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Original Article

Does Genetic Testing Influence Outcomes: Early Experience in Melanoma Case Series

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Abstract

Background: The treatment and prognosis of melanoma have historically been based on histologic stage and Breslow depth; however, due to the increase in surveillance, melanomas are being identified at an earlier stage and lower Breslow depth. Advances in genetic testing, such as Decision Dx®, mean that melanoma diagnostic decisions and prognosis can now be directed by genetics. The purpose of this project was to assess the influence of a Decision Dx® high-grade (Class 2A/B) classification on the treatment of melanoma patients at a regional medical center, particularly those not deemed high risk by conventional classification methods, including Breslow depth and Clark level. **Materials and Methods:** Melanomas that were diagnosed as Decision Dx® class 2A/B (high risk) at a single institution between 2019 and 2020 were retrospectively evaluated. Patients were stratified by recurrence and sentinel lymph node (SLN) positivity. **Results:** A total of 97 Decision Dx® high-risk patients were evaluated, in whom the average Breslow depth was 2.38 (0.45–7.5 mm), and three most common histologic stages were pT2a (19%), pT2b (18%), and pT4b (22%). Overall, 65% had oncology follow-up, 37% received immunotherapy, and 91% were alive. Recurrence was noted in 22% of the patients ($n = 22$); there was no significant difference in Breslow depth between those with and without recurrence. Significantly more of those with recurrence had Stage T3a ($P = 0.0390$; no recurrence 0%), oncology follow-up (95%; $P = 0.0030$), and immunotherapy (86%, $P = 0.0001$) but no difference in survival ($P = 0.3161$). Analysis of the patients with SLN biopsy (SLNBx) positivity showed that they were younger (mean: 63.3 years; $P = 0.0040$); however, no significant differences were found in histologic variables. Oncology follow-up was higher in the patients who were SLNBx positive (90%; $P = 0.0126$) as was immunotherapy ($P = 0.0001$); however, due to the Decision Dx® high-risk classification, 60% of the SLNBx-negative patients received oncology follow-up. Overall, recurrence and survival rates were not significantly different between cohorts. **Conclusion:** Although there were no significant differences in survival/recurrence, some patients would not have received additional follow-up based on the initial pathology who eventually developed recurrence. These data emphasize that genetic analysis can change management decisions and allow for more intensive surveillance, and that Decision Dx® can play an integral role in defining melanoma behavior along with histologic characterization. Larger studies to substantiate these results are warranted.

Keywords: Decision Dx®, genetic evaluation, long-term follow-up, melanoma prognosis

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Introduction

The treatment and prognosis of melanoma have historically been based on histologic stage and Breslow depth.[1] However, due to an increase in surveillance, melanomas are being identified at an earlier stage and lower Breslow depth, confounding the treatment plans and prognosis for these patients because there remains a risk of recurrence.[2] Patients with Stage 1–3 (pT3a with a Breslow depth of 2–4 mm without ulceration) with negative lymph nodes are traditionally managed through close follow-up, including routine physical exams and imaging (computed tomography [CT] and positron emission tomography [PET]) when patients exhibit symptoms. These evaluations usually involve dermatology and occasionally oncology/surgical oncology, consistent with current guidelines.[3] While there is a pathologic threshold at which increased surveillance would be initiated, a significant level of discordance in pathologic sub-staging has been noted, suggesting that accurate and reliable substage-based prognostication may not be possible in all cases.[4]

The 31-gene expression profile test Decision Dx® has previously been studied[5] and classifies recurrence risk as low risk (class 1) or high risk (class 2) as an adjunct to pathologic subtyping. A meta-analysis found that when Decision Dx® and sentinel lymph node biopsy (SLNBx) results were considered together, the sensitivity and negative predictive value for distant metastasis-free survival were both improved.[6] The genetic analysis provided by Decision Dx® to identify melanoma patients at increased risk of metastasis augments current risk stratification by reclassifying patients for heightened surveillance who were previously classified as being low risk.[6,7] A previous study reported that management was changed in 50% of patients tested with Decision Dx®, resulting in better outcomes than in those who were not tested.[8] However, the change in management in patients classified as being low risk histologically and high risk based on Decision Dx® has yet to be evaluated. Moreover, few studies have retrospectively analyzed histologic and tumor staging of Decision Dx® Class 2 patients and evaluated changes in clinical diagnosis, surgical interventions, and oncologic follow-up.

