



· 论 著 ·

早期乳腺癌术中快速冰冻切片病理学检查延迟诊断率分析：一项真实世界的回顾性研究

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[摘要] 背景与目的: 对于少数空芯针穿刺未能明确诊断的早期乳腺癌, 冰冻切片病理学检查的延迟诊断率尚不清楚。本回顾性队列研究旨在探讨术中快速冰冻切片病理学检查在这种情况下的临床应用价值。方法: 回顾性分析2006年5月1日—2019年12月31日在复旦大学附属肿瘤医院就诊的乳腺癌患者的临床资料。收集患者的临床特征、影像资料和病理学资料。采用logistic回归分析方法探索患者的临床特征与术中快速冰冻切片病理学检查延迟诊断的相关性, 并构建预测延迟诊断率的诺模图。本研究获得复旦大学附属肿瘤医院伦理委员会批准(伦理批号: 050432-4-2108*)。结果: 共876例患者符合入组标准而纳入本研究。对空芯针穿刺未能明确诊断的乳腺癌的术中快速冰冻切片病理学检查诊断率为67.7%, 延迟诊断率为32.3%。多因素分析中, 空芯针标本伴有非典型增生的乳头状病变[比值比(odds ratio, OR)=4.251, 95% CI: 2.804~6.492, $P<0.001$]和硬化性腺病(OR=3.727, 95% CI: 1.897~7.376, $P<0.001$)是导致冰冻切片延迟诊断的正相关因素, 乳房X线摄影见簇状微钙化(OR=0.345, 95% CI: 0.216~0.543, $P<0.001$)和超声诊断结果依据乳腺影像报告和数据系统(Breast Imaging Reporting and Data System, BI-RADS)分类为4C~5类(OR=0.250, 95% CI: 0.081~0.777, $P=0.016$)是术中诊断率高的正相关因素。通过这些因素构建的诺模图能较好地预测术中快速冰冻切片病理学检查的延迟诊断率, 从而更好地筛选出适合术中快速冰冻切片病理学检查的病例。结论: 术中快速冰冻切片病理学检查对空芯针穿刺未能明确诊断的乳腺癌有一定的延迟诊断率, 通过模型预测的方法可有效地筛除延迟诊断的病例, 避免一些不必要的术中快速冰冻切片病理学检查。

[关键词] 冰冻切片; 乳腺癌; 延迟诊断; 预测模型; 空芯针穿刺
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Predicting delayed diagnosis rate of intraoperative rapid frozen section pathological examination for early-stage breast cancer: a real-world retrospective study XUE Jiale^{1, 2}, LI Jianwei¹, GONG Yue¹, LIU Guangyu¹, LIU Zhebin¹

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[Abstract] **Background and purpose:** For few of early-stage breast cancers who are undiagnosed by core needle biopsy, the delayed diagnosis rate of intraoperative rapid frozen section pathological examination is unclear. The purpose of this retrospective cohort study was to investigate the clinical application value of frozen sections in this situation. **Methods:** This study reviewed data of 876 breast cancer patients that were undiagnosed by core needle biopsy in Fudan University Shanghai Cancer Center from May 1, 2006 to December 31, 2019. Clinical characteristics and image data and pathological data of patients were collected. The correlation between clinical features and delayed diagnosis rate (DDR) of frozen section was explored using logistic regression analysis, then a nomogram was constructed to predict the probability of delayed diagnosis. This study was approved by Ethics Committee of

