

¹⁸F-FDG PET/CT参数和炎症标志物在鼻咽癌预后预测中的应用进展

Application progress on ¹⁸F-FDG PET/CT parameters and inflammatory markers in prognostic prediction of nasopharyngeal carcinoma

Liang Huan, Wang Zhengjie, Li Mengdan, Jing Xingguo

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·综述·

¹⁸F-FDG PET/CT 参数和炎症标志物在鼻咽癌预后预测中的应用进展

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【摘要】 鼻咽癌是一种在中国及东南亚国家高发的头颈部恶性肿瘤, 具有易复发、易转移的特点。临床上, ¹⁸F-氟脱氧葡萄糖(FDG)PET/CT 显像及生化指标监测已成为管理鼻咽癌患者必不可少的一环。¹⁸F-FDG PET/CT 参数和炎症标志物的联合应用可能在提高鼻咽癌诊断准确率及开展个体化治疗方面具有巨大潜力, 并对鼻咽癌患者临床预后的改善起到重要作用。笔者系统地综述了¹⁸F-FDG PET/CT 参数和炎症标志物在鼻咽癌患者预后预测中的应用进展。

【关键词】 鼻咽癌; 炎症; 氟脱氧葡萄糖 F18; 正电子发射断层显像术; 体层摄影术, X线计算机; 预后

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Application progress on ¹⁸F-FDG PET/CT parameters and inflammatory markers in prognostic prediction of nasopharyngeal carcinoma

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【Abstract】 Nasopharyngeal carcinoma is a malignant tumor prevalent in China and Southeast Asian countries, characterized by a high recurrence and metastasis rate. Clinically, ¹⁸F-fluorodeoxyglucose (FDG) PET/CT imaging and monitoring of biochemical indicators have become indispensable components of the management of patients with nasopharyngeal carcinoma. The combined use of ¹⁸F-FDG PET/CT and inflammatory markers may have significant potential in improving the accuracy of nasopharyngeal carcinoma diagnosis and personalized treatment. This combination also plays a crucial role in enhancing the clinical prognosis of nasopharyngeal carcinoma patients. The authors systematically reviewed the application progress of ¹⁸F-FDG PET/CT parameters and inflammatory markers in predicting the prognosis of nasopharyngeal carcinoma patients.

【Key words】 Nasopharyngeal carcinoma; Inflammation; Fluorodeoxyglucose F18; Positron-emission tomography; Tomography, X-ray computed; Prognosis

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鼻咽癌是一种起源于鼻咽上皮内黏膜的头颈部肿瘤, 在中国和东南亚国家中高发^[1]。由于早期症状不典型, 70% 的患者在初诊时已是局部晚期^[2]。近年来, 调强适形放射治疗(intensity-modulated radiation therapy, IMRT)的出现明显提高了鼻咽癌患者的生存率^[3]。令人惋惜的是, 鼻咽癌一旦发生转移, 患者5年生存率仍低至15%^[3]。目前TNM分期是预测鼻咽癌预后、指导不同风险人群治疗策略制定最主

要的工具; 然而, 处于同一分期的患者治疗效果往往不同^[4]。这可能与TNM分期只考虑了肿瘤浸润的解剖结构, 没有考虑肿瘤细胞或患者机体的功能状态有关^[5]。因此, 确定其他独立预后因素, 从而推动鼻咽癌患者的个性化诊治, 提高临床干预的准确性和有效性是非常必要的。

最新的中国临床肿瘤学会(CSCO)及美国国立综合癌症网络(NCCN)指南均建议在治疗高危鼻咽癌患者前使用

^{18}F -FDG PET/CT 显像评估患者病情^[6-7]。 ^{18}F -FDG PET/CT 作为一种非侵入性的分子影像显像技术,可同时提供肿瘤的解剖和功能信息,已被广泛应用于包括鼻咽癌在内的各种肿瘤的精准分期、预后预测等^[8]。此外,越来越多的研究结果表明炎症在肿瘤的发生、侵袭和转移中起着关键作用^[9]。总之, ^{18}F -FDG PET/CT 参数和炎症标志物与鼻咽癌患者的生存显著相关。本文综述了对鼻咽癌预后具有重要预测价值的相关指标。

