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Incidence of major hemorrhage after aggressive image-guided liver mass biopsy in the era of individualized medicine

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Abstract

Purpose: To analyze a large volume of image-guided liver mass biopsies to assess for an increased incidence of major hemorrhage after aggressive liver mass sampling, and to determine if coaxial technique reduces major hemorrhage rate.
Methods: Patients who underwent image-guided liver mass biopsy over a 15-year period (December 7, 2001–September 22, 2016) were retrospectively identified. An aggressive biopsy was defined as a biopsy event in which ≥ 4 core needle passes were performed. Association of major hemorrhage after aggressive liver mass biopsy and other potential risk factors of interest were assessed using logistic regression analysis. For the subset of aggressive biopsies, Fisher's exact test was used to compare the incidence of major hemorrhage using coaxial versus noncoaxial techniques.
Results: Aggressive biopsies constituted 11.6% of biopsy events ($N = 579/5011$). The incidence of major hemorrhage with <4 passes was 0.4% ($N = 18/4432$) and with ≥4 passes 1.2% ($N = 6/579$). In univariable models, aggressive biopsy was significantly associated with major hemorrhage (OR 3.0, 95% CI 1.16–6.92, $p = 0.025$). After adjusting for gender and platelet count, the association was not significant at the $p = 0.05$ level (OR 2.58, 95% CI 0.927–6.24, $p = 0.067$). The rate of major hemorrhage in the coaxial biopsy technique group was 1.4% ($N = 3/209$) compared to 1.1% ($N = 4/370$) in the noncoaxial biopsy technique group, which was not a significant difference ($p = 0.707$).
Conclusions: Although aggressive image-guided liver mass biopsies had an increased incidence of major hemorrhage, the overall risk of bleeding remained low. The benefit of such biopsies will almost certainly outweigh the risk in most patients.

Key words: Liver—Biopsy—High-pass—Hematoma

The world of personalized medicine - where tailored therapies are delivered after identifying vulnerable targets based on molecular abnormalities - has officially arrived and is quickly becoming the new standard of care [1, 2]. Driving this medical revolution are advances in molecular profiling and genomic analysis of harvested tissue, often obtained via image-guided percutaneous biopsy [3]. As a result, the role for image-guided percutaneous biopsy is rapidly expanding. Tissue sampling is now being requested for initial diagnosis, biomarker status, prognostic prediction, detection of progression, guidance in therapy, and increasingly for research [4].

Personalized medicine has specifically increased the demand for tissue from image-guided liver mass biopsy. Liver biopsy has been performed safely for decades [5], though major hemorrhage is the most feared adverse event and does rarely occur. Numerous studies have attempted to identify risk factors for biopsy-related hemorrhage, often with a focus on coagulation factors such as prothrombin time, activated partial thromboplastin time, and platelet count. The results of these studies and

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the recommendations thereof have been variable [6–12]. Other studies showed that biopsy-related factors such as needle caliber and number of passes did not predict hemorrhagic risk [5, 8, 13–15]. Yet, a large recent study evaluating 6613 image-guided liver biopsies found that >2 passes, platelets ≤50,000/μL, and female gender are significant risk factors for major hemorrhage [16]. While the low-risk of hemorrhage from liver biopsy has shown long-term reproducibility in the literature, there are no published data specifically addressing the safety of aggressive liver mass biopsy required in the age of personalized medicine. The data regarding liver mass biopsy are essential for determining the risk profile and future viability of liver mass biopsy for precision medicine.

The purpose of this study is to analyze a large volume of image-guided liver mass biopsies performed over a 15-year period at our institution to determine if there is an increased incidence of major hemorrhage after aggressive liver mass sampling, and to assess if a coaxial technique reduces the rate of major hemorrhage.

Material and methods

This study was approved by our institutional review board and was compliant with the Health Insurance Portability and Accountability Act. Informed consent was waived; however, all patients had previously approved inclusion of their data in research studies.