Fudan University Shanghai Cancer Center (No.: 050432-4-2108*). **Results:** A total of 876 patients met the inclusion standards. The intraoperative diagnosis rate of frozen section for breast cancers that were undiagnosed by core needle biopsy was 67.7%, and the DDR was 32.3%. In multivariate analysis, papillary lesion [odds ratio (OR)=4.251, 95% CI: 2.804-6.492; $P<0.001$] and sclerosing adenosis (OR=3.727; 95% CI: 1.897-7.376; $P<0.001$) accompanied by atypical epithelial hyperplasia on core needle biopsy (CNB) were positive correlation factors of delayed diagnosis, while clustered microcalcifications on mammography (OR=0.345; 95% CI: 0.216-0.543; $P<0.001$) and ultrasonic category 4C-5 according to Breast Imaging Reporting and Data System (BI-RADS) (OR=0.250; 95% CI: 0.081-0.777; $P=0.016$) were positive correlation factors of intraoperative diagnosis. The nomogram constructed by these factors could better predict the delayed diagnosis rate of frozen section and screen out low delayed diagnosis population. **Conclusion:** Frozen section has a certain delayed diagnosis rate for breast cancer that is not clearly diagnosed by core needle biopsy. The method of model prediction can effectively eliminate the delayed diagnosis cases and avoid some unnecessary frozen sections.

[**Key words**] Frozen section; Breast cancer; Delayed diagnosis; Prediction model; Core needle biopsy

超声或X线引导下空芯针穿刺活检 (core needle biopsy, CNB) 是目前术前确诊早期乳腺癌的主要诊断方法^[1]。本中心既往的研究^[2]显示,其准确率可达92.4%,但由于组织取材量有限,故仍然有低估肿瘤的可能,低估率约为7.6%。对于术前CNB诊断未能明确的疑似乳腺恶性肿瘤,临床医师通常会选择切除组织的病理学检查来获取完整的组织标本以获得最终的病理学诊断结果^[3-4]。此时,为了尽可能地减少二次手术,许多临床医师会采用术中快速冰冻切片病理学检查,尤其是在国内,术中快速冰冻切片病理学检查比较普遍。根据以往报道,术中快速冰冻切片病理学检查对浸润性乳腺癌的术中确诊率高^[5-7],但对分叶状肿瘤、梭形细胞病变、硬化性病变、乳头状病变、甚至原位癌等的术中确诊率偏低,延迟诊断率 (delayed diagnosis rate, DDR) 偏高^[8-12]。迄今为止,关于冰冻切片病理学检查在CNB未能明确诊断的乳腺癌中的诊断效能的研究报告鲜见,本回顾性队列研究旨在探讨术中快速冰冻切片病理学检查的临床应用价值,并为临床实践提供参考。

1 资料和方法

1.1 研究对象和入排标准

本研究从2006年5月1日—2019年12月31日在复旦大学附属肿瘤医院接受手术治疗的乳腺肿瘤患者中筛选研究对象。纳入标准为:①肿块空芯针穿刺标本病理学检查结果提示有导管上皮非典型增生者;②患者接受了乳腺肿物切除术或乳房切除术;③穿刺前,患者未接受新辅助化疗;④全身系统评估为无远处转移的患者。排除标准为:①肿块空芯针穿刺标本病理学检查或免疫组织化学检查已明确诊断为乳腺癌(包括浸润性癌及导管原位癌);②术后最终病理学检查结果显示为非乳腺癌;③术中未送检;④临床病史资料、超声及X线影像资料有缺失项者。研究对象总人群由符合以上全部4条纳入标准且不符合任

意1条排除标准者组成。

1.2 变量资料、主要观察指标和伦理审批

通过电子病案系统收集患者的临床特征资料、影像资料和病理资料。从数据资料中共提取11个临床相关的候选变量,分别为年龄、是否可触及肿块、是否有乳头溢血、超声回声密度、超声最大径、超声是否见密集点状强回声、超声诊断依据的乳腺影像报告和数据系统 (Breast Imaging Reporting and Data System, BI-RADS) 类别、乳房X线是否有簇状微钙化、乳房X线的BI-RADS类别、空芯针活检的非典型增生上皮是否含乳头状病变及是否含硬化性腺病。主要观察指标为术中快速冰冻切片病理学检查对乳腺癌的确诊率和延迟诊断率。延迟诊断定义为术中快速冰冻切片病理学检查未明确诊断为乳腺癌,而石蜡包埋切片或免疫组织化学检查诊断为乳腺癌。本研究获复旦大学附属肿瘤医院伦理审查委员会的批准(伦理批号:050432-4-2108*),所有患者术前均签署知情同意书。