1 ^{18}F -FDG PET/CT 参数

1.1 SUV_{max}

SUV_{max} 是 PET/CT 显像中最常用的描述参数,反映了病灶内最活跃区域的代谢活动情况^[10]。研究表明,原发肿瘤和颈部淋巴结的 SUV_{max} 可能是预测将接受 IMRT 治疗的鼻咽癌患者远处转移风险的敏感代谢参数^[11]。Xie 等^[12]报道治疗前低水平 SUV_{max} 的鼻咽癌患者的总生存期(overall survival, OS)和无病生存期明显优于高水平 SUV_{max} 患者。Hung 等^[13]对 371 例接受不同治疗方案治疗的不同分期的鼻咽癌患者进行了一项研究,他们采用 ROC 曲线确定原发肿瘤 SUV_{max} ($\text{SUV}_{\text{max-T}}$) 的最佳临界值为 9.3,淋巴结 SUV_{max} ($\text{SUV}_{\text{max-N}}$) 的最佳临界值为 7.4,发现 $\text{SUV}_{\text{max-T}} \geq 9.3$ 和 $\text{SUV}_{\text{max-N}} \geq 7.4$ 的患者的无远处转移生存率(distant metastasis-free survival, DMFS)和 OS 明显更差。以上这些研究结果表明 SUV_{max} 对鼻咽癌患者具有良好的预后预测价值,对于 SUV_{max} 高的患者可以考虑行更积极的全身治疗。

1.2 淋巴结与原发肿瘤 SUV 比值 (SUV ratio of lymph node-to-primary tumor, NTR)

NTR 是一种连接原发肿瘤和淋巴结 SUV_{max} 的参数,可以弥补由于部分体积效应的影响而导致的对 SUV 的低估^[14]。Hung 等^[15]及 Gihbid 等^[14]发现 NTR 与 OS、DMFS 和无进展生存期(progression free survival, PFS)显著相关,有助于对患者进行风险分层,识别转移风险高的患者。此外,Shen 等^[16]报道,无论鼻咽癌的 TNM 分期如何,NTR 高(>0.61)的患者的 DMFS 明显较低。NTR 现已被认为是新兴的评估肿瘤侵袭性、转移潜能以及患者死亡风险的有力指标。

1.3 肿瘤代谢体积 (metabolic tumor volume, MTV) 和病灶糖酵解总量 (total lesion glycolysis, TLG)

MTV 是指肿瘤区域内所有高糖酵解活性的组织的体积总和,TLG 是 MTV 与病灶平均标准化摄取值(mean standardized uptake value, SUV_{mean}) 的乘积。MTV 和 TLG 克服了 SUV_{max} 仅能显示肿瘤病灶内简单的葡萄糖代谢情况,无法评估肿瘤总体摄取的异质性这一限制^[17],可较全面地反映肿瘤代谢活性和负荷,目前引起了研究者越来越

多的关注。有研究表明,高 MTV 和高 TLG 与鼻咽癌患者的不良生存率密切相关^[18]。

1.4 肿瘤异质性指数 (heterogeneity index, HI)

HI 即 SUV_{max} 与 SUV_{mean} 的比值,是一种用于评估肿瘤组织内代谢活性差异的参数。它可以反映肿瘤内不同部位的代谢水平和异质性程度,从而提供更全面的肿瘤评估信息^[19]。Yang 等^[19]招募了 40 例局部晚期鼻咽癌患者,评估了包括 SUV_{max} 、 SUV_{mean} 、MTV 和 TLG 在内的常规 ^{18}F -FDG PET/CT 参数,结果显示这些常规参数的预后预测价值有限,但 HI 对这些患者的预后预测非常有效,原发肿瘤的 HI (HI-T) ≥ 2.9 及颈部淋巴结的 HI (HI-N) ≥ 2.3 的患者的 PFS 明显更短。NTR、MTV、TLG 和 HI 均是从 SUV_{max} 演变而来的参数,可以准确反映肿瘤代谢负荷并包含更多信息。因此,与 SUV_{max} 相比,这些参数可能更适合用于治疗效果的预测,但其价值仍需要更多的研究去证实。

