 0.0001$
Prostate cancer	14.81 (3.13, 70.12), $P = 0.001$
Lung cancer	15.12 (3.99, 57.27), $P < 0.0001$
Biopsy site: unspecified location (reference: skin)	
Colorectal cancer	0.44 (0.15, 1.26), $P = 0.13$
Melanoma	0.26 (0.09, 0.80), $P = 0.02$
Breast cancer	1.31 (0.40, 4.27), $P = 0.65$
Prostate cancer	0.38 (0.06, 2.25), $P = 0.29$
Lung cancer	0.22 (0.04, 1.06), $P = 0.06$
Biopsy site: blood (reference: skin)	
Colorectal cancer	37.64 (9.28, 152.68), $P < 0.0001$
Melanoma	11.28 (2.32, 54.76), $P < 0.003$
Breast cancer	18.87 (4.39, 81.16), $P < 0.001$
Prostate cancer	66.55 (5.01, 884.22), $P = 0.001$
Lung cancer	76.75 (8.08, 729.31), $P < 0.0001$
Biopsy site: bone biopsy (reference: skin)	
Colorectal cancer	0.28 (0.10, 0.82), $P = 0.02$
Melanoma	0.14 (0.05, 0.44), $P = 0.001$
Breast cancer	0.34 (0.10,1.16), $P = 0.09$
Prostate cancer	0.08 (0.010, 0.60), $P = 0.02$
Lung cancer	0.02 (0.002, 0.14), $P < 0.0001$
Biopsy site: liver biopsy (reference: skin)	
Colorectal cancer	0.58 (0.20, 1.62), $P = 0.30$
Melanoma	0.11 (0.04, 0.34), $P < 0.0001$
Breast cancer	0.13 (0.03, 0.46), $P = 0.002$
Prostate cancer	0.04 (0.005, 0.37), $P = 0.004$
Lung cancer	0.17 (0.03, 0.86), $P = 0.03$

Data are odds ratios with 95% confidence intervals and *P* values. For each biopsy site a skin biopsy has been used as the reference biopsy site, and data are represented for each of the five cancer cohorts investigated.

their research tissue (79%; 95% CI, 72–85%), and indicated that de-identification of their tissue sample was not important to them (60%; 95% CI, 52–68%).

3.6 | Factors influencing participation in research biopsies

For both APBs and RPOBs, there was little difference in barriers to consenting to research biopsies between the two groups. The most cited reasons for not consenting were pain (29.1% and 38.2% of 165 responses, respectively), concern regarding the risk of complications (23% and 25.5%, respectively) and anxiety (23% and 26.1%, respectively). Although less common, other barriers to consenting to APBs and RPOBs included the inconvenience of the procedure (14% and 18.2%, respectively), a lack of time (8.5% and 11%, respectively) and transportation difficulties (6.1% and 8.5%, respectively). Although the research biopsy does not bring direct benefit to the patient, this was only a barrier to participating in research biopsies in 4.8% and 6.7% of respondents, respectively.

Most patients indicated that the possibility of contributing to scientific research (72%; 95% CI, 65–79%), as well as knowing the overall outcome of the study (54%; 95% CI, 46–62%), and knowing the results of the tests performed on their own research biopsy (53%; 95% CI, 45–61%) would influence their willingness to consider undergoing a research biopsy. Forty-eight percent of patients indicated that a personal request from their doctor would positively influence their willingness to undergo a research biopsy (95% CI, 41–56%; Table 4).

4 | DISCUSSION

Patient-derived tumor tissue is a critical resource to better understand cancer biology, developing new therapies and identifying biomarkers of treatment response.[17] Although there have been great multinational efforts utilizing multiple cutting edge research platforms to study patient tumors, such as The Cancer Genome Atlas project, these have primarily focused on treatment-naïve primary tumors. There is still a lack of patient cancer tissue cohorts comprising treatment-resistant metastatic tumors, which is ultimately the cause of what the vast majority of patients with advanced cancers die from. Research biopsies, particularly from different metastatic sites, are therefore critical in this context. Currently, the majority of research biopsies are performed within the context of clinical trials. Obtaining research biopsies outside the clinical trial context will dramatically increase this important resource. We carried out a cross-sectional survey of patients with metastatic breast, colorectal, lung, melanoma and prostate cancers to evaluate their willingness to consent to donation of excess tumor tissue and research biopsies outside the clinical trial context, and identify factors that would influence their decision to participate in research biopsies. To our knowledge, this is the first paper to compare the differences of attitudes of patients between tumor streams.

