论著·“神经外科疾病诊疗新进展”重点号

微创手术可减少儿童神经母细胞瘤术中出血、加速术后恢复且未降低肿瘤切除完整性:一项前瞻性队列研究

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[**摘要**] **目的** 神经母细胞瘤(neuroblastoma,NB)是儿童常见颅外恶性肿瘤,手术切除是其综合治疗的重要组成部分。微创手术(minimally invasive surgery,MIS)虽可减少围术期创伤,但其在儿童NB中的肿瘤切除完整性、围术期获益及远期肿瘤学安全性仍需进一步评价。本研究旨在比较MIS与开放手术(open surgery,OPEN)治疗儿童胸腹部NB的临床疗效及预后差异,为儿童NB手术方式选择提供依据。**方法** 采用前瞻性队列研究设计,纳入2015年1月至2023年6月于重庆医科大学附属儿童医院肿瘤外科及胸心外科收治并接受手术治疗的胸腹部NB患儿289例。对于肿瘤体积较大或明显侵犯、包绕周围重要血管及脏器者优先选择OPEN,其余患儿按随机原则分配至MIS组或OPEN组。采用倾向性评分匹配方法,以1∶1比例按年龄、肿瘤最大径、肿瘤部位、术前国际神经母细胞瘤危险分组分期系统分期、病理类型及*MYCN*基因扩增状态等变量进行匹配。比较2组患儿的肿瘤部位、影像学定义危险因子(image-defined risk factors,IDRFs)类型、围术期指标、原发灶肿瘤全切率(gross total resection,GTR)、术中中转OPEN情况、术后并发症及无事件生存结局。生存分析采用Kaplan-Meier法,并采用60个月限制平均无事件生存(event-free survival,EFS)时间作为补充分析指标。**结果** 倾向性评分匹配后共纳入70例患儿,其中MIS组35例,OPEN组35例。2组肿瘤部位分布一致,均为腹部27例、胸部8例。围术期结果显示,MIS组术中出血量少于OPEN组[5.0(5.0,15.0) *vs* 20.0(7.5,37.5)mL,*P*=0.006];MIS组手术时间长于OPEN组[122.0(85.5,162.5)和88.0(71.0,110.0)min,*P*=0.008];MIS组术后恢复进食时间短于OPEN组[1.0(1.0,1.0) *vs* 2.0(1.0,3.0)d,*P*<0.001]。MIS组原发灶肉眼全切除率为94.3%,OPEN组为100.0%,差异无统计学意义。2组患儿术后1年EFS率均为100.0%;MIS组和OPEN组5年EFS率分别为93.1%和97.1%,差异无统计学意义。Kaplan-Meier分析显示,2组EFS差异无统计学意义(Log-rank *P*=0.536)。Cox回归分析显示,2组EFS结局差异无统计学意义(*HR*=2.10,95%*CI*:0.19~23.18,*P*=0.545)。MIS组和OPEN组60个月限制平均EFS时间分别为58.16月和58.71月,差异无统计学意义。2组患儿的IDRFs类型包括肿瘤侵犯同侧肾蒂、压迫同侧主支气管、包绕重要血管,以及肿瘤同时累及胸腔、颈部或腹腔。**结论** 经合理筛选后,MIS切除儿童胸腹部NB原发灶安全可行,可减少术中出血并促进术后恢复,且未明显降低肿瘤切除完整性。MIS适应证应结合风险分层、IDRFs类型、肿瘤大小、肿瘤部位及术者经验综合判断。

[**关键词**] 神经母细胞瘤;微创手术;开放手术;儿童肿瘤;恶性肿瘤生存率

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Minimally invasive surgery reduces intraoperative blood loss and accelerates postoperative recovery without compromising the completeness of tumor resection in children with neuroblastoma: a prospective cohort study