A retrospective analysis of an internally maintained biopsy registry was conducted between December 7, 2001 and September 22, 2016. This registry is composed of prospectively collected data on biopsies performed at our institution, and includes biopsy site, technique, and patient-related factors such as coagulation parameters. Adverse events related to biopsy were documented in the registry by radiology nurses, who performed routine telephone calls to the patient or his/her representative 24 h after biopsy to assess for potential adverse events. If unsuccessful, further call attempts were made at 48 and 72 h. Additionally, review of the patient's electronic medical record was performed at 24 h and 3 months following biopsy to record any acute or delayed (> 24 h after biopsy) adverse events.

All liver mass biopsies retrieved from the biopsy registry were performed with core needles. Patients excluded from this analysis include those who had multiple liver masses biopsied in the same setting ($N = 19$), patients who declined to be included in the biopsy registry ($N = 174$), those under 18 years of age ($N = 23$), and those whose data regarding the primary variable of interest could not be obtained after review of the medical record ($N = 1$). After all exclusions, there were a total of 4797 patients who underwent 5011 image-guided core needle liver mass biopsy events. A biopsy "event" was defined as an image-guided biopsy with one or more passes in the same setting. Multiple biopsy events, or settings, for a single patient, which were separated in time were considered independent of each other—each event with its own variable, temporal risk factors.

There were 3728 liver mass biopsy patients in this cohort from December, 2001 to December, 2013 that were included in a prior study evaluating the incidence of, and risk factors for, major adverse events – hematoma, infection, hemothorax, pneumothorax, death - after image-guided parenchymal and focal liver mass biopsy [16]; the current study differs in that it is focused on liver mass biopsies and the risk of major hemorrhage related to aggressive tissue sampling. Another publication assessing the role of aspirin in hemorrhage from percutaneous biopsy included this cohort as a subgroup from January, 2002 to February, 2008 [17].

Biopsy technique

Core needle liver mass biopsies were performed using real-time ultrasound guidance in 95.1% ($N = 4764/5011$) of cases (ACUSON sequoia, Siemens Medical Solutions; LOGIQ E9, GE Health Care). The liver mass biopsies were performed by one of our staff radiologists specializing in body imaging and image-guided intervention, or by a body fellow or radiology resident under direct staff supervision. Moderate sedation was given as needed by a radiology nurse under supervision of the proceduralist, but it was not administered routinely. An 18-gauge spring-loaded tray-mechanism biopsy device (Bard Monopty, CR Bard, Inc.) acquiring a 2 cm length core biopsy was used with few exceptions. Cytotechnologists were not routinely present intraprocedurally to assess adequacy of the biopsy specimen. Two core passes have historically been performed for routine liver mass biopsies at our institution, and this remains the current standard for cases requiring histopathologic analysis only. However, additional core samples are taken as necessary, including for research or precision medicine purposes, such as for the National Cancer Institute – Molecular Analysis for Therapy Choice (NCI – MATCH) clinical trial. In this trial, cytotechnologists were present in the procedural room to assess for tissue adequacy. Five diagnostic tissue cores were requested, and sometimes greater than five passes were needed to obtain adequate tissue.

We have defined ≥ 4 biopsy passes as "aggressive." For this cohort, 88% ($N = 4432/5011$) of biopsies were performed with ≤ 3 passes. Additionally, ≥ 4 passes is increasingly requested for research and personalized medicine purposes. To our knowledge, there is no guidance in the literature that has previously defined an "aggressive" number of liver core needle passes. Therefore, our rationale for defining what constitutes an "aggressive" biopsy was based on both historic and current practice trends at our institution.

The needle caliber used for noncoaxial technique biopsies was defined by the size of the core sample obtained, including 16, 18, 20, and 21-gauge samples for this cohort. Sixteen and 21-gauge core biopsies were performed rarely during the initial years of this cohort and are no longer performed with current technique. The needle caliber for coaxial technique was either reported as 17 or 19-gauge, and was based on the introducer used rather than the core sample obtained through the introducer needle (18-gauge core sample obtained through a 17-gauge introducer and 20-gauge core sample obtained through a 19-gauge introducer).

A chart review was performed on all cases where ≥ 6 passes were performed in order to identify the reason. Each case was assigned to one of six categories: no explanation identified, research, personalized medicine, lymphoma characterization, microbiologic analysis, or inadequate cores.