The majority of the patients in our study (82%) were willing to consent to the donation of excess tumor tissue. These results echo those of Hamilton *et al.* and Naim *et al.* where 100% of patients undergoing surgery and 83% of patients surveyed, respectively, indicated they would have been willing to donate their excess tumor tissue to research.[15,18] As the excess tumor tissue were sourced from surgically obtained tissue in excess of diagnostic requirements in previous studies,[19] the sentiments of patients cannot be extrapolated to research biopsies that require patients to undergo an additional invasive procedure. In our cohort, the majority of patients were not willing to undergo a research only biopsy. We identified factors that would improve their willingness to undergo a research biopsy, which included performing the research biopsy at the time of a diagnostic biopsy, and a personal request from their doctor, particularly if they knew that there was a possibility of contributing to scientific research through consenting to the process. Finally, patients indicated that being informed of the research outcomes resulting from their tissue influenced their

TABLE 4 Factors that influence a patient's willingness to undergo a research biopsy of any kind (number of responses)

	Yes	No	Did not answer
Contributing to scientific knowledge that may help other people in the future	119 (72%)	22 (13%)	24 (15%)
Learning about the overall results of the study	89 (54%)	51 (31%)	25 (15%)
Learning about the research of tests performed on the biopsy, even though this would not directly affect care	88 (53%)	50 (30%)	27 (16%)
Personal request from their doctor	80 (48%)	59 (36%)	26 (16%)
Learning more about the risks of a biopsy	65 (39%)	73 (44%)	27 (16%)
Talking to a patient who has undergone a research biopsy	52 (32%)	87 (53%)	26 (16%)
Informational brochure about research biopsies	50 (30%)	87 (53%)	28 (17%)
Time taken away from home or work to come into hospital	48 (29%)	91 (55%)	26 (16%)
Costs associated with coming into hospital (transportation, parking)	47 (28%)	93 (56%)	25 (15%)

Data are number of responses out of 165 and this represented in a percentage. Participants were given the option of not answering these questions and this is represented in the "did not answer" column.

willingness to provide a research biopsy. This information has direct clinical relevance, and can inform the design of research protocols which require research biopsies, patient consents forms, patient feedback and influence the consenting clinician's approach to asking patients to participate in such research studies.

The patients in our study were more willing to consider research biopsies of less invasive sites, such as blood or skin, compared to any invasive site, such as bone and liver. This is consistent with findings of the results of prior studies.[13,14] With new technology that allows for the capture and characterization of circulating tumor cells (CTCs) and cell-free DNA (cfDNA) in the plasma there is now increasing data of the utility of such an approach as an alternative strategy to characterize the tumor.[20] CTCs and cfDNA have been shown to be representative of the metastatic tumors, and potentially allows one to track the evolution of the tumor in the patient in response to therapy and over time.[21,22] Although not currently in routine clinical use, such an approach may complement and eventually render the need for more invasive metastatic biopsies obsolete.

The majority of the patients in our study (79%) were willing for data from their excess tumor tissue to be linked to their medical records without de-identification. Clinical annotation of tissue allows for the matching of the tumor molecular characteristics with patient characteristics, and other important data such as therapies received, and disease tempo. Increasingly, researchers require the appropriate guidance to best manage the information that may arise from the analysis of their tissue and the protection of patient data.

Our findings concur with a study in a large cohort of patients with cancer receiving systemic anticancer therapy, whereby the majority of patients indicated a willingness to donate tissue for research, and for their samples to be linked to their medical records.[23] A key difference is that this study focused on patient attitudes towards biobanking of surgical tissues in excess of diagnostic requirements. Our study suggests that patients are similarly willing to have additional biopsies for the purposes of research.

Most of the literature about patients' attitudes towards research biopsies that are not associated with a clinical trial has been conducted in single tumor streams.[14–16] There is limited data comparing the differences in attitudes of patients with varying cancer types towards research biopsies. In our study, patients with metastatic cancer had different attitudes towards research biopsies; patients with metastatic melanoma were most likely to consider undergoing research biopsies. This contrasts with results from a study that demonstrated that women with gynaecologic cancer and breast cancer more frequently underwent optional biopsies.[6] We hypothesize that recent improvements stemming from new therapies in melanoma and access to these therapies through clinical trials may have positively influenced patients' attitudes towards participation in research biopsies. Physician's attitudes towards research biopsies may also influence patient's receptiveness to participation in a research biopsy. A recent survey of medical oncologists showed that there was a significant variation of comfort level in medical oncologists approaching patients for research biopsies, even at academic centers.[24]

