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Distribution of dysplasia and cancer in the gallbladder: An analysis from a high cancer-risk population

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Abstract

Gallbladder dysplasia can progress to cancer and may be associated with increased cancer risk at other biliary tract sites. Thus, its accurate identification is relevant both for etiologic understanding and for clinical purposes. Data on the frequency and distribution of gallbladder dysplasia are lacking due to limited gallbladder sampling and inability to visualize dysplasia grossly.

An expert pathology group used consensus criteria to review 140 totally sampled consecutive cholecystectomy specimens from Chilean women. Three cases (2%) revealed incidental invasive carcinoma, all T2, along with high-grade dysplasia (HGD). The surface area covered by dysplasia

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or cancer in these cases was 9%, 37%, and 87%. Although the first longitudinal (“diagnostic”) section of the whole gallbladder captured HGD or cancer in all three cases, the deepest focus of invasive carcinoma was not present in this section. Fourteen additional cases (10%) had low-grade dysplasia (LGD), which was typically very focal (covering <5% of the surface) and most often occurred in the fundus. LGD was not present in the diagnostic section of five cases (38%) and would have been missed without additional sampling. None of the cancers or dysplasias were grossly visible. Although HGD and carcinoma are likely to be identified in “diagnostic” sections, accurate staging requires total sampling. LGD is typically very focal and would often be missed in routine practice. To identify cancer precursors, additional sampling, particularly of the fundus, may be warranted. The predominance of LGD in the fundus also provides etiologic insight, supporting the contribution of gallstones and chronic inflammation.

Keywords

dysplasia; invasive carcinoma; gallbladder cancer; sampling; histopathology

Introduction

Gallbladder cancer is a highly lethal disease, with 5-year survival rates ranging from 5% to 20% [1–3]. Although the incidence of gallbladder cancer is low in much of the industrial world (e.g., 0.9 per 100,000 women and 0.5 per 100,000 men in the United States; 0.6 per 100,000 women and 0.3 per 100,000 men in the United Kingdom), the incidence is much higher in certain geographic regions, such as southern-central Chile, where the incidence is 21.2 per 100,000 women and 6.8 per 100,000 men [3]. While very superficial cancers can be cured through cholecystectomy [4], most cancers have spread by the time of diagnosis. Understanding the mechanisms and clinical/epidemiologic associations of gallbladder dysplasia offers the best chance for prevention of gallbladder cancer. Since the gallbladder is a model of the inflammation-carcinoma sequence [5], improving our understanding of this model and how inflammation contributes to the progression from chronic cholecystitis to metaplasia, dysplasia, and cancer could have implications for our understanding of carcinogenesis in other organs as well.

In addition, gallbladder dysplasia could reflect a field effect (*i.e.*, individuals with gallbladder dysplasia may be at increased risk of developing cancer in other parts of the biliary tract) [6–9]. To fully evaluate the risk of biliary tract cancer in patients with gallbladder dysplasia, we need to accurately identify gallbladder dysplasia. Properly identifying all outcomes of interest (including pre-malignant lesions such as high- and low-grade dysplasia) is important to facilitate research to identify biomarkers for these outcomes, which could lead to early detection and treatment.

Data on the frequency and clinicopathologic associations of early precursor lesions in the gallbladder are sparse, largely because of the limited sampling of this organ and partly due to the variability of diagnostic criteria. Sampling can affect estimates of the frequency and location of pre-malignant lesions in the gallbladder. In standard practice, routine sampling of gallbladders removed through cholecystectomy typically involves only a few sections of the

gallbladder. In areas with high-risk of gallbladder cancer, sampling may involve a diagnostic sample across the length of the gallbladder, which may lead to additional sampling based on the findings in the first section. Such limited sampling may miss important lesions, particularly low-grade gallbladder dysplasias.

The lack of proper understanding of the precursor lesions in the gallbladder is also partly attributable to the lack of agreement in the diagnosis of what constitutes dysplasia. In 2014, international consensus criteria were put forth for the diagnosis of dysplasia in a meeting held in Santiago, Chile [10].

In this study, we totally sampled 140 gallbladders from cholecystectomy patients in a high-risk region of Chile. We characterized the frequency of dysplasia and cancer, the percent area covered by these lesions, and the location of these lesions in the gallbladder. As a secondary aim, we explored the association of gallbladder dysplasia and cancer with sociodemographic characteristics and other histopathologic features. Gallbladders were evaluated by expert pathologists from two continents using the recently established consensus criteria.