The purpose of this project was to assess the influence of a Decision Dx® high-grade (Class 2A/B) classification on the treatment of melanoma patients at a regional medical center, particularly those not deemed high risk by conventional classification methods, including Breslow depth and Clark level.

Materials and Methods

Following IRB approval (IRBnet.org; Prisma Health; 2169802-1; 4/1/23). The need for patient consent was waived by the IRB, and assuring that all procedures were conducted in accordance with the ethics standards given in the 1964 Declaration of Helsinki, as revised in 2013, all patients diagnosed with melanoma by wide-local excision (WLE), shave or punch biopsy, and underwent Decision Dx® genetic typing (Castle Biosciences, Phoenix AZ, USA; https://castlebiosciences.com/tests/prognostic/decisiondx-melanoma/how-it-works) at a single institution between 2019 and 2020 and were classified as high risk (class 2A/B) based on Decision Dx® results were retrospectively evaluated. Patients without complete records were excluded (five patients were lost to follow-up). Typical demographics and clinicopathologic variables were collected, including histologic stage and Breslow depth,[1] SLNBx status, treatment, surveillance, outcomes, and recurrence/metastasis care and mortality. Differences between high-risk patients who had recurrence and those who did not were compared. SLNBx status, another known important prognostic factor that can direct follow-up examinations of patients, was also compared among the high-risk Decision Dx® patients.[9]

Decision Dx® has a reported sensitivity ranging from 70% to 91%, depending on the risk class cutoff and stage of disease. The sensitivity for predicting recurrence in high-risk patients (Class 2B) has been reported to be approximately 88%.[10,11] The specificity ranges between 60% and 85%, with specificity for early-stage melanoma (stage I–II; Class 1A) commonly being over 80%.[10,11] The positive predictive value based on prevalence and stage ranges between 55% and 70%,[11] while the negative predictive value for low-risk Class 1A lesions is reportedly over 95%.[10]

Pathologic data for each tumor, including the Clark level, Breslow thickness (mm), ulceration, dermal mitoses, regression, tumor-infiltrating lymphocytes, lymphovascular invasion, margins, and pathologic stage, were collected. Initial resection was recorded along with any recurrent surgeries for positive margins or recurrence of melanoma. Interval follow-up data were collected to determine the level of surveillance for each patient. All CT, magnetic resonance imaging (MRI), PET, ultrasound, chest X-ray, bone, computed tomography angiography, and dual-energy X-ray absorptiometry (DEXA) scans were identified and evaluated. The types of immunotherapies used as well as the interval of drug administration were recorded, and the status of each patient at the end of the study period was recorded as "alive" or "deceased;" the cause of death was also recorded. The time between diagnosis and death was not determined due to the limited follow-up period in this cohort.

As not all genetically high-risk patients present with a high-stage tumor, the risk of recurrence based on genetic testing was estimated as follows. The highest risk (class 2B) was defined as a risk of recurrence of 0.59–1.0 within 5 years. Intermediate risk (1B/2A) was defined as a risk of recurrence of 0.41–0.59, and the lowest risk (1A) was defined as a risk of recurrence of 0.0–0.41 within 5 years.[12] Decision Dx® also predicts the likelihood of a positive SLNBx at presentation of disease.

The patients were stratified by recurrence and SLN positivity. Associations between categorical variables were assessed with the Chi-squared test or Fisher's test, as appropriate, based on

contingency table cell counts; Fisher's test is more appropriate when the expected cell counts are small (e.g., <5). Associations between continuous and binary variables were assessed with *t*-tests. An alpha level of 0.05 was used to determine statistical significance. All analyses were conducted in R version 4.2.0.

Results

A total of 97 patients were identified as high-risk (class 2A/B) by Decision Dx®. The average age of the cohort was 71 years [range 37–96 years; confidence interval (CI) 68.82, 73.63; Table 1] with an average Breslow depth of 2.38 mm (range: 0.45–7.5 mm; CI 2.08, 2.67). The prevalence of histologic stages was as follows: T1a (0%), T1b (6%), pT2a (19%), pT2b (18%), T3a (13%), T3b (16%), T4a (6%), and pT4b (22%). Overall, 65% of the patients had oncology follow-up, and 37% received immunotherapy. At the conclusion of the study, 91% were still alive.