A major aim of our research was to identify factors that would influence a patient's participation in research biopsies. Consistent with the deterrents identified in other studies,[14,15,25,26] the three most cited deterrents for patients considering undergoing research biopsies were pain, anxiety and risk of complications of the procedure. It is critical that an accurate reflection of the additional risks posed from a research-only and an additional biopsy at various anatomical sites be reflected in the patient information consent sheet. Most studies indicate that research biopsies are safe with complication rates between 0.8% and 1.4% for major complications.[6,27] These studies did not specify if they were additional biopsies or research purpose only biopsies. In addition, other studies have demonstrated that patients were often unable to recall the risks associated with the procedure[28] and were willing to accept a higher risk of complications compared to medical oncologists and institutional review boards.[5] Factors such as the inconvenience of the procedure and transportation challenges also contributed to a patient's willingness to have a research biopsy in our study, albeit in a minority of patients. These, however, represent more easily addressable issues to increase participation rates. We should not rely entirely on the altruism of the patient to participate in research biopsies, but holistically address all factors to ensure that the process comes at a minimal inconvenience to them.

Our study has a number of limitations. The completion of a questionnaire presenting hypothetical scenarios may not be truly reflective of patients' actual decisions if approached to undergo a research biopsy. Our study did not assess the motivations behind patients' willingness to consider research biopsies, and some patients may attribute a personal and direct benefit from research biopsies, also known as therapeutic misconception, which is often not the case.[29] We specifically conducted this study outside the context of a clinical trial to minimize the potential for therapeutic misconception and a sense of obligation. This study was an anonymous questionnaire, and we were unable to cross reference from the patient's medical record if data were incomplete.

Our study and others demonstrate that there is a high level of acceptance toward the donation of tissue for research in patients with cancer. In our study there was a greater willingness to consent to APBs compared to RPOBs. As such, to increase the quantity of patient tissue for research, protocols should be in place whereby patients are routinely approached and consented for the use of their tissue for research when undergoing surgery or a diagnostic biopsy. The anatomical site of biopsy was found to influence patients' willingness to consent to research biopsies. It is important therefore that the consent process accurately describes site-specific risks. In our study the most commonly stated factors that influenced patients' willingness to participate in research biopsies was a sense of altruism (contributing to scientific knowledge that may help other people in the future), and an interest in the outcomes of the research project. This behooves researchers to better communicate research outcomes with patients who generously donate their tissue, and who are critical partners in the research endeavor. Protocols involving research biopsies should be designed with these influencing factors in mind.

5 | CONCLUSION

Patients show a greater willingness of considering an additional biopsy compared to a research purpose only biopsy, as well as biopsies performed at less invasive body sites. Patients with metastatic melanoma are more willing to consider a research biopsy than any other cancer type. Further research to address patients' and clinicians' motivations for and barriers to research biopsies should be considered to increase the availability of this importance resource.

ACKNOWLEDGMENTS

We would like to thank that participating patients in this study and the clinical staff at The Olivia Newton-John Cancer and Wellness Center.