1.3 统计学处理

采用单因素logistic回归检验术中冰冻切片病理学检查的延迟诊断情况与临床特征之间的关系,再通过多因素logistic回归与逆向选择法,以确定独立的相关因素。根据多因素logistic回归结果绘制列线图(诺模图),并将列线图的预测结果量化成对应的延迟诊断百分率^[13]。绘制受试者工作特征(receiver operating characteristic, ROC)曲线,通过计算ROC曲线下面积(area under ROC curve, AUC)来评估预测模型的准确性。采用Harrell c指数评价判别能力^[14]。使用自举法进行校准,以说明延迟诊断概率和实际观测的延迟诊断率之间的关系^[15]。 $P<0.05$ 为差异有统计学意义。所有统计方法及列线图绘制均使用R 3.4版(R Foundation for Statistical Computing)统计软件实现。

2 结 果

2.1 研究人群的基线特征

从2006年5月1日—2019年12月31日, 共876例患者符合最终纳入标准(图1)。其中593例通过术中快速冰冻切片病理学检查确诊, 283例通过后续的石蜡切片或免疫组织化学检测确诊。据此得出术中快速冰冻切片病理学检查的确诊率为67.7%, 延迟诊断率为32.3%。将研究对象按照7:3的比例随机分配到训练集和验证集, 并构建预测延迟诊断的诺模图。研究人群的筛选过程见图1, 患者的变量信息见表1。

2.2 Logistic回归分析

在训练集的613例患者中, 205例为术中快速冰冻切片病理学检查延迟诊断, 延迟诊断率为33.44%。在单因素分析中, 患者年龄 ≥ 60 岁[比值比(odds ratio, OR) 1.653, 95% CI: 1.029~2.686, $P=0.040$]、空芯针活检的非典型增生上皮含乳头状病变(OR=5.037, 95% CI: 3.468~7.366, $P<0.001$)或硬化性腺病(OR=2.133, 95% CI: 1.161~3.917, $P=0.014$)均是术中快速冰冻切片病理学检查延迟诊断的正相关因素。超声显示低回声(OR=0.286, 95% CI: 0.158~0.505, $P<0.001$)、超声见密集点状强回声(OR=0.205, 95% CI: 0.128~0.319, P

<0.001)、超声BI-RADS 4C~5类(OR=0.273, 95% CI: 0.101~0.737, $P=0.009$)、乳房X线见簇状微钙化(OR=0.203, 95% CI: 0.138~0.294, $P<0.001$)以及钼靶BI-RADS 4C~5类(OR=0.203, 95% CI: 0.190~0.750, $P=0.005$)均是术中诊断率高的正相关因素。

多因素分析结果显示, 非典型增生上皮含乳头状病变(OR=4.251, 95% CI: 2.804~6.492, $P<0.001$)或硬化性腺病(OR=3.727, 95% CI: 1.897~7.376, $P<0.001$)是术中快速冰冻切片病理学检查延迟诊断的独立因素(正相关), 而超声BI-RADS 4C~5类(OR=0.250, 95% CI: 0.081~0.777, $P=0.016$)和乳房X线见簇状微钙化(OR=0.345, 95% CI: 0.216~0.543, $P<0.001$)则是术中诊断率高的正向独立因素。此外, 超声见密集点状强回声与术中快速冰冻切片病理学检查延迟诊断呈负相关趋势(OR=0.595, 95% CI: 0.335~1.044, $P=0.073$, 表2)。