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[**Abstract**] Objective Neuroblastoma (NB) is a common extracranial solid malignancy in children, and surgical resection is an important component of multimodal treatment. Although minimally invasive surgery (MIS) may reduce perioperative trauma, its effects on resection completeness, perioperative outcomes, and long-term oncological safety in pediatric NB require further evaluation. This study aims to compare the clinical efficacy and prognosis of MIS and open surgery (OPEN) for thoracoabdominal NB in children, and to provide evidence for surgical decision-making. Methods A prospective cohort study was conducted on 289 children with thoracoabdominal NB who underwent surgical resection in Department of Surgical Oncology and Department of Thoracic and Cardiovascular Surgery at Children's Hospital of Chongqing Medical University between January 2015 and June 2023. OPEN was preferentially selected for patients with large tumors or tumors with obvious invasion or encasement of major vessels or adjacent organs; the remaining patients were randomly allocated to the MIS group or OPEN group. Propensity score matching (PSM) was performed at a 1∶1 ratio based on age, maximum tumor diameter, tumor location, preoperative International Neuroblastoma Risk Group Staging System (INRGSS) stage, histopathological type and *MYCN* amplification status. The 2 groups were compared with respect to tumor location, image-defined risk factors (IDRFs) type, perioperative parameters, gross total resection (GTR) rate of the primary tumor, intraoperative conversion to OPEN, postoperative complications, and event-free survival (EFS) outcomes. Survival analysis was performed using the Kaplan-Meier method, and 60-month restricted mean EFS time was used as a supplementary endpoint. Results After PSM, 70 patients were included, with 35 patients in the MIS group and 35 in the OPEN group. The distribution of tumor locations was comparable between the 2 groups, with 27 abdominal and 8 thoracic cases in each. Perioperative outcomes showed that compared with the OPEN group, the MIS group had less intraoperative blood loss [5.0 (5.0, 15.0) *vs* 20.0 (7.5, 37.5) mL, P=0.006], longer operative time [122.0 (85.5, 162.5) *vs* 88.0 (71.0, 110.0) min, P=0.008], and shorter time to postoperative oral intake [1.0 (1.0, 1.0) *vs* 2.0 (1.0, 3.0) d, P<0.001]. The GTR rate of the primary tumor was 94.3% in the MIS group and 100.0% in the OPEN group, with no statistically significant difference. The 1-year EFS rate was 100.0% in both groups, and the 5-year EFS rates were 93.1% in the MIS group and 97.1% in the OPEN group. Kaplan-Meier analysis showed no significant difference in EFS between the 2 groups (Log-rank P=0.536). Cox regression analysis also showed no statistically significant difference in EFS outcomes between groups (*HR*=2.10,95%*CI*: 0.19 to 23.18, P=0.545). The 60-month restricted mean EFS time was 58.16 months in the MIS group and 58.71 months in the OPEN group, with no statistically significant difference. IDRFs types in both groups included involvement of the ipsilateral renal pedicle, compression of the ipsilateral main bronchus, encasement of major vessels, and simultaneous tumor involvement of the thoracic cavity and the cervical or abdominal region. Conclusion With appropriate patient selection, MIS for resection of the primary tumor is safe and feasible for children with thoracoabdominal NB. MIS may reduce intraoperative blood loss and facilitate postoperative recovery without substantially compromising resection completeness. The indications for MIS should be determined comprehensively according to risk stratification, IDRFs types, tumor size, tumor location, and surgeon experience.

[**Key words**] neuroblastoma; minimally invasive surgery; open surgery; pediatric tumor; malignant tumor survival rate

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神经母细胞瘤(neuroblastoma,NB)是儿童最常见的颅外恶性肿瘤之一,在小儿肿瘤领域具有较高的发病率和疾病负担[1-2]。目前,NB的治疗通常采取多学科综合治疗模式,包括观察随访、手术治疗、化学治疗、放射治疗、免疫治疗、分化治疗以及自体造血干细胞移植等[3-4]。其中,手术切除在NB综合治疗中占据重要地位,部分患儿可通过单纯手术获得治愈[5]。近年来,微创手术(minimally invasive surgery,MIS)在成人恶性肿瘤的外科治疗中的应用日益广泛。与传统开放手术(open surgery,OPEN)相比,MIS被认为可缩短住院时间、降低术后并发症发生率,且不影响患者远期生存率[6-9]。然而,MIS在儿童恶性肿瘤中的应用仍存在一定争议[10-12]。尽管现有证据尚未明确证实MIS会对儿童肿瘤的分期及预后产生不利影响,但仍有部分研究认为,MIS在肿瘤患儿中存在潜在肿瘤学风险,包括肿瘤破裂或播散、切缘评估不足、分期不充分、淋巴结取样不足及CO_2气腹对肿瘤细胞生物学行为的潜在影响等[13-16]。

目前,NB的治疗仍面临诸多尚待解决的临床问题,尤其是在术后恢复及并发症管理方面仍存在一定挑战[17-18]。随着精准医学的发展,分子靶向治疗及免疫治疗等新型治疗手段逐渐成为NB综合治疗的重要组成部分[19]。多种治疗方式的联合应用为高危患儿,尤其是对化疗耐药或复发的病例,提供了新的治疗策略与希望。近年来,腹腔镜手术在部分病例中显示出与OPEN相当的疗效,但其在复杂肿瘤病例中的应用仍需审慎评估,尤其是当肿瘤与重要血管或神经结构关系密切时,其安全性与根治性问题更应引起重视[20]。

近年来,关于MIS对肿瘤生物学行为影响的研究亦逐渐增多。既往研究表明,与传统OPEN相比,MIS在促进术后恢复、减轻患者痛苦方面具有明显优势,尤其在降低术后并发症发生率及缩短住院时间方面表现突出[21-22]。然而,腹腔镜技术的推广应用在一定程度上仍受术者技术水平及临床经验的影响,不同医疗机构之间的手术效果可能存在差异,这亦成为限制其进一步规范化应用的重要因素。基于当前医学技术的发展现状及上述临床实践中存在的问题,本研究对腹腔镜手术与OPEN在NB患儿中的疗效进行比较分析,以期为MIS在儿童肿瘤外科中的应用提供更为严谨的循证依据。

本研究自2015年1月起在本中心开展,将符合纳入标准的NB患儿分配至MIS组或OPEN组。对2组患儿的术中指标、术后恢复情况及远期预后进行系统比较。本研究旨在补充现有关于腹腔镜技术在儿童NB治疗中应用效果的证据,为优化临床外科治疗路径及制定更为规范的手术策略提供实践依据。