ORCID

Danielle H. Robinson http://orcid.org/0000-0003-0384-704X

REFERENCES

1. Weigel MT, Dowsett M. Current and emerging biomarkers in breast cancer: prognosis and prediction. *Endocr Relat Cancer*. 2010;17:R245–R262.
2. Peppercorn J, Shapira I, Collyar D, et al. Ethics of mandatory research biopsy for correlative end points within clinical trials in oncology. *J Clin Oncol*. 2010;28:2635–2640.
3. Helft PR, Daugherty CK. Are we taking without giving in return? The ethics of research-related biopsies and the benefits of clinical trial participation. *J Clin Oncol*. 2006;24:4793–4795.
4. Welfare AIoHa. Cancer in Australia: an overview 2014. Canberra, Australia; 2014.
5. Agulnik M, Oza AM, Pond GR, et al. Impact and perceptions of mandatory tumor biopsies for correlative studies in clinical trials of novel anticancer agents. *J Clin Oncol*. 2006;24:4801–4807.
6. El-Osta H, Hong D, Wheler J, et al. Outcomes of research biopsies in phase I clinical trials: the MD anderson cancer center experience. *Oncologist*. 2011;16:1292–298.
7. Lemech C, Dua D, Newmark J, et al. Patients' perceptions of research biopsies in phase I oncology trials. *Oncology*. 2015;88:95–102.
8. Olson EM, Lin NU, Krop IE, et al. The ethical use of mandatory research biopsies. *Nat Rev Clin Oncol*. 2011;8:620–625.
9. Pentz RD, Harvey RD, White M, et al. Research biopsies in phase I studies: views and perspectives of participants and investigators. *Irb: a Review of Human Subjects Res*. 2012;34:1–8.
10. Peppercorn J. Toward improved understanding of the ethical and clinical issues surrounding mandatory research biopsies. *J Clin Oncol*. 2013;31:1–2.
11. Saggese M, Dua D, Simmons E, et al. Research biopsies in the context of early phase oncology studies: clinical and ethical considerations. *Oncol Rev*. 2013;7:e5.
12. Judge JM, Chianese-Bullock KA, Schroen AT, et al. Usefulness of prestudy assessment of patient willingness to undergo tissue biopsy for correlative studies in a melanoma vaccine trial. *Clin Trials*. 2013;10:143–150.
13. Yusuf RA, Rogith D, Hovick SR, et al. Attitudes toward molecular testing for personalized cancer therapy. *Cancer*. 2015;121:243–250.
14. Seah DS, Scott SM, Najita J, et al. Attitudes of patients with metastatic breast cancer toward research biopsies. *Ann Oncol*. 2013;24:1853–1859.
15. Naim F, Ballinger R, Rombach I, et al. Patient attitudes towards undergoing additional breast biopsy for research. *Breast*. 2013;22:850–855.
16. Moorcraft SY, Begum R, Cunningham D, et al. Attitudes of patients with gastrointestinal cancers toward research biopsies. *Clin Colorectal Cancer*. 2016;16(3):e181–e189.
17. Vaz-Luis I, Zeghibe CA, Frank ES, et al. Prospective clinical experience with research biopsies in breast cancer patients. *Breast Cancer Res Treat*. 2013;142:203–209.
18. Hamilton S, Hepper J, Hanby A, et al. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics*. 2007;33:229–233.
19. Morrell B, Lipworth W, Axler R, et al. Cancer as rubbish: donation of tumor tissue for research. *Qual Health Res*. 2011;21:75–84.
20. Ignatiadis M, Dawson SJ. Circulating tumor cells and circulating tumor DNA for precision medicine: dream or reality? *Ann Oncol*. 2014;25:2304–2313.
21. Butler T, Johnson-Camacho K, Peto M, et al. Exome sequencing of cell-free DNA from metastatic cancer patients identifies clinically actionable mutations distinct from primary disease. *PLoS ONE*. 2015;10:e0136407.
22. Kidess E, Jeffrey S. Circulating tumor cells versus tumor-derived cell-free DNA: rivals or partners in cancer care in the era of single-cell analysis? *Genome Med*. 2013;5:70.

23. Bryant J, Sanson-Fisher R, Fradgley E, et al. Oncology patients overwhelmingly support tissue banking. *BMC Cancer*. 2015;15:413.
24. Seah DS, Scott S, Guo H, et al. Variation in the attitudes of medical oncologists toward research biopsies in patients with metastatic breast cancer. *Oncologist*. 2015;20:992–1000.
25. Hong DS, George GC, Iwuanyanwu EC, et al. Factors related to biopsy willingness in patients with advanced cancer in a phase 1 clinic for molecularly targeted therapy. *J Cancer Res Clin Oncol*. 2013;139:963–970.
26. Brown AP, Wendler DS, Camphausen KA, et al. Performing nondiagnostic research biopsies in irradiated tissue: a review of scientific, clinical, and ethical considerations. *J Clin Oncol*. 2008;26:3987–3994.
27. Overman MJ, Modak J, Kopetz S, et al. Use of research biopsies in clinical trials: are risks and benefits adequately discussed? *J Clin Oncol*. 2013;31:17–22.
28. Abadie R, Kimmelman J, Lafleur J, et al. Consent for nondiagnostic research biopsies: a pilot study of participant recall and therapeutic orientation. *IRB: Ethics and Human Research*. 2014;36:9–15.
29. Pentz RD, White M, Harvey RD, et al. Therapeutic misconception, misestimation, and optimism in participants enrolled in phase 1 trials. *Cancer*. 2012;118:4571–4578.

How to cite this article: Robinson DH, Churilov L, Lin NU, Lim E, Seah D. Attitudes of patients with metastatic cancer towards research biopsies. *Asia-Pac J Clin Oncol*. 2017;1–8. https://doi.org/10.1111/ajco.12783