CT-guided liver mass biopsies were always performed with coaxial technique and accounted for 4.9% (N = 245/5011) of the biopsy events. With ultrasound guidance, the use of coaxial technique was used at the discretion of the interventionalist, most commonly if an aggressive number of passes was anticipated at the onset of the procedure or if there was concern for potential seeding of the biopsy tract. An introducer needle was used in 36% (N = 209/579) of instances when ≥ 4 passes were performed. Gel-foam is not routinely used at our institution for biopsies performed with coaxial technique. The radiology report was reviewed for all cases where ≥ 4 passes was performed to verify whether or not an introducer was used.

The coagulation guidelines used included a platelet count of 50,000/μL or greater and an international normalized ratio (INR) of 1.5 or less. Performing biopsies in patients with a lower platelet value or higher INR was at the discretion of the interventionalist and referring clinician. There were 30 biopsy events with platelet values < 50,000/μL (4 in the ≥ 4 pass group) and 70 biopsy events with INR > 1.5 (8 in the ≥ 4 pass group).

Adverse event definition

Post-biopsy hemorrhage was the major adverse event measured in this study. Major hemorrhage was standardized using criteria of grade 3 or more from the Common Terminology Criteria for Adverse Events, Version 4.0 [18]. Grade 3 hemorrhages include those necessitating blood transfusion, or radiologic, endoscopic, or surgical intervention. Life-threatening events and death constitute grades 4 and 5, respectively. Post-biopsy pain requiring admission for pain control and small hemorrhages identified on imaging were not considered significant in the absence of criteria meeting grade 3 or greater. A thorough review of the electronic medical record was performed by one author (JHB) for all cases retrieved from the biopsy registry as having a hemorrhagic complication. Post-biopsy imaging and electronic medical record review of the treatment for hemorrhage (including confirmation of blood transfusion(s) and percutaneous angiographic intervention) was performed to verify each patient that met criteria for grade 3 or greater hemorrhage.

Data collection and statistical analysis

Descriptive statistics for the liver mass biopsy cohort are provided as number of observations, median and interquartile range (IQR), or count and percentages. Comparison of baseline characteristics between groups used Wilcoxon rank-sum or Chi-square tests for continuous and categorical variables, respectively. Confidence intervals (CIs) for the estimated incidence of major hemorrhage used the Wilson/Score method. In the subset of biopsies performed with ≥ 4 passes, for comparison of major hemorrhage rates between coaxial and noncoaxial technique groups, Fisher's exact test was used.

The outcome of interest was major hemorrhage as defined above. The primary risk factor of interest was aggressive biopsy technique. Other potential risk factors included patient age at biopsy, INR, imaging modality, and needle gauge. Final models were adjusted for the effect of gender and platelet count, as a previous publication has demonstrated that these are the risk factors for major bleeding after image-guided liver biopsy [16]. Association between aggressive biopsy with incidence of major hemorrhage was analyzed using logistic regression analysis. p values and 95% confidence intervals were based on the likelihood ratio test. Platelet count was ln-transformed prior to modeling. Needle gauge was categorized by size for modeling. Variables with indications of quasi-complete separation were modeled using Firth's penalized logistic regression. Missing data were not imputed. A sensitivity analysis using general estimating equations logistic regression was performed to test for potential effect due to patients with multiple biopsies on the final multivariable model. Significance was defined as a p value < 0.05. Analysis was performed in R (version 3.4.2; Vienna, Austria).

Results

The cohort was 54.7% male, with a median [IQR] age of 64 [55–73]. A total of 11.6% of biopsies had ≥ 4 passes (N = 579/5011). The number of passes ranged from 1 to 15. The distribution for the percentage of liver mass biopsies using ≥ 4 passes by procedure year is presented in Figure 1. There were statistically significant differences between the < 4 and ≥ 4 pass groups for age, INR, imaging modality, number of passes, and needle gauge (Table 1). Significant differences were also observed between men and women for age (66 vs. 63) and platelet