Materials and Methods

Study Population

From January 2013 to September 2014, we consecutively recruited 140 consecutive elective female cholecystectomy patients (aged 40–60 until January 2014 and all ages thereafter) at two public hospitals in Temuco and Pucón, Chile. Both hospitals are located in the area of Chile at highest risk of gallbladder cancer and serve patients who are covered under public health insurance. We identified cholecystectomy patients and recruited patients who did not have a previous diagnosis of cancer (other than non-melanoma skin cancer). The study was approved by institutional review boards of the US National Cancer Institute, Pontificia Universidad Católica, and the Chilean Ministry of Health. All participants provided written consent.

Gallbladder Processing

All 140 gallbladders were processed at the Department of Pathology at Dr. Hernán Henríquez Aravena Hospital in Temuco, which serves as the pathology referral center for the region; all local public hospitals send cholecystectomized gallbladders to this pathology department. Once received at the Temuco Department of Pathology, each gallbladder was stretched and pinned over a solid paraffin plate to allow for fixation in a 10% buffered formalin bath overnight. A macroscopic photograph was taken of the mucosal side of the gallbladder (Fig. 1). To facilitate molecular analyses for future studies, in 32 gallbladders, approximately 8 sections were taken prior to fixation and frozen at -80°C . The remainder of the gallbladder was fixed and processed into FFPE blocks. The day after fixation, the hepatic side, serosal surface, cystic duct margin, and (after the cystic duct margin was removed) remaining free edge were stained per the study protocol (blue for the hepatic side, red for the serosal surface, and yellow for the cystic margin and free edge). Once staining was complete, the ink was set using a 5% solution of alcohol acetic acid. Longitudinal cuts

approximately 8 mm apart were made from the fundus to the cystic duct. Horizontal cuts were made over the longitudinal cuts, with a maximum length of 2.8 cm.

Another macroscopic photograph was taken documenting the sections that were created after the entire gallbladder had been cut (*i.e.*, totally sampled). Each section of the gallbladder was then systematically numbered starting from the bottom left corner of the fundus and proceeding left-to-right to end at the cystic duct. Depending on the thickness of the gallbladder, two to four consecutive sections were included in the same FFPE block. The mean number of blocks created was 7.8 (standard deviation [SD]: 3.3). The specimen was then sent to the pathologist along with the macroscopic photograph of the cut gallbladder, which allowed for the correct orientation of the slides upon examination and creation of slides.

Outcome Definition

All gallbladders were reviewed at three locations (Temuco, Santiago, and Atlanta, Georgia) and were classified according to international consensus criteria for the diagnosis of dysplasia [10]. The final diagnosis was determined by consensus review with adjudication of discrepant cases by a panel of nine pathologists from Chile and the United States. In cases where there was disagreement, the final diagnosis was based on the diagnosis of the majority. The primary outcomes of interest were cancer, high-grade dysplasia (HGD), and low-grade dysplasia (LGD). Secondary outcomes of interest included intestinal metaplasia (IM) and pseudopyloric metaplasia (PM), which were defined based on agreement of at least two out of three pathologists in the original pathology review. For some cases, IM ($n = 11$) and PM ($n = 10$) were not evaluated by all three pathologists. These cases were considered missing for IM and PM in analysis. Fig. 2 shows examples of normal gallbladder epithelium with minimal subadjacent inflammatory infiltrate and each primary and secondary outcome.

Statistical Analysis

We evaluated associations between outcomes and sociodemographic and histologic characteristics. Welch's two sample t-tests were used for continuous variables and Pearson's chi-squared tests with Yates' continuity correction were used for categorical variables. Using multivariate logistic regression models, we also calculated odds ratios (ORs) and 95% confidence intervals (CIs) adjusting for age and education (measured categorically: none/primary [≤ 6 years completed]; Jr. middle [7-9 years completed]; Sr. middle [10-12 years completed]; some college [≥ 13 years completed]). In addition, we conducted a sensitivity analysis excluding 32 patients with fresh frozen samples, since fresh frozen blocks were not histopathologically evaluated.