Overall, 23% of the patients ($n = 22$) had recurrence during the study period [Table 1]. The mean age of those with recurrence was 72.43 years (range: 37–88 years; CI: 66.5, 79.2), compared to 70.72 years (range: 42–96 years; CI: 67.9, 73.4) in those without recurrence ($P = 0.5168$). The mean Breslow depth on those with recurrence was 2.22 mm (range: 0.60–4.90 mm; CI: 1.7, 2.8), which was not significantly different compared to those without recurrence (CI: 2.1, 2.8; $P = 0.5644$). The initial pathologic stages for those with recurrence were T1b (5%, $n = 1$), T2a (32%, $n = 7$), T2b (5%, $n = 1$), T3a (0%), T3b (18%, $n = 4$), T4a (9%, $n = 2$), and T4b (32%, $n = 7$), and the difference between those without recurrence was not significantly different ($P = 0.0575$).

Overall, 95% ($n = 21$) of those with recurrence had oncology follow-up, significantly more than those without recurrence (56%, $n = 42$; $P = 0.0081$). Immunotherapy was used in significantly more of those with recurrence (86%, $n = 19$) compared to those without recurrence (22%, $n = 17$; $P \leq 0.0001$). Interestingly, this did not translate to a significant survival difference, with 86% ($n = 22$) of the patients with recurrence and 89% ($n = 66$) of those with no recurrence still alive at the end of the study ($P = 0.8156$).

In total, 90 patients (93%) received a SLNBx (positive $n = 20$; negative $n = 70$). When stratified by SLNBx positivity [Table 2], the positive cohort was significantly younger (mean: 63.3; range: 37–86 years; CI: 56.4, 70.2; $P = 0.0203$). The mean Breslow depth was not significantly different between groups ($P = 0.6678$), and there was no significant difference in initial pathologic stage ($P = 0.0180$). Significantly more of the SLNBx + cohort received oncology follow-up (SLNBx + 90%, $n = 18$ vs. SLNBx- 60%, $n = 42$; $P = 0.0250$) and immunotherapy (SLNBx + 85%, $n = 17$ vs.

Table 1: Decision Dx® 2a/2b patients and recurrences

	Total ($n=97$), *n* (%)	Recurrence ($n=22$), *n* (%)	No recurrence ($n=75$), *n* (%)	*P**
Mean age†	71.12	72.82	70.63	0.5168
Range	37–96	37–88	42–96	
Mean Breslow‡ (mm)	2.38	2.22	2.43	0.5644
Range	0.45–7.50	0.60–4.90	0.45–7.50	
Histologic stage	*n*=97	*n*=22	*n*=75	0.0575
T1a	0	0	0	-
T1b	6 (6)	1 (5)	5 (7)	-
T2a	18 (19)	7 (32)	11 (15)	-
T2b	17 (18)	1 (5)	16 (21)	-
T3a	13 (13)	0	13 (17)	-
T3b	16 (16)	4 (18)	12 (16)	-
T4a	6 (6)	2 (9)	4 (5)	-
T4b	21 (22)	7 (32)	14 (19)	-
Oncology follow-up	63 (65)	21 (95)	42 (56)	0.0081
Immunotherapy	36 (37)	19 (86)	17 (22)	<0.0001
Type	Pembrolizumab=25 (26)	Pembrolizumab=13 (57)	Pembrolizumab=12 (16)	
	TMZ=1 (1)	Ipi/Nivo=3 (13)	TMZ=1 1	
	Ipi/Nivo=3 (3)	Nivo=2 (9)	Ipi/Nivo=0	
	Nivo=5 (5)	Taf/Mek=1 (4)	Nivo=3 (4)	
	Taf/Mek=1 (1)	Nivo, relatinimab=1 (4)	Taf/Mek=0	
	Trametinid and dabrafenib=1 (1)		Trametinid and dabrafenib=1 (1)	
	Nivo, relantinimab=2 (2)		Nivo, relatinimab=1 (1)	
Multiple	10 (10)	9 (39)	1 (1)	<0.0001
Alive¶	88 (91)	22 (96)	66 (89)	0.8156

**P*-values denote the comparison between stratified groups, †The 95% CI for the mean age of those positive for recurrences is 66.5–79.2 and negative 67.9–73.4, ‡The 95% CI for Breslow depth for those with recurrences is 1.7–2.8 and those without 2.1–2.8, ¶Survival was noted as a categorical variable for this study, CI: Confidence interval

