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• 临床研究 •

高级别肉瘤患者肺部不确定性质结节胸部CT影像学特征与转归：一项单中心回顾性研究

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Chest CT Imaging Features of Indeterminate Pulmonary Nodules and Outcomes in Patients with High-grade Soft Tissue Sarcoma: A Single-center Retrospective Study

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Abstract: Objective To explore the imaging features, clinical outcome, and prognosis of indeterminate pulmonary nodules (IPN) in patients with high-grade soft tissue sarcoma. **Methods** A retrospective study of 82 patients with high-grade soft tissue sarcoma who have IPNs. The clinical characteristics, imaging features of IPN, and survival of patients were analyzed with statistical software. **Results** The IPN size of 82 patients was 6.453 ± 0.864 mm. IPN diameter, shape, density, and nodule discovery interval may be CT imaging features related to malignancy tendency. Age ($HR=1.047$, $95\%CI: 1.007-1.088$) and interval between each nodule discovery ($HR=3.194$, $95\%CI: 1.052-9.694$) are independent factors that affect the survival of patients with malignant IPN. **Conclusion** The imaging features of chest CT may provide important guidance for determining the nature and survival prognosis of benign and malignant nodules.

Key words: High-grade soft tissue sarcoma; Pulmonary nodules; Computer tomography; Prognosis

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摘要: 目的 分析肺部高级别软组织肉瘤患者肺部不确定性质结节 (IPN) 的影像学特征与转归。**方法** 回顾性分析82例伴IPN的高级别肉瘤患者的临床资料, IPN的CT影像学特征以及转归。**结果** IPN平均大小 6.453 ± 0.864 mm。IPN直径、形状、密度及结节发现间期可能是恶性转归相关的CT影像特征。年龄 ($HR=1.047$, $95\%CI: 1.007-1.088$) 与结节发现间期 ($HR=3.194$, $95\%CI: 1.052-9.694$) 是影响恶性IPN患者生存期的独立因素。**结论** 胸部CT的影像学特征可能为良恶性结节性质和生存预后的判断提供重要指导意义。

关键词: 高级别软组织肉瘤; 肺结节; 计算机断层摄影; 预后

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0 引言

肺部是非肺恶性肿瘤常见的转移部位, 肺结节是肺转移灶的前期状态。肺结节通常是指肺内

单发或多发、直径 ≤ 3 cm、影像学表现为密度增高的病灶, 主要分为磨玻璃密度结节、部分实性结节和实性结节^[1]。随着胸部CT技术的高速发展和定期筛查的普及, 胸部结节的检出率逐年增高。Hanamiya等^[2]通过使用2 mm厚度的薄层CT技术发现75%的肺外恶性肿瘤患者存在非钙化肺结节。

高级别软组织肉瘤 (soft tissue sarcoma, STS) 恶性程度高, 异质性强, 约占所有恶性肿瘤的1%。高级别STS主要转移到肺部, 是导致死亡的主要原因^[3]。据统计, 在四肢高级别STS患者中, 大约20%的患者病程中会出现肺部转移^[4]。已有研究表明, 肺部转移灶的手术切除和首诊时肺部

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转移灶的直径大小与高级别STS患者预后显著相关^[5-6]。由于肺转移的诊断显著影响治疗结果和预后,因此关于高级别STS患者肺部转移的早期诊断至关重要。高级别STS往往发生于成人,而肺结节在成人中往往也有着较高的检出率,因此该结节可能为转移灶,也有可能为炎性结节或肉芽肿等病变。肺部不确定性质结节(indeterminate pulmonary nodules, IPN)是指通过影像学资料无法判断病变良恶性的单发或多发结节^[7]。Rissing等^[8]回顾性报道1/5的肉瘤患者发现IPN,其中大约70%的肺部IPN被证实为转移灶。因此对于高级别STS伴IPN患者,如何有效地对IPN进行鉴别诊断其良恶性,评估其风险,对高度怀疑恶性结节提高复查频率并及早干预,同时对低风险结节避免不必要的过度治疗,是高级别STS进展期诊断治疗关键。