1 资料与方法

1.1 研究对象

本研究采用前瞻性队列研究设计,选取2015年1月至2023年6月重庆医科大学附属儿童医院肿瘤外科及胸心外科收治的289例接受手术治疗的胸腹部NB患儿。纳入标准:①原发肿瘤位于胸部或腹部;②诊断符合国际神经母细胞瘤病理学分类(International Neuroblastoma Pathology Classification,INPC)的诊断标准,并经术后病理检查确诊;③接受原发灶次全切除或肉眼全切除,切除范围≥95%;④临床、手术及随访资料完整。排除标准:①仅接受肿瘤活检或部分切除,切除范围<95%;②原发肿瘤位于颈部、盆腔或其他非胸腹部部位;③缺少关键临床资料或无法获得有效随访资料。鉴于肿瘤疾病的特殊性,所有患儿的手术方式无法完全随机分配。对于肿瘤体积较大,或存在明显侵犯、包绕周围重要血管及脏器的患儿,优先选择OPEN;肿瘤条件不符合上述情况者,再按照随机原则分配至MIS组或OPEN组。本研究已通过重庆医科大学附属儿童医院伦理委员会审查批准[(2023)年伦审(研)第487号],研究过程遵循《赫尔辛基宣言》相关原则,所有患儿监护人均已签署知情同意书。

1.2 患儿筛选及术前评估

所有NB患儿的诊断均参照INPC的诊断标准,接受手术治疗者均于肿瘤切除术后获得病理诊断结果。影像学定义危险因子(image-defined risk factors,IDRFs)由放射科医师与外科医师共同判定。本研究观察到的IDRFs包括:①肿瘤侵犯同侧肾蒂;②肿瘤压迫同侧主支气管;③肿瘤包绕重要血管;④肿瘤跨越相邻解剖区域,同时累及胸腔与颈部或胸腔与腹腔。为便于制定MIS方案,将M期患儿中原发灶无IDRFs者定义为M1期,存在至少1个IDRFs者定义为M2期。根据切除范围将患儿分为3组:全切除(gross total resection,GTR)、次全切除(切除范围≥95%)及部分切除(切除范围<95%)。术中事件根据外科医师和麻醉医师的记录进行收集,并记录术后开始进食时间。自手术日起,通过门诊、住院、电话及电子邮件对患儿进行预后随访。

1.3 测量与评价指标

收集患儿以下资料:①基线及肿瘤特征,包括年龄、肿瘤最大径、肿瘤部位、术前INRGSS分期、病理类型、IDRFs的类型及数量,以及*MYCN*基因扩增状态;②围术期指标,包括术中出血量、手术时间、术后恢复进食时间、输血情况、MIS术中中转OPEN情况及术后并发

症;③肿瘤切除完整性,根据术中记录及术后影像学资料评价原发灶切除范围,分为肉眼GTR、次全切除(切除范围≥95%但未达到GTR)和部分切除(切除范围<95%);④随访及预后指标,包括随访时间和无事件生存(event-free survival,EFS)结局。EFS时间自手术日期起计算,终点事件定义为肿瘤复发、进展或死亡。本研究的随访仍在持续,本次分析的数据截止日期为2026年1月31日。对于截至数据截止日期尚未发生终点事件的患儿,于其末次获得随访信息的日期进行右删失。鉴于终点事件数较少且删失比例较高,EFS分析结果仅作探索性解释。为进一步评估EFS分析结果的稳健性,本研究以60个月为限制时间点,采用限制平均无事件生存时间(restricted mean event-free survival time,RMEFST)作为补充预后评价指标。