Table 2: Decision Dx® 2a/2b patients and sentinel lymph node biopsy status

	Total (*n*=90), *n* (%)	SLNBx+ (*n*=20), *n* (%)	SLNBx− (*n*=70), *n* (%)	*P**
Mean age†	70.12	63.3	72.07	0.0203
Range	37–96	37–86	42–96	-
Mean Breslow‡ (mm)	2.41	2.54	2.38	0.6678
Range	0.6–7.5	1.0–7.0	0.6–7.5	-
Histologic state	*n*=90	*n*=20	*n*=70	0.0180
T1a	0	0	0	-
T1b	4 (4)	0	4 (6)	-
T2a	16 (18)	6 (30)	10 (14)	-
T2b	17 (19)	1 (5)	16 (23)	-
T3a	12 (13)	1 (5)	11 (16)	-
T3b	16 (18)	3 (15)	13 (19)	-
T4a	6 (7)	3 (15)	3 (4)	-
T4b	19 (21)	6 (30)	13 (19)	-
Oncology follow-up	60 (67)	18 (90)	42 (60)	0.0250
Immunotherapy	34 (38)	17 (85)	17 (24)	0.0001
Recurrence	21 (23)	7 (35)	14 (20)	0.1642
Alive¶	76 (84)	18 (90)	64 (91)	0.8026

**P*-values denote the comparison between stratified groups, †The 95% CI for the mean age of those with a SLNBx+ was 56.4–70.2 and those with SLNBx− 69.5–74.6, ‡The 95% CI for mean Breslow depth for SLNBx+ is 1.8–3.2 and SLNBx− is 2.0–2.7, ¶Survival was noted as a categorical variable for this study. SLNBx: Sentinel lymph node biopsy, CI: Confidence interval

SLNBx- 24%, n = 17; $P \leq 0.0001$). However, recurrence rate (positive 35%, n = 7, and negative 20%, n = 14) and survival rate (positive 90%, n = 18 and negative 91%, n = 64) were not significantly different between groups (P = 0.1642 and P = 0.8026, respectively).

Patients within our cohort of Class 2A/B Decision Dx® who were classified as high risk based on Breslow depth alone (T3/4; n = 44) were evaluated separately. Of these patients, 52.3% (n = 23) received immunotherapy for the primary lesion, and 29.5% (n = 13) had recurrence. Of those with recurrence, 85% (n = 11) had recurrence despite also receiving immunotherapy [Figure 1].

Patients with a positive SLNBx (n = 20) were also analyzed separately. Of these patients, 85% (n = 17) received immunotherapy and 35% (n = 7) had recurrence. Specifically, of those with recurrence, 41.2% who received immunotherapy also developed recurrence (n = 6) [Figure 1].

Interestingly, SLNBx-negative patients (n = 70) who did not receive immunotherapy (n = 53) had a recurrence rate of 5.67% (n = 3). Within the patients with a low-risk Breslow depth (T1-3a) (n = 53), 46 (85.1%) had negative SLNBx and six (13.0%) had recurrence.

Discussion

The treatment of melanoma has historically been driven by the analysis of histologic features and depth of invasion, first classified as the depth of invasion from the dermis into the subcutaneous fat by Wallace Clark in 1966.[13] He concluded that patients with a deeper cutaneous invasion (level III–V) were more likely to have lymph node invasion, thus recommending lymph node dissection if invasion was past the papillary dermis. In 1970, Alexander Breslow evolved the classification by creating a staging system based on the thickness of the tumor.[14,15] He determined that patients with a thinner melanoma (Stages I and II) had a better chance of survival, whereas patients with a thickness of 1.5 mm or greater had a significantly higher incidence of metastasis, and consequently that lymph node dissection was recommended for these patients.[16] A prospective evaluation of primary cutaneous melanoma patients at a single institution in the 1990s established that patients with a positive SLNBx were at a significantly higher risk of recurrence than patients with a negative SLNBx.[17]

The current treatment recommendations for melanocytic lesions incorporate Clark level and Breslow depth to direct WLE and SLN dissection, if warranted; a stage IB lesion (Breslow thickness <0.8 mm with ulceration or 0.8–1.0 mm) would be considered for a SLNBx. In the Multicenter Selective Lymphadenectomy Trial (MSLT)-II trial, 1939 patients with a positive SLN were randomized into two groups: ultrasound observation group and complete lymph node dissection group. The trial concluded that there was no survival benefit to an immediate completion of lymph node dissection with WLE; however, there was evidence of value regarding staging and regional control.[18] While there are recommendations for the diagnosis and treatment of melanotic lesions, the question of follow-up still remains.