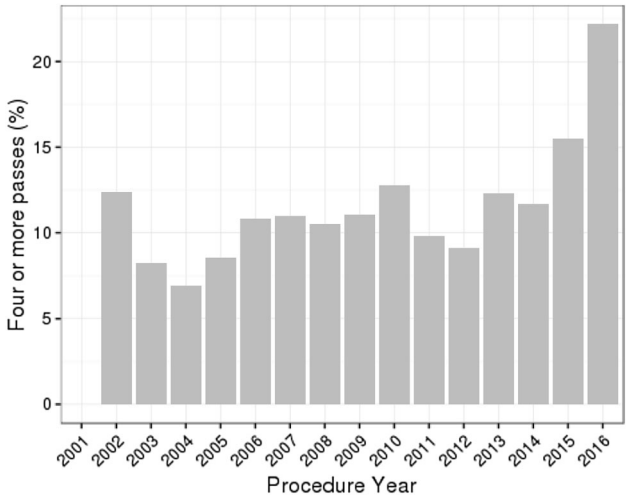

Fig. 1. Percentage of liver mass biopsies using ≥ 4 passes by procedure year.

count (229,000/μL vs. 259,000/μL), although these were not considered significant for the analysis.

The overall incidence of grade 3 or greater hemorrhage was 0.5% for the entire cohort [95% CI 0.34–0.74] ($N = 25/5011$). The incidence of major hemorrhage with < 4 passes was 0.4% [95% CI 0.26–0.64] ($N = 18/4432$), and the incidence of major hemorrhage with ≥ 4 passes was 1.2% [95% CI 0.59–2.47] ($N = 7/579$). Four or more passes were associated with a statistically significant increase in major hemorrhage [OR 3.0 (95% CI 1.16–6.92), $p = 0.025$] in the univariable logistic regression model. Recognizing the known risk associated with platelet count and gender, after adjustment, ≥ 4 passes remained associated with an increased risk of major hemorrhage but this increase was no longer statistically significant [OR 2.58(95% CI 0.927, 6.24), $p = 0.067$].

There were no significant changes in estimate or conclusion when general estimating equations models

Table 1. Descriptive statistics for the liver mass biopsy cohort comparing < 4 passes with ≥ 4 passes

	< 4 ($N = 4432$)	≥ 4 ($N = 579$)	Total ($N = 5011$)	p value
Age				0.018
Median (IQR)	65 (55, 73)	63 (53, 71.5)	64 (55, 73)	
Sex				0.119
F	2024 (45.7%)	244 (42.1%)	2268 (45.3%)	
M	2408 (54.3%)	335 (57.9%)	2743 (54.7%)	
Imaging modality				< 0.001
N Missing	3	0	3	
CT	168 (3.79%)	76 (13.1%)	244 (4.87%)	
US	4261 (96.2%)	503 (86.9%)	4764 (95.1%)	
Passes				< 0.001
Median (IQR)	2 (2, 3)	4 (4, 5)	2 (2, 3)	
Passes				< 0.001
1	265 (5.98%)	0 (0%)	265 (5.29%)	
2	2338 (52.8%)	0 (0%)	2338 (46.7%)	
3	1829 (41.3%)	0 (0%)	1829 (36.5%)	
4	0 (0%)	382 (66%)	382 (7.62%)	
5	0 (0%)	116 (20%)	116 (2.31%)	
6	0 (0%)	52 (8.98%)	52 (1.04%)	
7	0 (0%)	10 (1.73%)	10 (0.2%)	
8	0 (0%)	11 (1.9%)	11 (0.22%)	
9	0 (0%)	2 (0.345%)	2 (0.04%)	
10	0 (0%)	3 (0.518%)	3 (0.06%)	
12	0 (0%)	2 (0.345%)	2 (0.04%)	
15	0 (0%)	1 (0.173%)	1 (0.02%)	
Needle gauge				< 0.001
16	43 (0.97%)	2 (0.345%)	45 (0.898%)	
17 (Introducer)	114 (2.57%)	181 (31.3%)	295 (5.9%)	
18	4007 (90.4%)	358 (61.8%)	4365 (87.1%)	
19 (Introducer)	66 (1.49%)	28 (4.84%)	94 (1.88%)	
20	198 (4.47%)	10 (1.73%)	208 (4.15%)	
21	4 (0.09%)	0 (0%)	4 (0.08%)	
INR				0.047
N Missing	18	2	20	
Median (IQR)	1 (1, 1.1)	1 (1, 1.1)	1 (1, 1.1)	
Platelet count				0.467
N Missing	25	4	29	
Median (IQR)	243 (186, 310)	238 (180, 304)	242 (185, 309)	