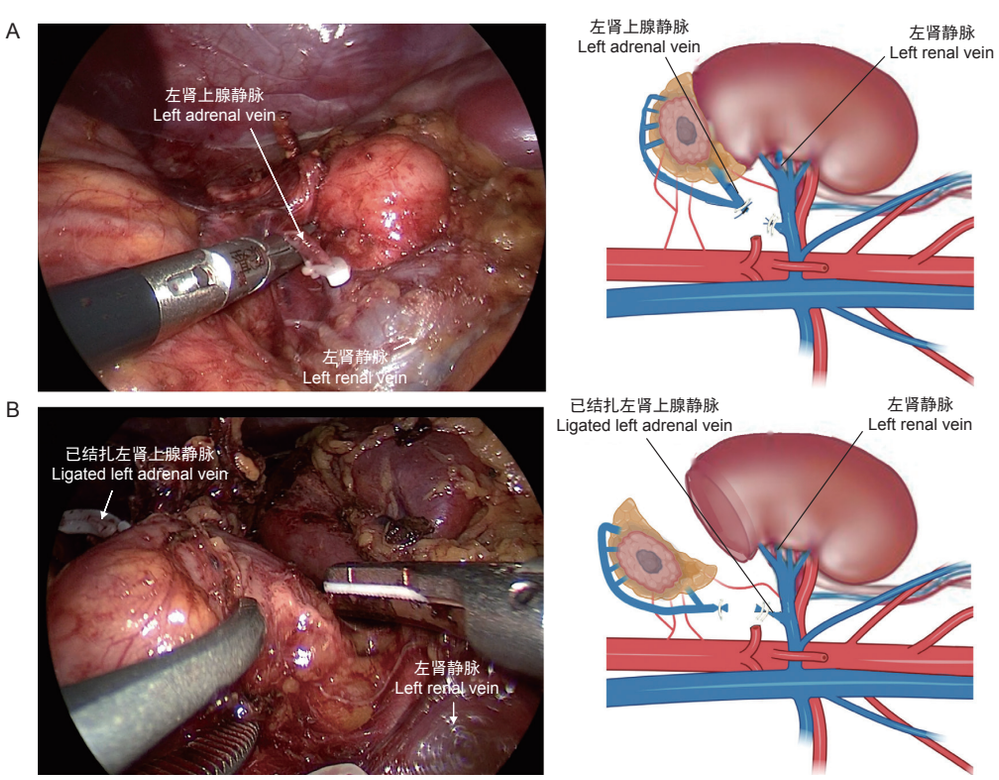
1.4 倾向性评分匹配

鉴于本研究中手术方式未能完全随机分配,为降低基线差异及选择偏倚对研究结果的影响,在符合纳排标准的患儿中进行倾向性评分匹配(propensity score matching,PSM)。以手术方式(MIS或OPEN)为处理变量,将年龄、肿瘤最大径、肿瘤部位、术前INRGSS分期、病理类型及*MYCN*基因扩增状态等术前变量纳入倾向性评分模型,计算每例患儿接受MIS的倾向性评分,并按照1∶1比例进行匹配。

1.5 手术方法

肿瘤位于左侧肾上腺区者,全身麻醉后取右侧倾斜60°卧位。经脐部置入穿刺套管并建立气腹,采用低流量充气,并维持腹压在10~12 mmHg。于左上腹另置入2个穿刺套管,使用电外科器械或超声刀进行分离。离断膈结肠韧带与胃结肠韧带后,沿腹膜后间隙充分游离左侧结肠系膜,使其自然滑向右腹腔,充分显露左肾中下极的肾前筋膜。沿肾筋膜表面游离脾肾韧带及脾膈韧带,将脾脏充分游离并翻转,直至显露胃底,使脾脏自然下滑至右侧腹腔。紧贴肾筋膜分离胰尾,并将其向下翻转,显露左肾静脉。轻柔打开左肾静脉鞘,显露左肾上腺静脉。分离并显露左肾上腺静脉约1~2 cm,以Hem-o-lok夹闭后离断。随后打开肾筋膜,显露肾上腺肿瘤边缘。使用超声刀钝性或锐性分离肾上腺肿瘤与肾脏,使2者完全分离。将肾上腺肿瘤与腹主动脉间的血管及组织以Hem-o-lok夹闭后离断,完整切除肾上腺及肿瘤(图1)。

肿瘤位于右侧肾上腺区时,患儿取左侧倾斜45°卧位。以肝脏牵开器向上牵开肝脏,采用超声刀沿肝



A: Dissection and exposure of the left adrenal vein for approximately 1 to 2 cm, followed by clipping with Hem-o-lock clips and division; B: Complete separation of the adrenal tumor from the kidney using blunt and sharp dissection with an ultrasonic scalpel

图1 腹腔镜左肾上腺区神经母细胞瘤切除术

Figure 1 Laparoscopic resection of left adrenal neuroblastoma

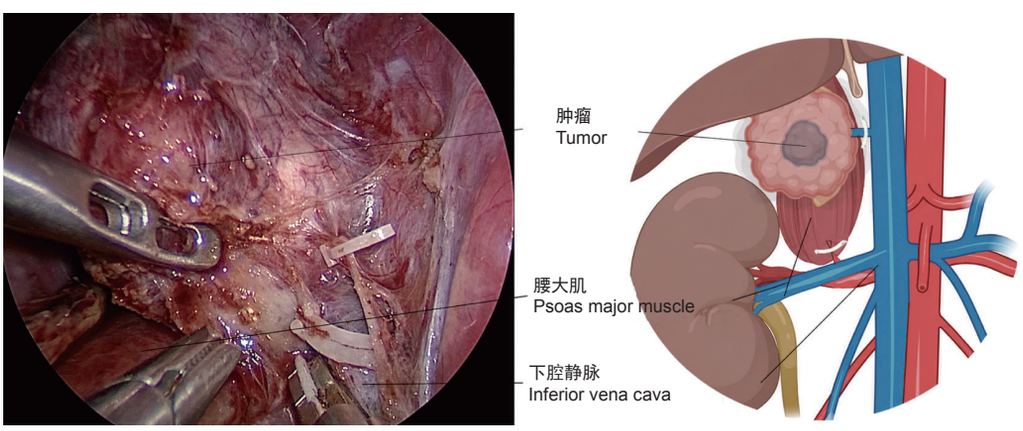
脏下缘切开肝肾韧带,充分显露肾上腺及肾上腺肿瘤上缘。沿下腔静脉右缘打开腹膜。建立5 mm辅助操作孔,以肠钳将肾上极向足侧轻压,超声刀打开肾包膜,将肾上腺肿瘤下方分离至腰大肌。沿腰大肌平面分离肾上腺及肿瘤,以超声刀及Hem-o-lok夹闭并离断肾上腺下动脉,以Hem-o-lok夹闭并结扎肾上腺中央静脉。将肾上腺及肿瘤从膈肌及肝脏下缘游离,以Hem-o-lok夹闭肾上腺上动脉,完整切除肾上腺及肿瘤(图2)。