The frequency of clinical surveillance varies among the current recommendations, ranging from every 3 months to annually. Studies have found that peak recurrence rates occur during the first 2 to 3 years after the initial melanoma diagnosis.[19] Imaging

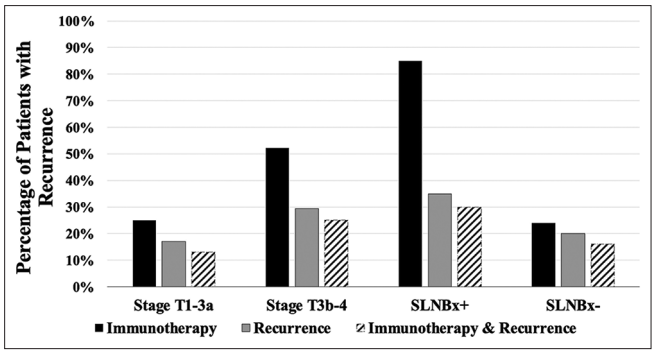

Figure 1: Comparing relative percentages of patients with recurrence between groups that were defined based on pathologic stages and SLNBx status. Percentages refer to the recurrences out of the total number of patients per group. There were higher rates of recurrence in those patients with more advanced pathologic staging and positive SLNBx results

surveillance, including PET-CT, computed tomography scan of the Chest, Abdomen, and Pelvis (CT-CAP), and MRI, are not currently recommended for patients with stage 0–IIA melanoma due to the concerns of false positive scans. However, follow-up is currently directed by staging and thickness and does not consider the genetic predisposition of the lesion. Follow-up imaging at our institution is determined by a multidisciplinary team consisting of the surgical and medical oncologists, considering the specifics of each case.

In a study utilizing Decision Dx® to assess genetic recurrence risk in melanoma patients, 70% of 259 high-risk Class 2 node-negative patients developed metastasis.[20] In Dhillon's study, more patients classified as high-risk Class 2 by Decision Dx® developed metastasis compared to those who did not receive genetic testing based on pathologic staging (20.5% vs. 14.1%).[21] Overall, six patients (6%) in our high-risk Decision Dx® cohort with pathologic Stage T1-3A and who were SLNBx-negative had recurrence. In comparison, 3 of the 8 (37.5%) patients with pathologic Stage T1-3A who were SLNBx-positive had recurrence. When considering all low pathologic Stage (T1-3A) patients in our study, regardless of SLNBx status, 11% had recurrence [Figure 1]. It is anticipated that a patient with a positive SLNBx result may have a higher likelihood of recurrence; however, in our cohort, the recurrence rate in the SLNBx-negative patients did not show a significant difference compared to the SLNBx-positive patients. Despite the small size of our cohort, our data align with other studies, suggesting that a positive SLNBx alone is not a definitive indicator of recurrence potential.[22,23] The Decision Dx® 31-gene expression test allowed for 11% of the low-staged melanoma patients to be upgraded in recurrence risk and therefore to be followed more closely. Notably, among the six patients with T1-3a stage and negative SLNBx who ultimately experienced recurrence, all were scheduled for oncology and surgical oncology follow-up within 6 months. In contrast, in the SLNBx-positive T1-3a patients, only 50% (27 of 54) had a follow-up appointment, and only 59.3% (16 of 27) attended their scheduled follow-up. Among these patients, 16.7% (9 of 54) subsequently had recurrence.

A national cohort study of 25,720 patients with melanoma of all stages[24] evaluated recurrence rates based on pathologic tumor staging. The results showed that 3% (n = 845) of the patients with low-risk pathologic tumor stages of IA through IIA (Breslow depth and nodal status; pathologic stage T1a-T3b and SLNBx negativity) developed recurrence of melanoma. All SLNBx-positive patients were reclassified as Stage III regardless of pathologic depth of invasion. The rate of recurrence in this group was 3.3%.[24] In comparison, the rate of recurrence in our low-low risk pathologic stage patients who were classified as genetically high risk was 9.3%, most likely due to increased surveillance. However, the relatively small sample size (n = 97), limited number of recurrence events (n = 22), and relatively short follow-up may have constrained the statistical power of our study, and larger studies with longer follow-up times are warranted to verify the recurrence rate of pathologic staged low-risk patients who were classified as Decision Dx® high-risk.