Percent area covered by cancer, HGD, or LGD on each slide was determined through pathology review. We used the average area of the slides with cancer, HGD, or LGD that underwent pathology review to estimate the total area for each gallbladder. The cystic duct margin was assumed to cover an area of 1 cm². To evaluate the proportion of lesions that occurred in the fundus, body, and neck of the gallbladder, we divided the number of sections with LGD in each region (*i.e.*, fundus, body, neck) by the total number of sampled sections in that region to calculate the proportion of sections with LGD by region. We then calculated

a weighted average for each region of the gallbladder to account for the number of sections that each case contributed to each region.

Analyses were conducted in R (R Foundation, Vienna, Austria). We also used STATA version 13 (StataCorp LP, College Station, TX) to obtain 95% CIs for the prevalence estimates.

Results

The mean age of the 140 female cholecystectomy patients included in this study was 48 (SD 7, range 37–69) years. The majority were Chilean Hispanic ($n = 78$, 55%), had symptoms of intense abdominal pain ($n = 123/135$ with complete data, 91%), and had a family history of gallstones ($n = 72/139$ with complete data, 52%). Body mass index (BMI) was relatively high, with a mean of 30 (SD: 5). More than a third (37%) of the patients had hypertension, and more than 27% were ever smokers.

Seventeen of the 140 participants (12%, 95% CI 7–19%) had the primary outcomes of gallbladder cancer ($n = 3$, 2%, 95% CI: 0.4–6%) or dysplasia ($n = 14$, 10%, 95% CI 6–16%). All cancer cases were T2 (Fig. 2F), and all cases of dysplasia without cancer were low-grade (Fig. 2D). The prevalence of histological abnormalities was similar if the 32 patients who had fresh frozen samples taken were excluded ($N = 108$): 2 (2%) with cancer and 13 (12%) with LGD only. Compared with patients without cancer or dysplasia, those with cancer or dysplasia were more likely to have IM with or without PM (76% vs. 23%, Table 1).

IM was clearly associated with cancer/dysplasia (OR 10.0, 95% CI 3.1–39.3) (Table 1), even after adjusting for the presence of PM (OR 9.8, 95% CI 2.9–39.9). In contrast, the magnitude of the OR for the association between PM and cancer/dysplasia was much lower and not statistically significant (OR 2.1, 95% CI 0.7–7.3). After adjusting for the presence of IM, the association essentially disappeared (OR 1.3, 95% CI 0.4–4.8). The relation between epidemiological characteristics and gallbladder cancer/dysplasia was difficult to evaluate given the small number of outcomes. However, patients with cancer or dysplasia tended to be less educated, to have higher BMI, and to be Mapuche (the major Amerindian group in Chile) (Table 1). There was some suggestion that smoking was protective (Table 1).

The area of the gallbladder covered by cancer or dysplasia varied widely in the three cancer cases. In the first case, cancer only covered 0.5% (Table 2), but HGD covered 29% and LGD 7%, for a total of 37% covered by dysplasia or cancer. In the second case, cancer covered 8% and HGD 1%, for a total of 9% covered by dysplasia or cancer. The third case had 85% covered by cancer and 2% covered by HGD, for a total of 87% covered by dysplasia or cancer. Although the first longitudinal section taken from the whole gallbladder (*i.e.*, fundus, body, and neck) captured HGD or cancer in all three cancer cases, the deepest focus of invasive carcinoma was not present in this section in any of the cases. In addition, none of the cancers were grossly visible, including the case where cancer covered 85.2% of the surface of the gallbladder epithelium (Fig. 1). We had lesion area and location information for 13 of the 14 LGD cases without cancer. The vast majority (8/13, 62%) of LGD lesions in these cases covered a small area (<5%) of the gallbladder (Table 2). The mean coverage was

5% (median: 3%), with a range from 0.2% to 16%. LGD was not present in the diagnostic section for five (38%) of these cases. None of LGD lesions were grossly visible. Thus, these cases would have been missed without additional sampling.

In addition to analyzing percent coverage of the lesions, we also analyzed the location of these lesions in the gallbladder. The first and third cancer cases had at least one LGD, HGD, or cancerous lesion detected in 100% of the sampled sections in both the fundus and the body of the gallbladder; in the neck, 57% and 78% of the sampled sections had at least one lesion, respectively. In the second case, however, only 43% of the sections in the fundus, 25% of the sections in the body, and 17% of the sections in the neck had at least one lesion.