2.3 诺模图构建

在多因素logistic回归分析的基础上构建了预测DDR的诺模图(图2)。根据各相关因素计算总分, 纳入的因素包括超声BI-RADS类别、超声是否见密集点状强回声、乳房X线是否见簇状微钙化、空芯针活检是否含有乳头状病变以及是否含有硬化性腺病。结果显示, 总分值越大则术中快速冰冻切片病理学检查的延迟诊断率越高。

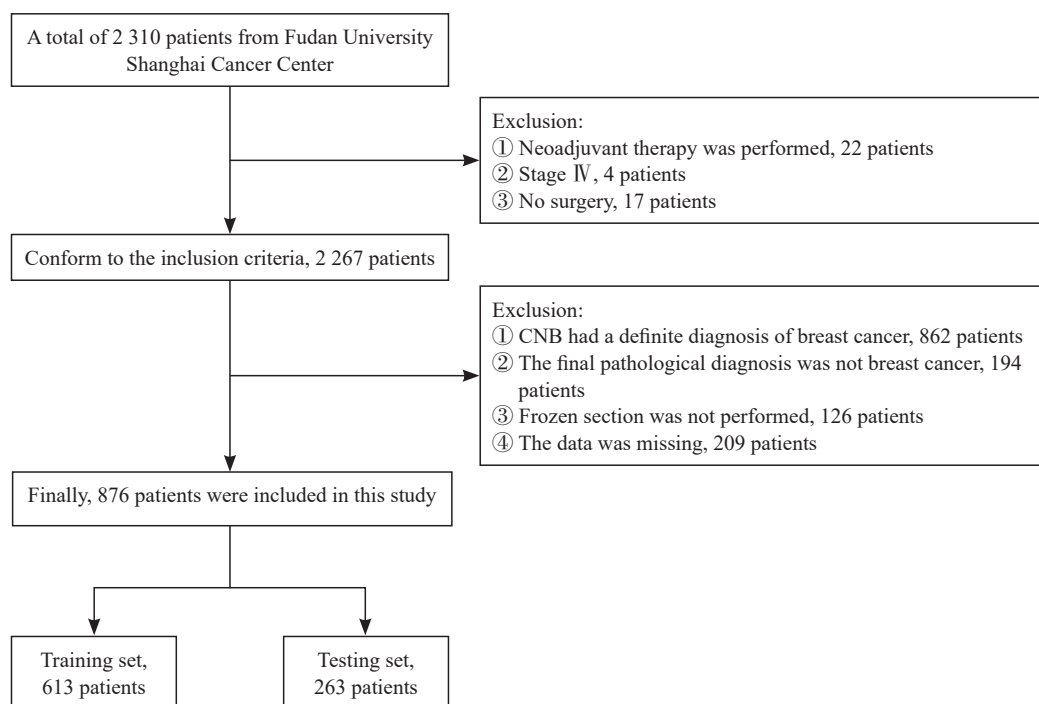


图1 研究人群筛选流程图

Fig. 1 Flow diagram of patients selecting

表1 研究对象的临床资料数据汇总

Tab. 1 Summary sheet of the clinical data of the patients

Item	[n (%)]		
	Total (n=876)	Training set (n=613)	Testing set (n=263)
Age/year			
Median age	53 (28.86)	54 (30.86)	51 (28.83)
<45	183 (20.9)	127 (20.7)	56 (21.3)
45-59	410 (46.8)	286 (46.6)	124 (47.1)
≥60	283 (32.3)	200 (32.6)	83 (31.6)
Ultrasonographic features			
Echo type			
Mixed echo	82 (9.4)	55 (9.0)	27 (10.3)
Low echo	764 (87.2)	538 (87.8)	226 (85.9)
Medium echo	30 (3.4)	20 (2.2)	10 (3.8)
Maximum diameter <i>D</i> /mm			
≤10	111 (12.7)	75 (12.2)	36 (13.7)
>10	765 (87.3)	538 (87.8)	227 (86.3)
Dense punctate strong echo			
Yes	298 (34.0)	201 (32.8)	97 (36.9)
No	578 (66.0)	412 (67.2)	166 (63.1)
BI-RADS			
1-3	29 (3.3)	18 (2.9)	11 (4.2)
4A or 0	192 (21.9)	136 (22.2)	56 (21.3)
4B	344 (39.3)	240 (39.2)	104 (39.5)
4C or 5	311 (35.5)	219 (35.7)	92 (35.0)
Mammographic features			
Microcalcifications			
Yes	420 (47.9)	297 (48.5)	123 (46.8)
No	456 (52.1)	316 (51.5)	140 (53.2)
BI-RADS			
1-3	71 (8.1)	45 (7.3)	26 (9.9)
4A or 0	269 (30.7)	182 (29.7)	87 (33.1)