若术中发现肾门部淋巴结肿大,需首先打开肾动静脉鞘。充分游离肾动静脉后,分别以牵引带牵开,注意保护输尿管及肾脏血管,完整切除肿大淋巴结(图3)。

将切除的肿瘤标本置入取物袋,经扩大的脐部或下腹部切口取出。

1.6 统计学分析

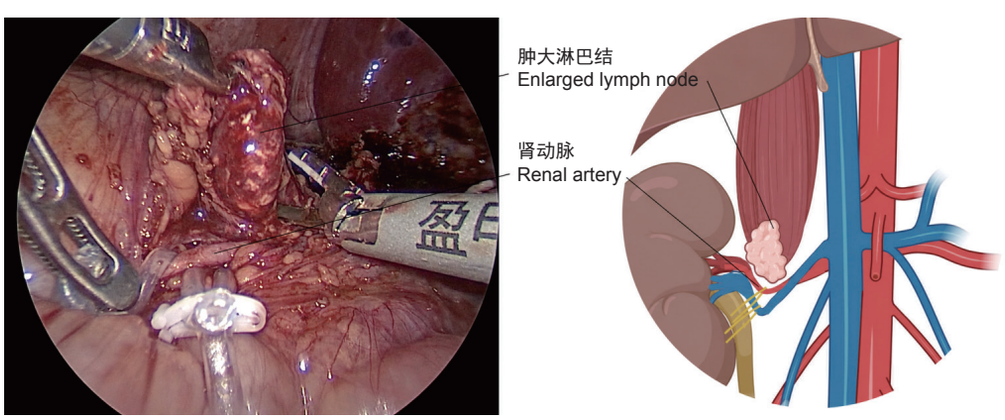
采用SPSS 27.0软件进行统计学分析。连续变量用$M(P_{25},P_{75})$表示,组间比较采用Mann-Whitney U检验;分类变量用频数(%)表示,组间比较采用Fisher确切概率法。采用Kaplan-Meier法估计EFS曲线,并采用Log-rank检验比较2组EFS的差异;采用Cox比例风险回归模型计算风险比(hazard ratio,*HR*)及其95%*CI*。为进一步评估EFS分析结果的稳健性,以60个月为限制时间点计算RMEFST。RMEFST定义为0~60个月内Kaplan-Meier EFS曲线下面积,表示患儿在该预设时间窗内预期处于无事件状态的平均时间;分别估计MIS组和OPEN组的RMEFST,并比较2组间的差异。所有检验均为双侧检验,$P<0.05$表示差异具有统计学意义。



The right adrenal tumor is dissected along the psoas major plane, with careful exposure of its anatomical relationship to the inferior vena cava and adjacent renal vessels

图2 腹腔镜右肾上腺区神经母细胞瘤切除术

Figure 2 Laparoscopic resection of right adrenal neuroblastoma



Before resection of the enlarged renal hilar lymph nodes, the renal artery and vein are isolated and retracted with vessel loops to obtain adequate exposure and protect the renal vessels

图3 腹腔镜肾门部肿大淋巴结切除术

Figure 3 Laparoscopic resection of enlarged renal hilar lymph nodes

2 结果

2.1 2组患儿基线资料分布均衡

本研究最终纳入70例患儿,其中MIS组35例,OPEN组35例。2组患儿中,肿瘤位于腹部者各27例,位于胸部者各8例。2组患儿的INRGSS分期、IDRFs数量、*MYCN*状态及病理组织类型分布一致。MIS组与OPEN组年龄分别为39.0(11.5,62.5)个月和29.0(9.7,60.5)个月,肿瘤最大径分别为4.06(3.48,5.83)cm和4.77(4.30,5.80)cm,差异均无统计学意义(表1)。

2.2 MIS组术中出血量减少、手术时间延长、术后恢复进食时间缩短

对2组患儿的手术相关指标进行统计学分析,结果显示,MIS组术中出血量少于OPEN组[5.0(5.0,15.0) *vs* 20.0(7.5,37.5)mL,*P*=0.006]。MIS组手术时间长于OPEN组[122.0(85.5,162.5) *vs* 88.0(71.0,110.0)min,*P*=0.008]。MIS组术后恢复进食时间短于OPEN组[1.0(1.0,1.0) *vs* 2.0(1.0,3.0)d,*P*<0.001]。见表2。

2.3 2组患儿随访时间和EFS率接近

2组患儿的随访时间分布较为均衡,MIS组和OPEN组中位随访时间分别为48.0(33.5,81.0)月和52.0(38.5,64.5)个月,差异无统计学意义。MIS组最长随访时间为113个月,OPEN组最长随访时间为122个月。在Kaplan-Meier分析中,末次随访时未发生复发、进展或死亡者按右删失处理,2组患儿术后1年EFS率均为100.0%;MIS组和OPEN组5年EFS率分别为

表1 2组患儿临床资料比较[例(%), $M(P_{25}, P_{75})$]

Table 1 Comparison of baseline clinical characteristics between the 2 groups of children[n(%), $M(P_{25}, P_{75})$]