Among the 13 LGD cases with lesion location information, the weighted average of sections with at least one LGD lesion was 51% in the fundus, 26% in the body, and 8% in the neck (Fig. 3). Only 1 of the 13 LGD cases had no lesions in the fundus.

Discussion

Gallbladder dysplasia may be missed through incomplete sampling. Identification of gallbladder dysplasia may have implications for clinical practice since individuals with dysplasia may progress to cancer and may be at increased risk of developing cancer at other sites in the biliary tract even after the gallbladder is removed [6, 9]. Missing these lesions also has implications for research since we need to accurately identify patients with dysplasia to identify biomarkers and risk factors for dysplasia. Our study represents the first systematic evaluation of total sampling of the gallbladder in over 20 years and is the only study published to date using the 2014 consensus criteria.

To characterize the true distribution of gallbladder dysplasias in a high-risk region of Chile, we completely sampled the gallbladders from 140 female cholecystectomy patients. We found gallbladder cancer ($n = 3$) or dysplasia without cancer ($n = 14$) in 12% (95% CI 7–19%) of the cholecystectomy patients from this high-risk region. The predominance of dysplastic lesions in the fundus of the gallbladder provides etiologic insight, supporting the contribution of gallstones and chronic inflammation, which occur primarily in the fundus [11]. Evaluating molecular changes from the fundus through the neck may increase our understanding of gallbladder carcinogenesis. In addition, IM was associated with dysplasia and cancer, as seen in other studies [12, 13], supporting its role as an important step in the gallbladder carcinogenesis process. Evaluation of molecular changes, such as genetic variation or immune response, across the natural history of disease from chronic cholecystitis through IM, LGD, HGD, and cancer may help elucidate the crucial aspects of disease progression.

In our study, all three cancer cases were identified in the first longitudinal section of the whole gallbladder (*i.e.*, tissue fragments from the fundus, body, and neck). HGD was present in all of these cases, similar to a 1993 study of precancerous lesions in totally sampled gallbladders from 32 Chilean gallbladder cancer cases, which found dysplasia in 81% of cases [14]. Two out of the three cancers would have been identified using routine sampling of one longitudinal section from the neck, body, and fundus of the gallbladder regardless

of where it was taken given that lesions were found in 100% of the sections in both the body and the fundus. However, it is possible that a different section may have missed one of the cancer cases, since only 9% of the gallbladder was covered in lesions, and more than half of sampled sections in the fundus, body, and neck had no lesions present. In addition, the deepest focus of invasive carcinoma was not present in the first section, indicating that if cancer is identified, total sampling is required to accurately identify the extent of invasion. This requirement has important clinical implications since depth of invasion is tied to stage, and stage is strongly associated with prognosis [3]. In patients without cancer, most dysplasias covered less than 5% of the gallbladder, and no dysplasia covered more than 20% of the gallbladder. Thirty-eight percent of LGD cases in this study would have been missed if only a single diagnostic section across the gallbladder had been taken. Since most dysplastic lesions occurred in the fundus, additional sampling of the fundus may increase identification of these lesions. Taken together, these findings suggest that many gallbladder dysplasias and perhaps some cancers may be missed by traditional sampling methods.

Few published studies have employed total sampling of the gallbladder. In 1993, Duarte *et al.* evaluated totally sampled gallbladders from 162 cholecystectomy patients in Chile and found carcinoma in situ in 2.5%, dysplasia in 16%, IM in 58%, and PM in 95% [13]. Nearly 25 years later, we identified a similar proportion of cancers (2%) to the Duarte study and a slightly lower proportion of patients with dysplasia (10%), although the 95% CI of 6-16% suggests that the prevalence may be comparable. Duarte *et al.* found that reviewing three samples representing one longitudinal section of the whole gallbladder (*i.e.*, fundus, body, and neck) would miss 65% of cases with dysplasia, and reviewing one random section alone would miss 85% [13]. Our results are similar; 62% of dysplastic lesions in patients without cancer covered less than 5% of the gallbladder, and 38% of these lesions would have been missed with one longitudinal section. Another study retrospectively evaluated formalin-preserved gallbladders from 72 primary sclerosing cholangitis patients who had undergone orthotopic liver transplant at Mayo Clinic in Rochester, Minnesota [7]. In this high-risk population, adenocarcinoma was identified in 10 (14%) gallbladders, dysplasia in 27 (37.5%) [15 HGD (21%) and 12 LGD (17%)], IM in 36 (50%), and PM in 69 (96%). The higher prevalence of cancer and dysplasia in this population with patients with primary sclerosing cholangitis is not surprising, especially compared to our population of routine cholecystectomies for gallstone disease, where all lesions were incidental. What is similar, however, is that the authors found that many of the dysplastic lesions were not present in the initial sections and thus would have been missed without additional retrospective sampling. Taken together, the results from the few studies that have conducted total sampling of the gallbladder strongly suggest that extensive sampling is needed to identify gallbladder dysplasia.