4B	247 (28.2)	171 (27.9)	76 (28.9)
4C or 5	289 (33.0)	215 (35.1)	74 (28.1)
Physical examination symptoms			
Palpable mass			
Yes	812 (92.7)	571 (93.1)	241 (91.6)
No	64 (7.3)	42 (6.9)	22 (8.4)
Nipple discharge			
Yes	96 (11.0)	69 (11.3)	27 (10.3)
No	780 (89.0)	544 (88.7)	236 (89.7)
Pathological features			
Papillary lesions			
Yes	252 (28.8)	174 (28.4)	78 (29.7)
No	624 (71.2)	439 (71.6)	185 (70.3)
Sclerosing adenosis			
Yes	61 (7.0)	45 (7.3)	16 (6.1)
No	815 (93.0)	568 (92.7)	247 (93.9)
Frozen section			
False negative	283 (32.3)	203 (33.1)	80 (30.4)
Ture positive	593 (67.7)	410 (66.9)	183 (69.6)

表2 训练集多因素回归分析结果 (n=613)

Tab. 2 Results of multivariate logistic model of the training set (n=613)

Variables	No. of patients (delayed diagnosis/total)	DDR/%	OR	95% CI	P value
Dense punctate strong echo					
No	176/412	42.7	1.000	-	-
Yes	27/201	13.4	0.595	0.335-1.044	0.073
US-BI-RADS					
1-3	9/18	50.0	1.000	-	-
0 or 4A	61/136	44.9	0.601	0.195-1.861	0.372
4B	88/240	36.7	0.434	0.143-1.321	0.137
4C-5	45/219	20.5	0.250	0.081-0.777	0.016
Microcalcifications on MG					
No	155/316	49.1	1.000	-	-
Yes	48/297	16.2	0.345	0.216-0.543	<0.001
Papillary lesions					
No	98/439	22.3	1.000	-	-
Yes	105/174	60.3	4.251	2.804-6.492	<0.001
Sclerosing adenosis					
No	180/568	31.7	1.000	-	-
Yes	23/45	51.1	3.727	1.897-7.376	<0.001