综上, ^{18}F -FDG PET/CT 参数弥补了 TNM 分期不能反映鼻咽癌肿瘤负荷和侵袭性的空白,具有可观的预后预测前景。

2 炎症标志物

2.1 血液学指标

肿瘤微环境(tumor microenvironment, TME)是目前肿瘤研究领域的热点。TME 指肿瘤周围的细胞和细胞外基质组成的复杂生态网络,炎症细胞、免疫细胞等是其重要组成部分。TME 与肿瘤细胞联系紧密、相互作用,共同决定了肿瘤的发展和预后。本文综述的炎症标志物主要包括 WBC 类 [如中性粒细胞、单核细胞、淋巴细胞、嗜碱性粒细胞(basophil, BAS)和嗜酸性粒细胞(eosinophil, EOS)]、血小板(platelet, PLT)、乳酸脱氢酶(lactate dehydrogenase, LDH)及血红蛋白(hemoglobin, Hb)。

2.1.1 中性粒细胞绝对值 (absolute neutrophil count, ANC)

中性粒细胞已被确定为全身炎症反应的标志物,其通过产生促炎细胞因子、基质金属蛋白酶 9 和血管内皮生长因子,从而促进肿瘤迁移和侵袭^[20]。He 等^[21]第一次证明了中性粒细胞百分比高与鼻咽癌的不良预后显著相关。随后, Lu 等^[22]在对鼻咽癌炎症浸润及其预后影响的研究中明确指出,具有低密度中性粒细胞浸润的鼻咽癌患者表现出明显更长的 OS 和 PFS。此外, Chen 等^[23]对 1753 例初诊鼻咽癌患者进行回顾性分析,检测不同治疗时期的 ANC,探究其与鼻咽癌患者预后的关系,结果显示放疗前 ANC 增大(> $7 \times 10^9/\text{L}$)和放疗期间 ANC 增大(> $5 \times 10^9/\text{L}$)是鼻咽癌患者的独立预后因素($P=0.002$ 、 0.044),并且他们推测中性粒细胞可能赋予了鼻咽癌对放疗的抵抗力。

2.1.2 单核细胞绝对值 (absolute monocyte count, AMC)

单核细胞可以分化成肿瘤相关巨噬细胞,它也是 TME

的重要细胞组成。肿瘤相关巨噬细胞可以通过分泌生长因子和细胞因子,如血管内皮生长因子、转化生长因子 α 等,加速肿瘤进展和血管生成^[24]。2013年,Li等^[25]首次揭示了单核细胞与鼻咽癌预后的相关性,结果显示AMC $<0.475 \times 10^9/L$ 的患者与更好的OS($P=0.012$)、无病生存期($P=0.011$)和DMFS($P=0.003$)相关。Liu等^[26]的一项研究结果表明,高 Δ AMC%与更差的临床结果显著相关(OS: $P=0.001$;PFS: $P=0.001$;DMFS: $P=0.034$);多变量分析结果显示, Δ AMC%是鼻咽癌患者OS($P=0.019$)和PFS($P=0.011$)的独立预后因素。这表明治疗期间检测AMC的动态变化具有重要意义。

2.1.3 淋巴细胞绝对值 (absolute lymphocyte count, ALC)

与上述2种白细胞相反的是,淋巴细胞通过抑制肿瘤细胞增殖和诱导细胞凋亡在抗肿瘤方面起着关键的作用^[27]。He等^[21]首次发现治疗前淋巴细胞百分比是鼻咽癌患者重要的预后因素。也有研究结果表明,肿瘤浸润淋巴细胞水平是鼻咽癌的独立预后因素^[28]。而Cai等^[29]的研究证实治疗前淋巴细胞百分比与肿瘤浸润淋巴细胞水平呈正相关。因此,我们猜测可以通过淋巴细胞百分比反映肿瘤浸润淋巴细胞水平,从而预测患者预后,但这仍需进一步的研究证实。