本研究通过回顾性分析本中心合并IPN的高级别STS患者的临床特征、CT影像学特征以及结节性质转归,旨在为高级别STS伴IPN患者的诊断和治疗提供依据。

1 资料与方法

1.1 纳入与排除标准

纳入标准:(1)2016年1月至2020年12月于东部战区总医院经治的软组织肉瘤患者;(2)明确病理诊断为高级别STS;(3)胸部筛查CT示肺部占位,最大结节直径 ≥ 5 mm且 < 10 mm,结节数量 < 5 个;(4)完整临床及随访资料。排除标准:(1)确诊时已有明确其他肺部疾病;(2)肺部非结节性阴影,如斑片状炎性阴影;(3)同时患有其他恶性肿瘤;(4)临床资料不全或随访资料不全。

1.2 一般资料

本研究已得到东部战区总医院医学伦理委员会的批准。2016年1月至2020年12月收治高级别STS 213例,患者经胸部CT筛查IPN患者82例,IPN发生率为38.5%。其中男47例、女35例,中位年龄53岁(38~82岁)。82例患者中,脂肪肉瘤25例、滑膜肉瘤18例、恶性纤维组织细胞瘤13例、腺泡状软组织肉瘤8例、平滑肌肉瘤5例、横纹肌肉瘤5例、纤维肉瘤4例、血管肉瘤4例。

1.3 观察指标

患者均采用厚1 mm,螺距1.0 mm薄层CT进行检查。筛查时机:(1)确诊为高级别STS时;(2)治疗周期中每3个月1次频率筛查;(3)治疗周期结束后,2年内每3个月1次筛查后无明显异常改为每6个月1次频率筛查。定义IPN转归为良性

的标准:(1)无治疗时,复查12个月内结节大小及数量无变化;(2)手术切除标本证实为非肿瘤性病变。定义IPN转归为转移灶的标准:(1)切除手术标本病理证实为高级别STS肺转移;(2)治疗过程中结节大小增大至10 mm或以上,或数量增多;(3)靶向药物治疗有效。

纳入IPN的CT影像学特征:IPN直径大小、IPN数量(单发/多发)、IPN位置(外周/中央)、IPN形状(类圆形/不规则)、IPN密度(钙化/实性/磨玻璃/混合性)、IPN边界(边界清晰/边界模糊)以及IPN发现间期(初次筛查/治疗后)。

1.4 统计学方法

SPSS26.0统计软件进行统计学分析,Graph Pad Prism 8.0绘制生存曲线及森林图。卡方检验比较良恶性转归中IPN影像学特征差异,Kaplan-Meier检验比较单因素对生存相关的相关性,Cox风险回归模型进行生存相关的多因素分析。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般结果

82例伴有IPN的高级别STS患者中男47例、女35例,中位年龄53岁(38~82岁)。82例患者肺部IPN平均大小 6.453 ± 0.864 mm,其中IPN单发35例、多发47例。IPN位于肺叶外周共44例、38例IPN位置位于肺中央。62例患者其IPN边缘光滑、20例边缘模糊。34例患者其IPN形状为类圆形、48例患者为不规则形。根据IPN于胸部CT上的结节密度,15例患者IPN为钙化的高密度影,28例患者为实性,21例患者为磨玻璃性质,18例患者为混合性。47例患者为确诊高级别STS时初次筛查肺部情况时发现,35例患者为开始治疗后定期筛查肺部情况时发现。

2.2 影响高级别STS患者IPN的转归相关因素

82例高级别STS患者随访发现,43例患者IPN进展为肺部转移,39例保持稳定,最终确诊为良性结节。将82例患者分为转移性结节组($n=43$)和良性结节组($n=39$)。比较两组患者胸部CT影像学特征发现,两组患者结节平均大小、结节数量、形状、密度以及结节发现间期差异有统计学意义,见表1。伴有IPN的高级别STS患者具有较大的IPN直径、类圆形、实性或混合性以及治疗后出现IPN可能具有更高的恶变倾向。

2.3 恶性转归IPN高级别STS患者的生存相关因素分析

43例恶性转归的IPN高级别STS患者中,25例

表1 IPN中转移性结节组与良性结节组的胸部CT影像学特征比较

Table 1 Comparison of chest CT imaging features between metastatic nodules and benign nodules in IPN