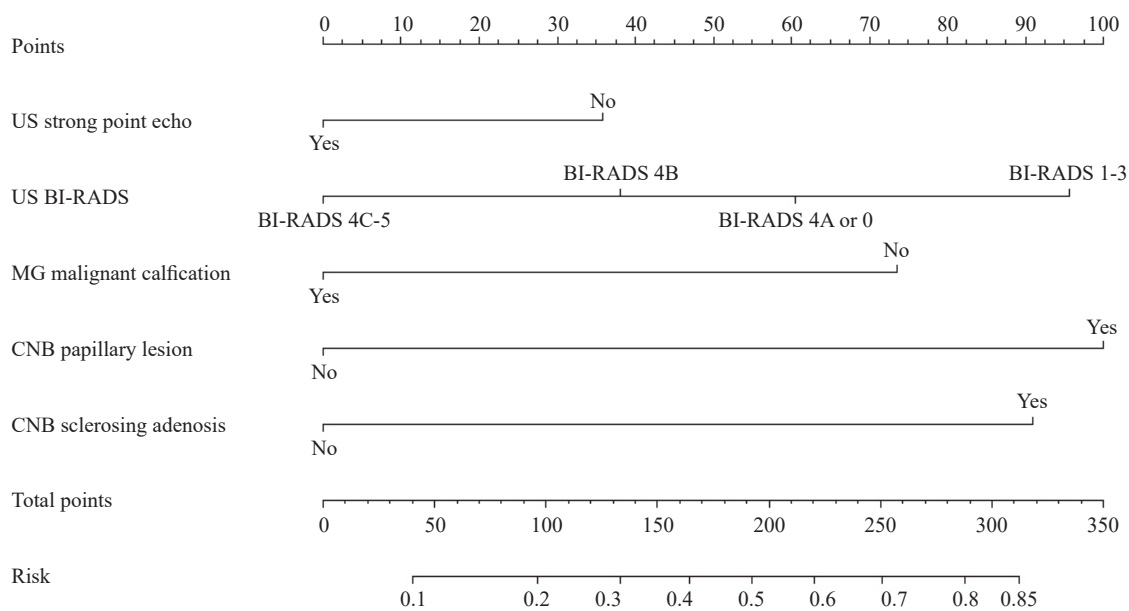


图2 预测术中快速冰冻切片病理学检查延迟诊断率的诺模图

Fig. 2 Nomogram for predicting the delayed diagnosis rate of pathological diagnosis by frozen section in surgery

US: Ultrasonography diagnosis.

2.4 模型验证

通过自举法进行内部验证得出预测模型在训练集中的AUC为0.794 (95% CI: 0.756~0.831), 而在263例患者组成的独立验证集中也显示了良好的预测准确性, AUC为0.800 (95% CI: 0.736~0.865), 表明此诺模图模型具有独立且良

好的预测效能 (图3)。对训练集和测试集进行内部校准后, 预测DDR和实际DDR之间差异无统计学意义 (P=1.000), 说明此预测模型校准良好 (图4)。不同总分段患者的预测DDR与对应的实际DDR见表3。

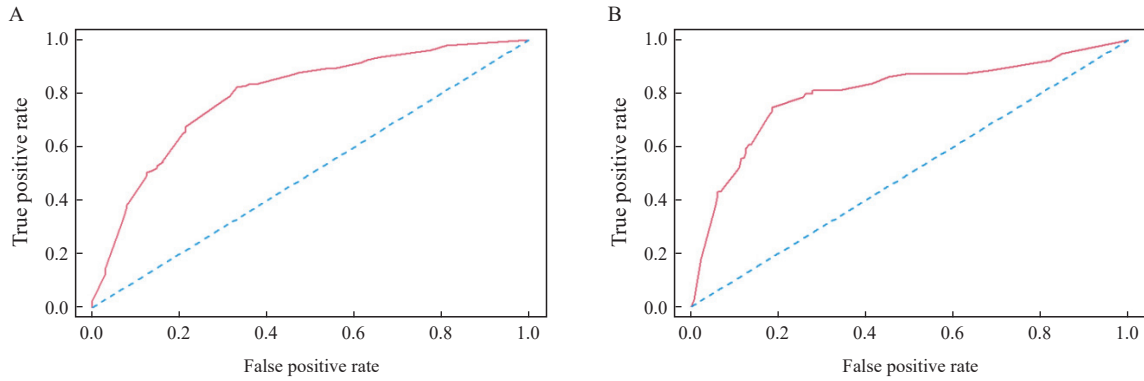


图3 预测模型的ROC曲线

Fig. 3 ROC curve of the prediction model

A: Training set with an AUC of 0.794 (95% CI: 0.756 to 0.831); B: Validation set with an AUC of 0.800 (95% CI: 0.736-0.865).