2.1.4 BAS 和 EOS

BAS和EOS在鼻咽癌预后预测中的作用研究相对较少。有研究结果表明,BAS可通过分泌血管内皮生长因子、血管生成素等细胞因子来促进肿瘤血管生成和细胞增殖^[30]。而EOS可以通过诱导肿瘤血管正常化、募集T细胞以增强淋巴细胞介导的抗肿瘤免疫,从而破坏肿瘤细胞^[31]。Zeng等^[32]首次探究了BAS和EOS与鼻咽癌预后的关系,结果表明高水平BAS与患者不良的OS显著相关,说明BAS可能具有潜在的预后预测价值;此外他们还发现了BAS和EOS是多种放疗不良反应的独立危险因素,如放射性皮炎、吞咽困难等。然而由于相关研究有限,关于BAS和EOS在鼻咽癌预后预测中的潜在作用仍有待进一步的研究证实。

2.1.5 PLT

大量研究结果表明,PLT的增加可能通过促进肿瘤细胞的免疫逃逸及外渗、阻碍自然杀伤细胞,导致癌细胞的转移^[33]。此外,Li等^[34]证实PLT可以通过上调整合素 $\beta 3$ (ITGB3)蛋白影响铁代谢,从而在鼻咽癌血行转移中起关键作用。Chen等^[35]于2015年首次研究了治疗前PLT计数对放疗后鼻咽癌患者预后的影响,回顾性分析了150例鼻咽癌患者,结果显示低PLT计数与同步放化疗患者的低OS率显著相关($P=0.012$),而高PLT计数与同步放化疗和单纯放疗患者的低OS率和DMFS率显著相关($P=0.02$ 、 0.028);在同步放化疗患者中,与高PLT计数相比,低PLT计数对OS率的负面影响更大,这表明治疗前PLT计数可能是影响鼻咽癌患者治疗效果的独立预后因素,值得

更多大规模临床研究予以验证。

2.1.6 LDH

LDH是TME中的关键代谢酶之一,能可逆地催化乳酸氧化为丙酮酸,LDH由2个不同的亚基LDHA和LDHB组成^[36]。在癌细胞中,即使存在氧气,糖酵解产生的大部分丙酮酸也会在LDHA的帮助下远离线粒体生成乳酸(Warburg效应),随着乳酸的积累,TME的pH值会发生改变,而这与肿瘤转移、血管生成、免疫抑制和治疗抵抗紧密相关^[37]。以往的研究已报道了在多种肿瘤中检测到LDH水平的失调,包括鼻咽癌^[38]。早在1997年,Liaw等^[39]回顾性分析了465例鼻咽癌患者的LDH水平,发现治疗前LDH水平正常的患者的生存结果更好($P=0.008$)。Wan等^[40]探讨了治疗前LDH水平对局部晚期鼻咽癌的预后预测价值,该研究结果显示LDH水平是局部晚期鼻咽癌的独立预后因素,并提出治疗前LDH水平与TNM分期相结合可能会更精确地评估肿瘤风险。以上这些研究结果表明LDH是鼻咽癌重要的预后预测指标。

2.1.7 Hb

Hb是人体的氧载体,其水平一直被认为是影响肿瘤氧合作用和放疗效果的关键因素^[41]。缺氧会促进实体瘤的增殖、转移、血管生成和治疗耐药性的产生^[42]。而贫血也被认为是反映肿瘤缺氧的间接指标。研究结果表明,低Hb水平是头颈部鳞状细胞癌患者疾病控制较差和生存不佳的有力预后指标^[43]。2015年,Guo等^[44]首次开展了治疗前Hb水平与接受IMRT治疗鼻咽癌患者预后关系的研究,发现治疗前贫血是DMFS不良的独立预后因素($P=0.007$)。而后Zhang等^[45]回顾性分析了1302例接受IMRT联合或不联合化疗的新诊断非转移性鼻咽癌患者,结果也证实了治疗前贫血会导致不良的DMFS($P=0.048$)。