17 and 19-gauge represent biopsies performed using introducer needles used for 18 and 20-gauge coaxial biopsy technique, respectively. INR, international normalized ratio; CT, computed tomography; US, ultrasound; IQR, interquartile range; N-Miss, number of patients in the registry with missing data

were used for the final multivariable modeling. Both imaging modality and needle gauge were assessed using Firth's penalized logistic regression. None of the other potential risk factors of interest were significant after adjustment for gender and platelet count [INR OR 0.628 (0.039–4.59), $p = 0.72$; Age (/10 years) OR 0.939 (0.715–1.26), $p = 0.66$; imaging modality CT vs. US OR 1.32 (0.146–5.17), $p = 0.76$; needle gauge 16 vs. 18 OR 1.86 (0.15–14.3), 20 vs. 18 OR 1.6 (0.318–5.04), $p = 0.69$].

None of the patients with an INR > 1.5 had major post-biopsy hemorrhage. There was one patient with a platelet value $< 50{,}000/\mu L$ that had major hemorrhage. The pre-procedural platelet value was 16,000/μL, and no platelets were transfused prior to the biopsy. Two passes with an 18-gauge core needle were performed. The patient experienced a major post-biopsy hemorrhage and underwent percutaneous angiography with successful coil embolization of an active hepatic arterial bleed.

The incidence of major hemorrhage for each pass number is presented in Table 2. Interestingly, all major hemorrhages in the aggressive biopsy group occurred in patients undergoing exactly 4 passes; 5–15 passes were performed in 3.9% of biopsy events ($N = 197/5011$) without major hemorrhage.

There were 81 biopsy events where ≥ 6 passes were performed. For the 57% ($N = 46/81$) of cases in which there was an identifiable reason for the number of passes, 30% ($N = 14/46$) were done for research, 28% ($N = 13/46$) for personalized medicine, 13% ($N = 6/46$) to obtain adequate tissue to characterize lymphoma, 11% ($N = 5/46$) to obtain additional tissue for microbiologic analysis, and 17% ($N = 8/46$) performed due to poor samples obtained during biopsy, such as necrotic/fragmented cores. All biopsies performed with 10, 12, or 15 passes ($N = 6$) were done for personalized medicine purposes, and a cytotechnologist was present in the room to inform the proceduralist when adequate diagnostic material had been obtained.

The descriptive statistics for the coaxial and non-coaxial technique biopsy groups are included in Table 3. Among those who had ≥ 4 passes, the rate of major hemorrhage in the coaxial technique group was 1.4% [95% CI 0.49–4.13] ($N = 3/209$) and in the noncoaxial technique group 1.1% [95% CI 0.42–2.75] ($N = 4/370$). No significant difference was found between these groups in major hemorrhage incidence ($p = 0.707$).

Table 2. Incidence of major hemorrhage for each pass number

Passes	Number of hemorrhages	Total *N*	OR[95% CI]
1	2	265	0.75 (0.21–2.71)
2	4	2338	0.17 (0.07–0.44)
3	12	1829	0.66 (0.38–1.14)
4	7	382	1.83 (0.89–3.73)
5	0	116	0 (0–3.21)
6	0	52	0 (0–6.88)
7	0	10	0 (0–27.75)
8	0	11	0 (0–25.88)
9	0	2	0 (0–65.76)
10	0	3	0 (0–56.15)
12	0	2	0 (0–65.76)
15	0	1	0 (0–79.35)

Three patients died within 30 days of liver biopsy (0.06%, $N = 3/5011$);one of the deaths was directly related to biopsy. These patients were included in a previous cohort [16]. The death directly related to biopsy involved a 67-year-old female that underwent ultrasound-guided liver mass biopsy with four 18-gauge passes to establish a diagnosis of metastatic renal cell carcinoma. Her pre-procedure hemoglobin was 13.6 g/dL, platelets 179,000/μL, and INR 0.9. An introducer was not used to perform the biopsy. The patient had an uneventful course post-procedurally and began taking low-molecular-weight heparin 30 h after biopsy. She subsequently presented three days after the procedure with hypotension and a large perihepatic hematoma. Despite aggressive treatment, she died 10 days later from multiorgan system failure related to hemorrhagic shock.