These findings inform a current debate in the literature as to whether cholecystectomized gallbladders should be routinely examined histologically and if so, to what extent. Some argue against routine sampling of the gallbladder, while others contend that routine sampling is necessary, especially in areas at high-risk of gallbladder cancer [15–24]. In our study, none of the three cancers were macroscopically visible. In addition, increased sampling leads to increased detection of gallbladder dysplasia and cancer [25], and the results of

our study suggest that many dysplastic lesions would have been missed without extensive sample.

The importance of detecting gallbladder cancer is clear, but accurate detection of gallbladder dysplasia may also have clinical implications. A recent study of patients with primary sclerosing cholangitis found that patients with gallbladder dysplasia, regardless of degree, were more likely to have cholangiocarcinoma and/or intrahepatic bile duct dysplasia, providing clinical evidence of a field effect in the biliary tract [7]. Patients without primary sclerosing cholangitis but with synchronous gallbladder and bile duct cancers also have been observed to have extensive dysplasia throughout the biliary tract [8]. A recent case report identified p53 over-expression in the normal epithelium of the cystic duct surgical stump after cholecystectomy for gallbladder cancer; the patient developed cancer in the bile duct 2.5 years after surgery, providing additional support for a field effect [26]. Furthermore, gallbladder cancer patients have a strongly increased risk of developing cholangiocarcinoma compared to the general population, with standardized incidence ratios of 11.8 (95% CI 1.4–42.6) for 40–59 year olds, 8.50 (95% CI 3.42–17.52) for 60–79 year olds, and 13.23 (95% CI 3.6–33.87) in 80+ year olds [9]. Although the absolute incidence varies for gallbladder, bile duct, and ampulla of Vater cancers, the age-specific incidence increases at the same rate across these sites, which together with the common embryologic origin of these organs (the embryonic foregut), supports a field effect [27].

This study has a number of strengths. It was conducted in a region with high-risk of gallbladder cancer where a standardized total gallbladder sampling procedure for gallbladders with dysplasia detected in the diagnostic sample has been in place for many years. In this study, we expanded this procedure to include every gallbladder, regardless of whether lesions were present in the first longitudinal section taken from the whole gallbladder. In addition, we conducted extensive pathology review, with an initial review by pathologist at three different locations and then a consensus panel review by nine pathologists from Chile and the United States. The study also has limitations. Frozen sections were not histologically evaluated. Thus, lesions in these sections could have been missed. The prevalence of histological abnormalities was similar if gallbladders with frozen sections were excluded, however. Although our study is similar in size to the previous study from Chile, our sample was small, which limited comparisons between dysplasia and cancer. Additional studies are needed to compare the prevalence and distribution of gallbladder dysplasia from this population at high-risk of gallbladder cancer to the prevalence in low-risk populations.

In conclusion, through total sampling of the gallbladder, we identified gallbladder dysplasia and cancer in 12% of cholecystectomy patients in a region of Chile that has among the highest rates of gallbladder cancer in the world. Many of the dysplastic lesions were quite small, covering less than 5% of the gallbladder, and would likely have been missed with normal, limited sampling. Accurate identification of gallbladder dysplasia may have clinical implications given the field effect in the biliary tract and potentially increased risk of developing cancer at other sites in the biliary tract. In addition, detection of gallbladder dysplasia is important for research so that the biologic behavior of and risk factors for gallbladder dysplasia can be better understood and so that biomarkers for dysplasia might

be identified. Taken together, these findings suggest that more extensive sampling of the gallbladder may be warranted, particularly in areas at high risk of gallbladder cancer.

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Highlights

- A single longitudinal section of the gallbladder often misses low-grade dysplasia
- Total sampling is needed for accurate staging of gallbladder cancer
- Low-grade dysplasia often occurs most in the fundus
- This predominance supports the role of gallstones and chronic inflammation

Fig. 1.