Item	MIS group(n=35)	OPEN group(n=35)	P
Site of primary tumor			1.000
Abdomen	27(77.1)	27(77.1)	
Thorax	8(22.9)	8(22.9)	
Age at operation/months	39.0(11.5, 62.5)	29.0(9.7, 60.5)	0.756
Preoperative INRGSS stage			1.000
L1	15(42.9)	15(42.9)	
L2	16(45.7)	16(45.7)	
M	4(11.4)	4(11.4)	
MYCN status			1.000
Amplified	2(5.7)	2(5.7)	
Non-amplified	33(94.3)	33(94.3)	
Histological type			1.000
Ganglioneuroma	7(20.0)	7(20.0)	
Ganglioneuroblastoma	12(34.3)	12(34.3)	
Neuroblastoma	16(45.7)	16(45.7)	
Number of IDRFs			1.000
No IDRF	16(45.7)	16(45.7)	
One IDRF	18(51.4)	19(54.3)	
More than one IDRF	1(2.9)	0(0.0)	
IDRF type			
Ipsilateral renal pedicle involvement	17(48.6)	15(42.9)	0.811
Ipsilateral main bronchus compression	0	1(2.9)	1.000
Other major-vessel encasement	1(2.9)	3(8.6)	0.614
Extension across adjacent anatomical regions	2(5.7)	0	0.493
Maximum tumor diameter/cm	4.06(3.48, 5.83)	4.77(4.30, 5.80)	0.205
Tumor size category/cm			1.000
<5	23(65.7)	22(62.9)	
≥5	12(34.3)	13(37.1)	

MIS: minimally invasive surgery; OPEN: open surgery; INRGSS: International Neuroblastoma Risk Group Staging System; IDRF: image-defined risk factor

表2　2组患儿手术结果及生存结果比较[例(%), $M(P_{25}, P_{75})$]

Table 2　Comparison of surgical and survival outcomes between the 2 groups[n(%), $M(P_{25}, P_{75})$]

Item	MIS group(n=35)	OPEN group(n=35)	P
Operation time/min	122.0(85.5, 162.5)	88.0(71.0, 110.0)	0.008
Intraoperative blood loss/mL	5.0(5.0, 15.0)	20.0(7.5, 37.5)	0.006
Time to oral intake/d	1.0(1.0, 1.0)	2.0(1.0, 3.0)	<0.001
Intraoperative transfusion	3(8.6)	5(14.3)	0.710
Gross total resection	33(94.3)	35(100.0)	0.493
Follow-up duration/months	48.0(33.5, 81.0)	52.0(38.5, 64.5)	0.902
EFS events[a]	2(5.7)	1(2.9)	1.000
1-year EFS rate/%	100.0	100.0	–
5-year EFS rate/%	93.1	97.1	0.536

MIS: minimally invasive surgery; OPEN: open surgery; GTR: gross total resection; EFS: event-free survival; a: Events are defined as recurrence, progression, or death

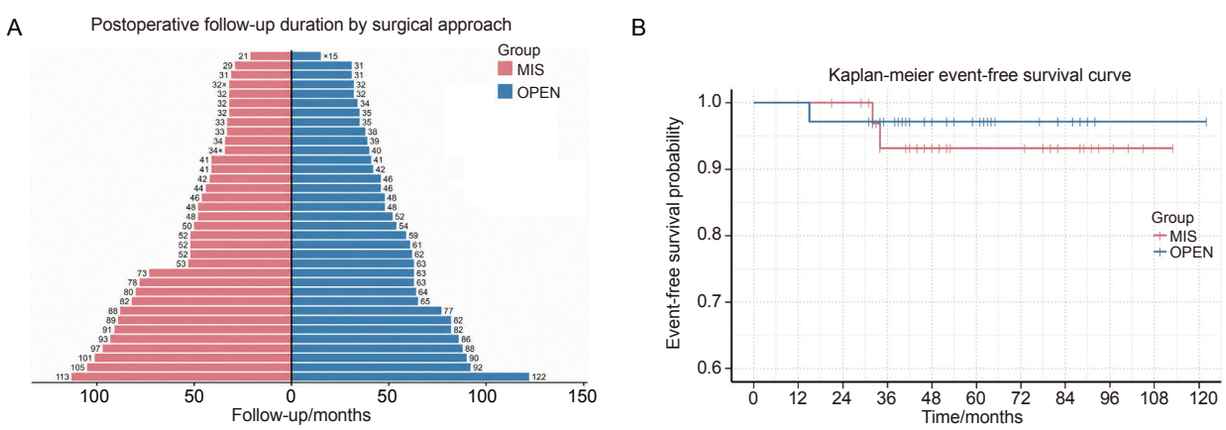
93.1%和97.1%,2组EFS曲线差异无统计学意义(Log-rank P=0.536,表2、图4)。Cox回归分析显示,2组EFS结局差异无统计学意义(HR=2.10,95%CI:0.19~23.18,P=0.545)。MIS组和OPEN组分别发生2例和1例事件,其余33例和34例均在明确的末次随访时间删失,无随访资料缺失。

2.4　2组患儿60个月RMEFST时间接近

鉴于2组终点事件数较少且右删失比例较高,单纯依赖Kaplan-Meier曲线可能影响曲线后段估计的稳定性。为进一步验证结果的稳健性,本研究采用60个月RMEFST作为补充分析指标。结果显示,MIS组和OPEN组60个月RMEFST分别为58.16(95%CI:55.68~60.63)个月和58.71(95%CI:56.23~61.20)个月,组间差值为-0.56(95%CI:-4.06~2.95)个月,差异无统计学意义,提示2组在60个月内平均EFS时间接近(图5)。上述结果仍应结合样本量及终点事件数有限的特点谨慎解释。