Features	Metastatic nodules (n=43)	Benign nodules (n=39)	P	Chi-square value/t
Average age (years)	55.205±9.105	56.442±10.133	0.422	-0.579
Gender			0.462	0.542
Male	23	24		
Female	20	15		
Average size of nodules(mm)	6.969±1.118	5.9372±0.609	0.001	5.258
Number of nodules			0.000	18.598
Single	15	32		
Multiple	28	7		
Position of nodules			0.358	0.845
Peripheral position	21	23		
Central position	22	16		
Nodule margin			0.444	0.587
Smooth	34	28		
Blurred	9	11		
Shape of nodules			0.000	13.450
Round	26	8		
Irregular	17	31		
Density of nodules			0.000	39.521
Calcification	2	13		
Solid	25	3		
Ground-glass	3	18		
Mixed	13	5		
Interval of nodule diagnosis			0.000	14.942
Initial screening examination	16	31		
Post-treatment	27	8		

死亡、18例存活，平均生存期为28.442±20.041个月。将患者性别及IPN的CT影像学特征对IPN诊断后生存期的影响进行单因素分析。结果显示，IPN位置以及结节发现间期与恶性转归的IPN高级别STS患者的IPN诊断后生存期相关，见表2、图1。进一步将表2中P<0.150以及文献中既往已报道与高级别肉瘤患者预后相关的因素纳入到多因素分析中。结果显示年龄 (HR=1.047, 95%CI: 1.007~1.088) 与结节发现间期 (HR=3.194, 95%CI: 1.052~9.694) 是影响伴恶性转归的IPN高级别STS患者IPN诊断后生存期的独立因素，见图2。年龄较大以及治疗后发现IPN导致患者具有更差的生存预后。

3 讨论

肺部是高级别STS转移最常见的部位，因此，胸部CT也成为最常用的肺部转移筛查手段。随着薄层CT的应用，肺外恶性肿瘤患者肺部结节的诊断率也从23%提高至75%^[2,9]。美国学者Rissing最早在软组织肉瘤患者的肺部随访中提出IPN的概

表2 影响高级别STS患者IPN诊断为恶性IPN后生存期的单因素分析

Table 2 Univariate analysis of survival after IPN diagnosis in patients with high-grade STS and malignant IPN

Factors	n	Mean survival time	P	χ ²
Gender			0.521	0.413
Male	23	26.913±19.289		
Female	20	36.050±20.783		
Number of nodules			0.069	3.317
Single	15	40.067±24.604		
Multiple	28	26.393±16.084		
Position of nodules			0.023	5.188
Peripheral position	21	25.810±15.348		
Central position	22	36.273±23.298		
Nodule margin			0.908	0.013
Smooth	34	32.382±20.427		
Blurred	9	26.556±20.231		
Shape of nodules			0.206	1.602
Round	26	29.615±16.317		
Irregular	17	33.529±25.583		
Density of nodules			0.238	4.228
Calcification	2	54.000±8.485		
Solid	25	28.880±16.207		
Ground-glass	3	54.333±14.012		
Mixed	13	26.692±24.955		
Interval of nodule diagnosis			0.018	5.569
Initial screening examination	16	37.687±24.013		
Post-treatment	27	27.296±17.043		

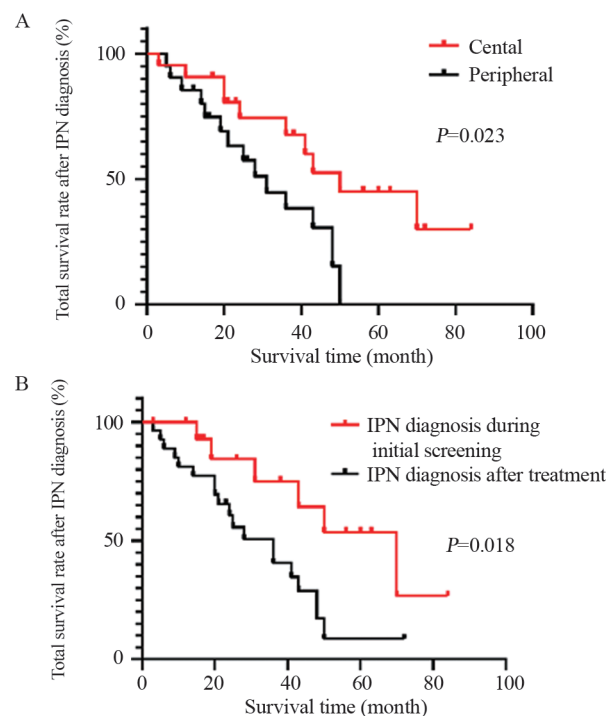


图1 恶性转归的IPN高级别STS患者不同IPN位置及结节发现间期的生存曲线

Figure 1 Survival curves of different IPN positions and nodule discovery intervals in patients with high-grade STS and malignant IPN