The other two patient deaths appeared to be related to underlying medical causes rather than liver mass biopsy. A 57-year-old male who died within 24 h after biopsy had originally presented with myocardial infarction from left anterior descending artery occlusion. He developed acute gastrointestinal bleeding, and numerous liver lesions were incidentally discovered on an ultrasound performed for acute renal failure. At the time of liver mass biopsy, his hemoglobin was 9.8 g/dL, platelets 193,000/μL, and INR 1.1. Three 18-gauge passes were performed under ultrasound guidance without an introducer. There was no evidence of bleeding after the procedure on ultrasound. The patient had been intubated and on pressor support for hypotension prior to the biopsy, but the evening after the biopsy his hypotension worsened, presumably related to worsening acute cardiac failure. Given the new diagnosis of metastatic disease in the liver, and poor prognosis from the acute myocardial infarction, the family elected to withdraw care, and the patient died.

The third death was a 79-year-old male with chronic lung disease who underwent CT-guided liver mass biopsy, using an intercostal approach, with four 20-gauge passes obtained through a 19-gauge introducer needle. He presented less than 24 h after biopsy with respiratory distress due to a large hemothorax that required chest tube placement for decompression. Pre-procedural laboratory values included a hemoglobin 15.5 g/dL, platelets 191,000/μL, and INR 1.0. While the hemothorax was considered secondary to injury of an intercostal vessel during liver mass biopsy, his respiratory status improved significantly over the next 24 h from treatment with a chest tube. However, during the hospital admission, he was diagnosed with metastatic lung cancer to the brain, mediastinum, and liver. Aggressive care was withdrawn 4 days after liver mass

Table 3. Descriptive statistics for coaxial and noncoaxial ≥ 4 pass cohort

	Introducer (N = 209)	No Introducer (N = 370)	Total (N = 579)	p value
Gender				0.782
M	123 (58.9%)	212 (57.3%)	335 (57.9%)	
F	86 (41.1%)	158 (42.8%)	244 (42.1%)	
Imaging modality				< 0.001
CT	76 (36.2%)	0 (0%)	76 (13.1%)	
US	133 (63.6%)	370 (100%)	503 (86.9%)	
Needle gauge				< 0.001
16	0 (0.0%)	2 (0.5%)	2 (0.3%)	
17 (Introducer)	181 (86.6%)	0 (0.0%)	181 (31.3%)	
18	0 (0.0%)	358 (96.8%)	358 (61.8%)	
19 (Introducer)	28 (13.4%)	0 (0.0%)	28 (4.84%)	
20	0 (0.0%)	10 (2.7%)	10 (1.73%)	
Passes				< 0.001
Median (IQR)	5 (4, 6)	4 (4, 4)	4 (4, 5)	
Passes				< 0.001
4	80 (38.1%)	302 (81.6%)	382 (66%)	
5	69 (32.9%)	48 (13.0%)	116 (20%)	
6	35 (16.7%)	17 (4.6%)	52 (9.0%)	
7	8 (3.81%)	2 (0.5%)	10 (1.7%)	
8	11 (5.24%)	0 (0%)	11 (1.9%)	
9	1 (0.476%)	1 (0.3%)	2 (0.3%)	
10	3 (1.43%)	0 (0%)	3 (0.5%)	
12	2 (0.952%)	0 (0%)	2 (0.3%)	
15	1 (0.476%)	0 (0%)	1 (0.2%)	

17 and 19-gauge represent biopsies performed using introducer needles used for 18 and 20-gauge coaxial biopsy technique, respectively. CT, computed tomography; US, ultrasound; IQR, interquartile range

biopsy, and the patient subsequently died, presumably related to his metastatic disease.

Discussion

The results of this large study of 5011 image-guided liver mass biopsies over a 15-year period at our tertiary care center demonstrate that the incidence of major hemorrhage was low at 0.5%. This is the same incidence of major hemorrhage for much of this cohort when previously analyzed for bleeding from both parenchymal and liver mass biopsies [16], and is similar to other published data [7, 13].