2.5　2组患儿的肉眼全切除率均较高、严重并发症均较少

2组患儿的IDRFs包括肿瘤侵犯同侧肾蒂、肿瘤压迫同侧主支气管、肿瘤包绕重要血管以及肿瘤同时累及胸腔、颈部或腹腔。MIS组35例患儿中,2例术中中转OPEN:1例为原发于腹部的NB,存在2个IDRFs,肿瘤延伸至胸腔的部分无法在腔镜下切除,故增加开放肋缘下切口完成切除;另1例为L2期胸部NB,因肿瘤侵犯膈肌并致严重粘连而中转OPEN。MIS组原发灶肉眼全切除率为94.3%(33/35),OPEN组为100.0%(35/35),差异无统计学意义(表2):MIS组中1例为胸部NB延伸至颈部,另1例为胸部神经节细胞瘤侵犯邻近椎管;OPEN组35例患儿均实现肉眼全切除。OPEN组中1例胸部NB患儿术后发生严重乳糜胸,经禁食8 d并接受全肠外营养后恢复,其余患儿术后均未出现严重并发症。



A: Distribution of postoperative follow-up duration. Each horizontal bar represents one patient, and the bar length indicates the follow-up duration in months; the "×" symbol indicates recurrence, progression, or death; B: Kaplan-Meier curves of postoperative event-free survival

图4　MIS组与OPEN组神经母细胞瘤患儿术后随访时间及无事件生存情况

Figure 4　Postoperative follow-up duration and event-free survival in children with neuroblastoma in the MIS and OPEN groups

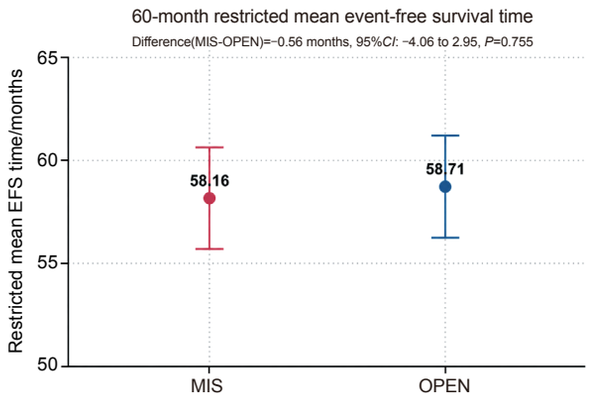


图5 MIS组与OPEN组患儿60个月RMEFST比较

Figure 5 Comparison of the 60-month restricted mean event-free survival time between the MIS and OPEN groups

3 讨论

3.1 MIS有助于减少创伤并加快恢复,但不必然缩短手术时间

NB是儿童最常见的颅外实体肿瘤,手术治疗是综合治疗中的重要环节。MIS可以提供放大的手术视野,帮助术者进行精细解剖[20]。对患儿而言,MIS具有切口小、术后美容效果好、减少肠粘连发生及减轻术后疼痛等优势[22-23]。也有观点认为,MIS可能存在肿瘤破裂或播散、切缘评估不足、分期不充分、淋巴结取样不足等潜在风险,且CO_2气腹可能影响肿瘤生物学行为[13-16],但目前临床研究尚未证实上述因素会导致不良肿瘤学结局。

本研究显示,经倾向性评分匹配后,MIS组术中出血量少于OPEN组,术后恢复进食时间短于OPEN组,提示MIS在围术期恢复方面具有一定优势。这一结果与既往关于儿童NB及胚胎性肿瘤MIS的研究结论基本一致[24-27]。然而,本研究中MIS组手术时间长于OPEN组,与部分既往研究结果并不完全一致[24,27-28]。其原因可能与本研究纳入较多L2期及M2期患儿有关,此类患儿常伴有更复杂的局部解剖关系,腔镜下分离、显露及血管处理所需时间更长。因此,MIS的围术期获益并不意味着所有病例均可缩短手术时间,手术时间仍受肿瘤部位、IDRFs类型、肿瘤大小及术者经验等因素影响。

3.2 MIS未明显影响肿瘤切除完整性,但生存结局仍需谨慎解释

肿瘤学安全性是儿童恶性肿瘤MIS能否推广的核心问题。本研究中,2组肉眼全切除率比较差异无统计学意义,提示在合理筛选病例后,MIS并未明显降低原发灶切除完整性。既往研究亦显示,对于经选择的NB患儿,MIS可获得与OPEN相近的肿瘤切除率及生存结局[24-27]。

本研究进一步采用EFS作为结局指标,事件定义为复发、进展或死亡。结果显示,2组1年及5年EFS率差异无统计学意义,60个月RMEFST时间亦接近,提示在目前样本及随访条件下,MIS未显示出较OPEN更差的EFS结局。需要指出的是,本研究终点事件数较少,右删失比例较高,Kaplan-Meier曲线后段稳定性有限。因此,生存分析结果应作为探索性结果解释,不能据此简单推断2种手术方式在长期预后方面完全等同。

3.3 MIS适应证应建立在风险分层基础上

NB具有显著的生物学异质性,临床预后不仅取决于肿瘤部位及手术切除程度,还与年龄、INRGSS分期、病理类型、*MYCN*扩增状态、DNA倍体及染色体节段性异常等因素密切相关[29-32]。因此,NB的手术方式选择不应脱离风险分层单独讨论,而应纳入风险适应性综合治疗策略中综合评估。