2.2 C反应蛋白 (C-reactive protein, CRP)、CRP/白蛋白 (albumin, ALB) 比值

CRP作为一种炎症急性期蛋白,是最灵敏的全身炎症标志物之一。已有研究证实,CRP水平升高的幅度与癌症患者(尤其是晚期患者)的生存情况呈负相关^[46]。Tang等^[47]及Chen等^[48]均指出CRP与OS和DMFS存在很强的相关性。ALB反映了机体的营养状况,ALB水平 $<35 g/L$ 在临床上被归类为低白蛋白血症。2020年,一项包括7339例鼻咽癌患者在内的荟萃分析研究结果表明,治疗前ALB水平可用于鼻咽癌患者的危险度分层^[49]。此外,多项研究结果均表明CRP/ALB比值对鼻咽癌患者的OS具有关键的预后预测价值^[50-51]。

2.3 炎症预后评分系统

近年来,不少研究者认为血清学标志物的组合比单一指标在癌症预后预测方面的价值更高^[51]。血清学标志

物组合,例如中性粒细胞与淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR)、血小板与淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)、淋巴细胞与单核细胞比值(lymphocyte-to-monocyte ratio, LMR)、格拉斯哥预后评分(Glasgow prognostic score, GPS)、全身免疫炎症指数(systemic immune-inflammation index, SII)、全身炎症反应指数(systemic inflammation response index, SIRI)和全身炎症评分(systemic inflammation score, SIS)在鼻咽癌中都表现出不同程度的预后观测价值^[32]。

2.3.1 NLR、PLR、LMR及GPS

2010年, An等^[52]首次研究了NLR与鼻咽癌预后的关系, 回顾性分析了363例鼻咽癌患者, 发现治疗前NLR是预测鼻咽癌患者生存期的一个强有力的预后因素。2013年, Li等^[25]率先探索了LMR与鼻咽癌预后的关系, 结果显示较高的LMR水平(≥ 5.220)与良好的OS、无病生存期和DMFS显著相关(均 $P < 0.001$)。2014年, Chen等^[53]同时评估了NLR、PLR、GPS对接受顺铂治疗的转移性鼻咽癌患者的预后预测价值, 首次证实了GPS是影响转移性鼻咽癌患者OS和PFS的独立预后因素(均 $P < 0.001$), 并得出其预后预测效能优于NLR和PLR。实际上, GPS是一种可同时评估ALB和CRP水平的评分系统。其评分标准为: CRP水平升高(> 10 mg/L)和低白蛋白血症同时存在的患者评分为2分, 仅存在其中一种情况的患者评分为1分, 二者均不存在的评分为0分。值得一提的是, 在Chen等^[53]的研究中并未发现PLR对鼻咽癌的预后预测价值。然而, Jiang等^[54]于2015年首次发现PLR的升高(> 153.64)分别与更好的OS($P < 0.001$)、癌症特异性生存期($P < 0.001$)和DMFS($P = 0.011$)显著相关。目前, 关于PLR在鼻咽癌预后预测方面的作用仍存在争议。2017年, Li等^[55]评估了388例鼻咽癌患者治疗前炎症标志物(NLR、PLR、LMR及GPS)在预后预测中的意义, 结果显示, GPS为1~2分、NLR > 2.5 、PLR > 166 和LMR ≤ 2.35 与不良的5年疾病特异性生存率相关(P 值分别为 < 0.001 、 < 0.001 、 0.002 和 < 0.001), 在该研究中治疗前GPS、NLR和LMR是鼻咽癌患者的独立预后因素($P = 0.02$ 、 0.049 、 0.048), 然而, 该研究并未得出PLR是鼻咽癌患者的独立预后因素的结论。目前, 关于以上几种基于炎症的预后评分系统中哪种是鼻咽癌预后预测的最优评分系统仍是一个极具争议的话题。