The importance of image-guided biopsy for the development and widespread implementation of precision medicine cannot be overstated. However, image-guided biopsy is only of value if it results in tissue adequacy. Poor sample quality led to a recent large precision medicine trial being paused for interim analysis since only 87% of cases submitted had enough tissue to complete tumor testing [19]. A research consensus panel by the Society of Interventional Radiology in 2016 highlighted the future challenge of obtaining sufficient and representative tissue reliably for genomic analysis [4]. Developments in needle design, steerable needle technologies, and standardization of biopsy technique (e.g., type of device, needle gauge, and number of passes) are active areas of research and discussion in an effort to produce high diagnostic yield rates.

To accommodate the tissue acquisition demands of precision medicine in our own practice, the most significant change in biopsy technique has been performing an increased number of passes. Thacher et al proved that tumor cellularity was significantly associated with the number of tissue samples obtained [20]. Concomitant with a recent increase in requests to obtain tissue for genomic and molecular testing, our percentage of liver mass biopsies with ≥ 4 passes substantially increased to 22.2% in 2016, much higher than the range of 6.9–12.4% from 2002 to 2014. We expect this percentage to trend upward over the forthcoming years.

Our data show that the incidence of major hemorrhage for ≥ 4 passes remained low at 1.2%. While this was higher than the 0.4% incidence of major hemorrhage in liver mass biopsies performed with < 4 passes, the difference did not remain statistically significant when taking other known risks of low platelets and female gender into account. This suggests that platelets and gender may play a stronger role in the risk of major hemorrhage compared to number of passes. Interestingly, Kitchin et al implemented less-stringent departmental pre-procedural platelet and INR guidelines for image-guided liver biopsy (INR ≤ 2.0 and platelets ≥25,000/μL) [12]. After reviewing 1199 biopsies performed with these guidelines, the major hemorrhage rate remained low at 1.6%. The above data reinforce the favorable safety profile of image-guided liver biopsy.

While our data did not show that an aggressive number of passes was significantly associated with major hemorrhage after adjusting for other known risk factors, given the low number of complications which limited statistical power and the odds ratio of 2.58 for ≥ 4 passes, the data do, however, suggest that aggressive sampling

may still increase the risk of biopsy-related major hemorrhage. Interestingly, all major hemorrhages in the aggressive biopsy cohort occurred in patients undergoing exactly 4 passes, while no major hemorrhage occurred within the range of 5–15 passes. However, the number of biopsies performed in the 5–15 pass range was small, and additional data will be necessary to assess for any potential incremental increase in risk with an increasing number of biopsy passes.

Traditionally, a coaxial technique has been used to decrease the number of liver capsule punctures in high pass biopsies, and therefore theoretically decrease the risk of bleeding. Our data show that performing ≥ 4 liver mass biopsies using coaxial technique with an introducer had an unexpectedly higher incidence of major bleeding events compared to biopsies without an introducer. This difference was not significant, and it should be noted that the low incidence of major hemorrhage in this cohort subset ($N = 7/579$) likely limits any reliable conclusions that can be drawn from the data.

There are several important limitations with this study. First, the low incidence of biopsy-related major hemorrhage limits power for statistical analysis, including our ability to assess for potential interactions among variables. For example, as our biopsy registry grows, we may be able to better assess the role of coaxial technique in liver mass biopsy in the future. Second, there may be instances where patients who experienced an adverse event were lost to follow-up and were not captured in the biopsy registry during electronic medical record review. Third, our biopsy registry is maintained by multiple radiology nurses and includes a large number of data points on thousands of patients over a long period of time. While we would hope for 100% accuracy, we do acknowledge that some errors/omissions are inevitable. Finally, inherent selection biases in biopsy technique are unavoidable over time, with operators modifying technique based on perceived risks, such as tumor size or location, not considered prospectively.

Conclusion

Although aggressive image-guided liver mass biopsies had an increased incidence of major hemorrhage, the overall risk of bleeding remained low. The benefit of such biopsies will almost certainly outweigh the risk in most patients.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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