Gross image of a gallbladder with carcinoma. In this case, 85% of the gallbladder is involved with cancer.

Fig. 2. Hematoxylin & eosin stained microscopic images of normal gallbladder epithelium with minimal subadjacent inflammatory infiltrate (A), pseudopyloric metaplasia (B), intestinal metaplasia (C), low-grade dysplasia (D), high-grade dysplasia (E), and invasive cancer (F). $\times 400$.

Fig. 3.

Proportion of sampled sections containing low-grade dysplasia (LGD) by region.

Table 1.

Epidemiologic and pathologic characteristics of female cholecystectomy cases (N = 140) and associations with gallbladder dysplasia and cancer.

Cancer/Dysplasia (N = 17)							No Cancer or Dysplasia(N = 123)			p-value [‡]	OR for Gallbladder Cancer/Dysplasia OR [95% CI] ^{‡§}			
Mean ± SD	n (%)	N	Mean ± SD	n (%)	N									
Pathologic characteristics														
Intestinal metaplasia (at least two reviewers) ^{*‡}							26	(23%)	112	<0.001	10.0 [3.1, 39.3]			
Pseudopylorica metaplasia (at least two reviewers) ^{*‡}							58	(51%)	113	0.22	2.1 [0.7, 7.3]			
Epidemiologic characteristics														
Age							48 ± 7		17	49 ± 7	123	0.88	1.0 [0.9, 1.0]	
Education [*]														
None/primary (6 years completed)							9	(53%)	17	35	(29%)	121	0.20	Referent
Jr. Middle (7-9 years completed)							2	(12%)	17	34	(28%)	121		0.2 [0.0, 0.9]
Sr. Middle (10-12 years completed)							4	(24%)	17	40	(33%)	121		0.4 [0.1, 1.2]
Some college (13 years completed)							2	(12%)	17	12	(10%)	121		0.6 [0.1, 2.8]
Ethnicity [‡]														
Chilean Hispanic							7	(41%)	17	71	(58%)	123	0.30	Referent
Mapuche (Amerindian group)							10	(59%)	17	49	(40%)	123		2.0 [0.6, 7.2]
European							0	(0%)	17	5	(4%)	123		--
BMI							33 ± 6		17	30 ± 5		123	0.08	1.1 [1.0, 1.3]
Smoking (ever) [*]							1	(6%)	17	37	(30%)	122	0.07	0.2 [0.0, 0.9]
Symptoms (intense abdominal pain) [*]							16	(94%)	17	107	(91%)	118	0.72	0.8 [0.2, 1.4]
Family history of gallstones [*]							7	(41%)	17	65	(53%)	122	0.50	0.6 [0.2, 1.9]
Family history of gallbladder cancer [*]							0	(0%)	17	3	(2%)	122	1	--

^{*} N<140 due to missing data

[‡] Reference group: ethnicity (ref = Chilean Hispanic); intestinal metaplasia (ref = intestinal metaplasia identified by less than 2 reviewers); pseudopyloric metaplasia (ref = pseudopyloric metaplasia identified by less than 2 reviewers); gallbladder dysplasia/cancer (ref = no dysplasia or cancer)

[§] p-value: t-test for difference in means for continuous variables and Pearson's chi-squared with Yates' continuity correction for categorical variables

§OR=odds ratio. All ORs adjusted for age and education.

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Table 2.

Frequency of percent area of the gallbladder covered by lesions among cancer and low-grade dysplasia (LGD) cases.

	<u>Cancer Cases (N = 3)</u>		<u>LGD Cases (N = 13)</u>	
	<i>Coverage by Cancer</i>		<i>Coverage by LGD</i>	
	n	%	n	%
0-5%	1 *	33%	8	62%
5.1-10%	1 †	33%	3	23%
10.1-15%	0	0.0%	1	8%
15.1-35%	0	0.0%	1	8%
35.1-100%	1 ‡	33%	0	0.0%
TOTAL	3	100%	13	100%

* 0.5% cancer, 29% HGD, 7% LGD (37% any dysplasia/cancer)

† 8% cancer, 1% HGD, 0% LGD (9% any dysplasia/cancer)

‡ 85% cancer, 2% HGD, 0% LGD (87% any dysplasia/cancer, Fig. 1)