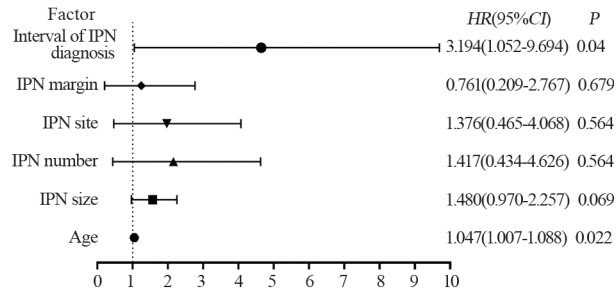


图2 恶性转归的IPN高级别STS患者的生存多因素分析的森林图

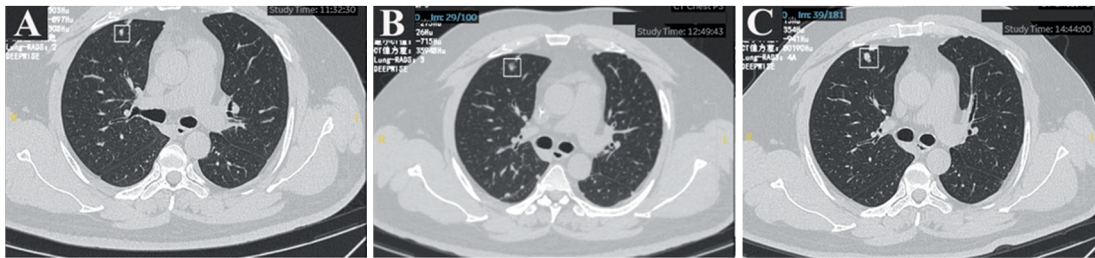
Figure 2 Forest plot for the multivariate analysis of survival in patients with high-grade STS and malignant IPN

念^[8], 并将IPN定义为至今≤10 mm的肺部结节。在331例肉瘤患者中, 共71例(21.45%)发现肺部IPN。71例伴有肺部IPN的患者最终20例发展为肺部转移, 结节恶性转归率为28.17%^[8]。Mayo等^[10]对149例肉瘤患者随访发现49例患者发现肺部IPN, IPN发生率为32.88%, 结节恶性转归率为

30.61%。本中心收治的213例患者中通过胸部CT筛查伴有IPN的高级别STS患者82例, IPN检出率38.5%, 稍高于上述文献报道, 可能原因如下:

(1) 本中心采用厚1 mm, 螺距1.0 mm薄层CT, 相对于上述2007年及2019年的研究中的胸部CT扫描层数更薄, 对胸部微小结节的筛查有更高的检出率; (2) 本项研究聚焦于高级别STS, 相较于STS恶性程度更高, 肺转移率更高; (3) STS异质性强, 不同病理类型的STS表现出不同的肺部转移能力, 因此肺部结节检出率也不尽相同。

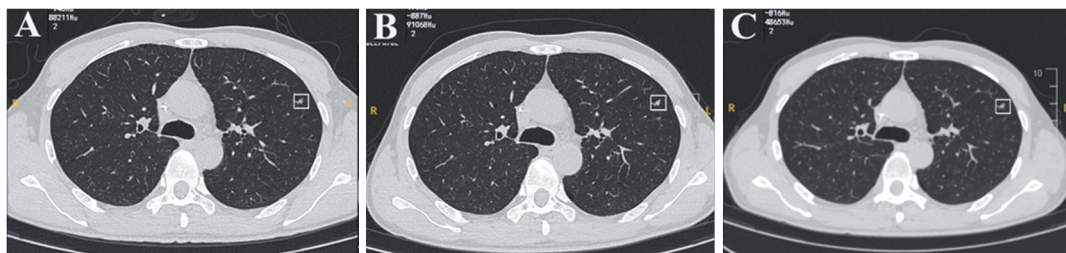
Tetta等^[11]在软组织肉瘤肺部结节的恶变率判断中发现临床特征联合CT影像学特点能够展现出更好的预测转归能力。本中心通过对比恶性IPN与良性IPN的胸部CT影像学特征发现, 恶性IPN直径平均大小为6.969±1.118 mm, 高于良性组, 见图3。这一点与Pontes等^[12]研究一致。这也意味着判断良恶性结节最主要的影像学特征首先是