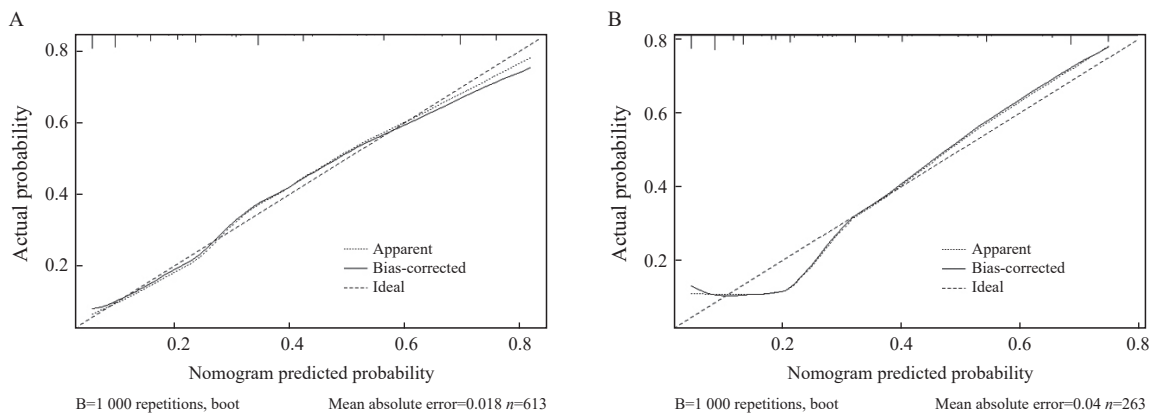


图4 校准曲线

Fig. 4 Calibration curve

A: Training set; B: Validation set. The horizontal axis represented the predicted DDR of the Nomogram, and the vertical axis represented the actual DDR ($P=1.000$).

表3 不同总分值段对应的预测DDR及实际DDR对照表

Tab. 3 The comparison table of predicted DDR and real DDR corresponding to different total score segments

Cut-off value		No. of patients <i>n</i>		Real DDR/%
Total score	Predicted DDR/%	Total	Delayed diagnosis	
≤40	≤10	220	22	10.0
≤76	≤15	246	25	10.2
≥190	≥50	235	152	64.7
≥220	≥60	159	114	71.7
≥251	≥70	60	44	73.3
≥288	≥80	8	7	87.5

3 讨论

临床实践中，对于CNB尚不能明确诊断的乳腺癌，术中快速冰冻切片病理学检查被广泛使用。本研究结果显示，术中快速冰冻切片病理学检查对CNB未能明确诊断的乳腺癌的诊断有一定的延迟诊断率，这说明在一些特定的情况下，该诊断准确率并不理想，如果能更精准地评估和

筛选适合冰冻切片检查的患者，可以进一步提高手术效率，同时减轻病理科医师的工作负担。根据本研究的诺模图分析预测模型，当总评分超过220时，术中快速冰冻切片病理学检查的DDR大于70%，当总评分超过288时，DDR高达87.5%。对于此类患者，免除术中快速冰冻切片病理学检查可避免病理科医师的无效工作和手术中外科医师的等待。相反，如果总评分低于76时，术中快速冰冻切片病理学检查确诊率接近90%，可以避免患者再接受二次手术。这一结果也证实了对患者进行有效评估和筛选的重要性。

在本研究中，相对于乳房X线无簇状微钙化灶的病灶而言，伴有簇状微钙化的病灶的术中快速冰冻切片病理学检查术中确诊率更高，这似乎与既往研究^[6, 16]的结论相矛盾。既往报道^[6, 16]显示，乳腺X线下微钙化型病灶的术中快速冰冻切片病理学检查的DDR更高。但在这些研究中，并未将浸润性癌及导管原位癌进行区分，而在微钙化型病灶的患者中导管原位癌的比例明显更高，而有研究^[8-12]发现术中快速冰冻切