对于低危或部分中危、原发灶局限且缺乏不良生物学因素的患儿,手术切除在局部控制中具有更核心的作用;在能够保证肿瘤完整切除及肿瘤学安全性的前提下,MIS可作为减少围术期创伤的合理选择。相反,对于高危或转移性患儿,预后更多受肿瘤生物学特征、化疗敏感性及全身治疗反应影响,原发灶手术的目标应更强调安全切除、减少并发症及避免延误后续治疗,而不宜单纯追求手术方式本身的微创化或切除范围最大化。本研究在倾向性评分匹配中纳入了年龄、INRGSS分期、病理类型及*MYCN*状态等因素,以尽量降低两组风险构成差异对结果的影响。但本研究未能完整纳入DNA倍体、11q异常及其他染色体节段性异常等分子分层因素,这也是解释结果时需要注意的局限。

3.4 IDRFs类型和肿瘤大小应共同用于判断MIS可行性

在风险分层框架下,IDRFs既是INRGSS分期的重要依据,也是评估MIS可行性的关键局部解剖因素。目前,NB的MIS适应证尚未形成统一标准,临床实践中仍较多依赖术者经验。既往研究认为,无IDRFs的局限性肿瘤更适合微创切除[25,27,33];但也有研究指出,IDRFs并非MIS的绝对禁忌证,部分IDRFs如肿瘤侵犯肾蒂,可能并不显著影响手术效果[33-35]。

本研究中,MIS组伴有IDRFs的病例多为肿瘤侵犯肾蒂。IDRFs阴性患儿与IDRFs阳性患儿在肿瘤切除程度方面差异无统计学意义,提示并非所有IDRFs

均应被视为MIS禁忌。关于肿瘤大小,既往多建议MIS适用于肿瘤最大直径<5 cm或体积<75 cm^3的病例[35-36]。本研究中,MIS组有12例患儿术前原发灶最大直径为5~10 cm,均实现肉眼全切除,提示单纯以肿瘤大小作为手术方式选择标准可能过于简单。综合本研究结果,MIS适应证应结合风险分层、IDRFs类型、肿瘤大小、肿瘤部位及术者经验共同判断,而不宜仅依据单一指标决定。

3.5 胸部肿瘤和部分转移性病例可能从MIS中获益

胸部NB约占全部NB的15%。与腹部NB相比,胸部NB的MIS已获得更广泛认可[37-39]。部分研究认为,胸腔镜手术可作为治疗纵隔神经源性肿瘤的重要手术方式[39-41]。其原因可能在于胸部通常具有相对较好的生物学特性和局限性[42],且MIS可避免与传统开胸手术相关的肩臂功能障碍、脊柱侧弯及慢性疼痛等并发症[41,43]。

转移性NB是否适合MIS仍存在争议。既往研究较少专门讨论M期患儿的原发灶微创切除问题。本研究中,4例M期患儿接受原发灶MIS,均实现肉眼完整切除。对于M期或MS期患儿,原发灶切除对生存的影响仍不完全明确[44-46],预后往往更多取决于转移病灶控制情况、*MYCN*状态及全身治疗反应。因此,对伴远处转移的患儿,手术目标应强调安全、低创伤和尽快衔接后续治疗。若原发灶局部条件允许,MIS可能有助于缩短恢复时间、减少治疗中断,为后续化疗等综合治疗争取时间[23,33]。本研究根据原发灶IDRFs数量将M期患儿进一步分为M1期与M2期,可作为INRGSS分期之外的局部手术可行性补充评估,但这一分层仍需更多病例验证。

3.6 本研究的局限性

本研究虽为前瞻性研究,但仍存在局限性:①受儿童肿瘤疾病特点限制,手术方式难以完全随机分配,在匹配过程中,未能实现每例患儿的绝对匹配,仅能进行最大程度的PSM;②MIS组中IDRFs类型相对有限,未能充分比较不同IDRFs类型对手术方式选择及切除效果的影响;③本研究纳入病例时间跨度较长,部分患儿随访时间仍较短,虽然所有患儿均处于持续随访过程中,但截至本次数据分析截点,较多患儿尚未发生复发、进展或死亡等终点事件,因此Kaplan-Meier曲线中右删失病例较多,可能影响曲线后段稳定性及长期预后差异判断。未来仍需开展更大规模的多中心前瞻性研究,并结合完整分子分层资料,进一步明确不同风险组患儿接受MIS的适应证及获益边界;仍需延长随访时间、增加终点事件数,并在更成熟的随访数据基础上进一步验证MIS与OPEN对患儿长期EFS结局的影响。

综上所述,经合理筛选后,MIS切除儿童NB原发灶安全可行,可获得与OPEN相近的肿瘤切除率,且未显示出对术后EFS结局的不利影响。既往研究亦证实,接受MIS的患儿可获得与OPEN相当的肿瘤切除率及生存结局[47],且MIS在减少术中出血、缩短住院时间及促进术后恢复等方面具有优势[48-49]。随着MIS适应证的不断完善,其有望成为符合条件患儿的重要手术选择。尤其对于肿瘤体积适中、IDRFs较少且经风险分层评估适宜手术的病例,MIS可能具有更为明显的临床获益。

利益冲突 本文所有作者声明不存在利益冲突

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