This patient was a 46-year-old male diagnosed with high-grade angiosarcoma in left leg. Eight months after the diagnosis of high-grade angiosarcoma, the patient underwent chest CT examination and showed a solid quasi circular nodule that had a clear boundary and a diameter of approximately 7 mm in the middle lobe of the right lung (A). It was included in the high-risk STS IPN follow-up. One month later, chest CT follow-up showed that the diameter of the nodule in the middle lobe of the right lung increased to 10 mm, presenting as a mixed-density nodule with a clear boundary (B). One month later, a follow-up CT scan of the chest revealed that the diameter of the nodule in the middle lobe of the right lung increased to 14 mm, presenting as a full-solid-density nodule with clear boundaries (C). The high-risk IPN was determined as metastatic, and the patient was treated with anlotinib. The patient is currently surviving well.

图3 一例高风险IPN高级别STS患者的胸部CT随访

Figure 3 Chest CT follow-up of a patient with high-grade STS and high-risk IPN



This patient was a 67-year-old male diagnosed with undifferentiated sarcoma of the left hip joint. Sixteen months after the diagnosis of undifferentiated sarcoma, the patient underwent chest CT examination that showed an irregular, ground glass nodule with a diameter of approximately 5 mm in the anterior segment of the left upper lobe and was included in the low-risk soft tissue sarcoma IPN follow-up (A). Two months later, chest CT follow-up showed that the size and nature of the ground glass nodule in the anterior segment of the left upper lobe were the same as before (B). After three months, chest CT follow-up showed no changes in the size and nature of the ground glass nodule in the anterior segment of the left upper lobe(C). The possibility of metastasis was ruled out, and regular follow-up was conducted every six months.

图4 一例低风险IPN高级别STS患者的胸部CT随访

Figure 4 Chest CT follow-up of a patient with high-grade STS and low-risk IPN

其直径，肺部结节的直径越大，结节为恶性的可能性也越大^[13]。本研究中，我们发现恶性IPN多为散发、类圆形，多以实性及混合性为主。因此对于伴有IPN的高级别STS患者具有较大的IPN直径、类圆形、实性或混合性可能具有更高的恶变倾向。同时，我们还注意到，治疗后新发的IPN恶性结节的可能性更高。除此之外，IPN发现间期是影响恶性转归的IPN高级别STS患者的独立因素，相较于初筛时发现IPN，治疗后新发的恶性IPN会导致更差的生存，可能与肿瘤细胞对化疗方案耐药有关。因此对于高级别STS患者肺部IPN，我们中心采取根据结节级别分级随访的策略。伴有上述高危因素的合并IPN高级别STS患者推荐每月复查一次胸部CT，直径大于10 mm或出现数量增加后诊断为转移灶，进行早期干预治疗。对于不伴有上述高危风险的合并IPN高级别STS患者推荐每2~3月复查一次，6月后病灶无明显改变，可转为常规随访，见图4。

Cipriano等^[14]回顾性分析青少年肉瘤患者肺部结节对生存的影响发现，除肿瘤大小外，结节的数量也与预后相关。Yamamoto等^[15]回顾性分析接受肺转移切除术的135例肉瘤患者生存预后发现无病生存间期、最大肺部转移灶直径以及肺部病灶数量与预后相关。Rissing在研究中发现IPN直径大于5 mm预后更差^[8]，而Mayo的研究发现生存预后似乎与结节大小无关^[10]。欧洲软组织肉瘤研究组对316例儿童非转移性横纹肌肉瘤患者进行研究，发现IPN不影响横纹肌肉瘤患者的预后，没有必要对诊断时存在IPN的横纹肌肉瘤患者进行活组织检查或预先诊断^[16]。本中心发现年龄与结节发现间期是影响伴恶性转归的IPN高级别STS患者IPN确诊后生存期的独立因素。年龄较大以及治疗后发现IPN导致患者具有更差的生存预后。这也提示高级别STS病理类型异质性大，影响其肺部结节患者的生存预后也不尽相同。本研究受限于较少的样本量，同时诸多研究间缺乏统一的纳入及研究因素，因此日后的研究中对于不同病理的STS伴IPN患者作出亚组分析将更有效的研究生存影响因素。

综上所述，肺部结节往往是肺转移灶的前期状态，考虑高级别STS易转移到肺部，因此对于伴有IPN的高级别STS患者需要密切随访。其中，胸部CT的影像学特征可能为良恶性结节性质和生存预后的判断提供重要指导意义。

利益冲突声明：

所有作者均声明不存在利益冲突。

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