In analysis stratified by SLNBx outcome, significantly more patients who were SLNBx-positive received oncology follow-up (P = 0.0100), consistent with standard of care. The patients who were low stage and SLNBx-negative generally would not have been offered more comprehensive follow-up without being classified as high risk by genetic testing. Interestingly, of the 41 SLNBx-negative patients with low pathologic stage tumors, 48% (n = 20) had oncology follow-up despite still being considered genetically high risk and being offered more comprehensive longitudinal care. This can be compared to the 29 SLNBx-negative and high pathologic stage patients who had a follow-up rate of 90% (n = 26). The question remains as to why patients who are genetically high risk but not pathologically high risk adhere less to follow-up care.[25] Further studies are needed to explore the psychological impact of genetic versus pathological diagnoses.

Regardless of pathologic stage and SLNBx outcome, there were no differences in the rates of recurrence or survival in the Decision Dx® high-risk group in our study. These findings coincide with the MSLT-II trial, which found no difference in survival when comparing patients who received SLNBx to those who did not.[18] Interestingly, a previous study suggested that the long-term rate of metastatic melanoma in SLNBx-negative patients at a single institution may be higher than reported in the literature,[26] suggesting a role for Decision Dx® in prognostication in this group. While SLNBx is currently recommended by the National Comprehensive Care Network (NCCN) Guidelines based on lesion histologic features and size, it is also used to determine staging and the risk of metastasis. Decision Dx® is used under the same premise: determining the possible risk of metastasis and recurrence. This offers additional information to determine the risk of recurrence and the optimal method of follow-up.

Overall, seven of the high-risk DDx patients did not receive SLNBx; three died before surgery or follow-up and could not be evaluated. One patient moved away and was lost to

follow-up. The last three patients had concurrent unrelated cancers and either elected to not undergo any more treatment or elected to treat a different cancer that was perceived as a higher risk.

Currently, Decision Dx® is not used solely to direct treatment and follow-up for each patient, rather, it is used as an adjunct indicator of recurrence risk. However, what is considered a high-risk melanoma remains to be clarified. Class 2A or 2B (high-risk by genetic standards) Decision Dx® should be considered a high-risk melanoma when planning surveillance. If a patient is classified as Class 2A/2B Decision Dx® then follow-up should be considered every 3 months for a year with CT/PET imaging conducted once every 6 months.[27] If there is no recurrence after 1 year, then follow-up should be conducted every 6 months with imaging annually. This surveillance strategy provides a framework based on our data, as well as a hypothesis-generating process for a prospective validation that would be of use to other institutions. A possible issue may arise with insurance coverage. While coverage of follow-up visits may vary by provider, the American Cancer Society states that insurance generally covers follow-up visits every 6–12 months for low-stage melanoma and every 3–6 months for high-stage melanoma. With more supportive data on the use of Decision Dx®, coverage for more frequent surveillance could be implemented and successfully identify patients at high risk of recurrence.

The limitations of this study include the small sample size and limited follow-up. In addition, selection bias is possible as the study was conducted at one institution, and one surgical oncologist managed 98% of the patients.

Conclusion

Although there were no significant differences in survival/recurrence, six patients with melanoma recurrence would not have had close follow-up without Decision Dx® genetic evaluation. Ultimately, this testing changed these patients' management and outcomes. Our results suggest that genetic sequencing may influence follow-up and identify patients who need closer follow-up compared to those with a similar stage with lower class presentation, thus optimizing patient outcomes. Future investigations would benefit from longer follow-up and multi-institutional cooperation to address the complexity of decision-making and the prospective goals of assessing the relationship between Decision Dx® class and surgical treatment, and adjuvant versus long-term imaging follow-up.

Author contributions

Reyes–Literature search, data acquisition, manuscript preparation, manuscript editing, and manuscript review. Skenteris–Literature search, data acquisition, manuscript preparation, manuscript editing, and manuscript review. Self–Statistical analysis, manuscript editing. Schammel–Concept, design, definition of intellectual content, manuscript preparation, manuscript editing, manuscript review. Trocha–Concept, design, definition of intellectual content, manuscript editing, manuscript review. All authors have read and agreed to the final version of the manuscript.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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