2.3.2 SII、SIRI、SIS

$SII = (PLT \times ANC) / ALC$; $SIRI = (AMC \times ANC) / ALC$ 。SIS则同时反映了ALB和LMR的水平, 其评分标准为: ALB < 40 g/L和LMR < 3.05 则评分为2分; ALB ≥ 40 g/L或LMR ≥ 3.05 则评分为1分; ALB ≥ 40 g/L和LMR ≥ 3.05 则评分为0分^[56]。2017年, Jiang等^[57]首次发现SII是鼻咽癌患者的

独立预后指标, 并指出其预后预测价值优于PLR、NLR。随后, Chen等^[58]首次将SIRI引入鼻咽癌预后评估的研究中, 发现SIRI是鼻咽癌患者OS的独立预后因素($P < 0.001$)。次年, Zeng等^[59]也首次指出SIS与鼻咽癌患者不良的OS显著相关($P = 0.01$)。

3 ^{18}F -FDG PET/CT参数联合炎症标志物在鼻咽癌中的应用

近年来, ^{18}F -FDG PET/CT参数与炎症标志物联合应用评估鼻咽癌患者预后的相关研究呈现逐年增多的趋势。Zhong等^[60]首次进行了将 SUV_{max} 与炎症标志物联合作为鼻咽癌患者预后预测指标的研究, 结果表明, 颈部淋巴结 SUV_{max} (N- SUV_{max})和中性粒细胞是PFS和DMFS的独立预后指标, 并且N- SUV_{max} 与中性粒细胞联合应用有助于改善患者的风险分层和预后评估。但是, 该研究仅联合了 SUV_{max} 与WBC、ANC、AMC来预测鼻咽癌患者的生存结果。Xiao等^[61]采用N分期、EB病毒(EBV)DNA水平、性别、Hb水平和LDH水平等风险因素开发了列线图, 以指导 ^{18}F -FDG PET/CT在预测鼻咽癌患者原发性远处转移中的个体化应用。Xian等^[62]的研究结果表明, 当 $SUV_{max} < 9.7$ 时, 低PLR(< 132.98)患者的5年PFS显著高于高PLR(≥ 132.98)患者; 无论PLR高低, 低 SUV_{max} 患者(< 9.7)的5年PFS均显著高于高 SUV_{max} (≥ 9.7)患者。这表明 SUV_{max} 联合PLR可以更准确地对鼻咽癌患者进行风险分层, 制定更合适的个体化治疗方案, 有利于改善患者预后和生活质量。Chiang等^[63]对18项有关鼻咽癌患者炎症标志物和 ^{18}F -FDG PET/CT参数的研究进行了系统回顾, 结果显示NLR、CRP/ALB比值、Hb、红细胞分布宽度、PLT、LDH和原发肿瘤TLG(TLG-T)、 SUV_{max-T} 为强推荐的预后参数, 具有优化TNM分期的巨大潜力。

^{18}F -FDG PET/CT参数可以反映肿瘤糖代谢情况, 而炎症标志物则用于评价机体的整体状况, 二者联合可以提供更全面的鼻咽癌患者信息, 从而准确预测预后, 延长生存期。然而目前关于二者联合的研究仍较少, 需要进一步的研究确定二者的联合评估是否可以指导治疗策略的制定并改善患者的预后, 这将是未来的研究热点。

4 小结与展望

总之, ^{18}F -FDG PET/CT参数与炎症标志物的联合应用展现了潜在的临床应用前景。该方法能对患者的疾病状态、预后进行准确评估。这2种无创性检查方法优势互补, 克服了TNM分期的局限性, 同时减少了患者的不适和不良反应。充分挖掘 ^{18}F -FDG PET/CT与炎症标志物联合预测鼻咽癌患者预后的潜在益处, 为鼻咽癌患者提供更个性化的精准医疗服务, 仍需开展进一步的研究和探索。

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