片病理学检查对导管原位癌的诊断敏感性偏低, 这可能是造成DDR差异的真正原因。在本研究中, 由于患者在术前都接受了空芯针活检, 使得大多数易诊断的浸润性癌已经被排除在外, 导致纳入的导管原位癌的比例显著升高, 并且最终的术后病理学检查结果显示, 在微钙化组和无微钙化组中, 以导管原位癌为主要成分(包括纯导管原位癌和导管原位癌伴微浸润)的患者的比率非常接近(57.3% vs 59.7%), 这就避免了因非浸润性癌的比率不均造成的偏倚。

本研究结果显示, 乳头状癌的DDR较高, 与既往的研究结论一致^[5, 8]。乳头状癌是一组特殊类型的乳腺癌, 包括导管内乳头状癌、包被性乳头状癌、实性乳头状癌、浸润性乳头状癌等。这些病变在不同区域可能存在形态学上的差异。多项研究^[17-21]显示, 乳头状癌的诊断常需通过充分取材、石蜡包埋组织切片及免疫组织化学与良性乳头状瘤相鉴别。在术前评估方面, 超声图像上乳头状癌多为实囊性病变, 乳房X线一般为团块样的致密影, 边缘可呈分叶状, 少数可伴有微钙化, 组织学分化程度较高。由于取材量有限, 许多乳头状癌在术前的空芯针活检时通常仅可诊断为乳头状病变或非典型病变^[22]。综上所述, 本研究中乳头状病变可增加术中快速冰冻切片病理学检查的DDR的结果。

本研究结果显示, 伴上皮非典型增生的硬化性腺病也是造成术中快速冰冻切片病理学检查延迟诊断的独立因素。回顾性研究^[23]显示, 混合硬化性腺病的乳腺癌的CNB假阴性率为36%。该病变在不同区域可能存在形态学上的差异, 有些区域完全是腺病形态, 有些区域可能伴有不典型增生甚至是癌, 故对这类病灶进一步行切除活检非常必要。硬化性腺病在影像及显微镜下的表现常常易与浸润性癌混淆, 尤其在同时伴有癌变时, 原位癌累及硬化性腺病的病变特征可能进一步增加过度诊断为浸润性癌的风险^[24]。一些小样本描述性研究及病例报告等提示对于累及硬化性腺病的乳腺病灶的诊断, 术后石蜡包埋组织切片病理学检查结合免疫组织化学检测要比术中快速冰冻切片病理学检查更加有效^[25-28]。因此, 病理科医师往往倾向于通过术后石蜡包埋组织切片病理学检查结合免疫组织化学检测对这类病灶作出最终的判断^[29-30]。

本研究尚存在一定的局限性。首先, 本研究是一项单中心回顾性研究, 未进行偏倚分析。其次, 乳腺磁共振成像未被纳入术前评估指标。此

外, 本研究未纳入接受真空辅助活检的患者, 主要原因是真空辅助活检费用较高, 在国内的大部分基层医院通常只被用于进行切除小的良性病变等以治疗目的为主的手术操作, 而在怀疑为恶性病变时则很少使用^[2, 31]。

对于术前CNB未能明确诊断的乳腺癌, 术中快速冰冻切片病理学检查亦有延迟诊断的可能, 因此, 对于此类病灶, 建议有所选择地进行冰冻切片检查。空芯针活检组织中含伴有非典型增生的乳头状病变或硬化性腺病的肿瘤更易延迟诊断, 而乳房X线摄影见簇状微钙化、超声见密集点状强回声和超声BI-RADS 4C~5类均有助于术中快速冰冻切片病理学检查确诊。利用诺模图模型进行预测可以较准确地判断术中快速冰冻切片病理学检查的延迟诊断率, 进而提高外科医师和病理医师的工作效率。此外, 本研究的结论尚需要前瞻性临床研究来进行验证。

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