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• 综　述 •

磁共振成像指导下宫颈癌调强放疗骨髓保护研究进展

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Advances in Bone Marrow Function Protection for Cervical Cancer Intensity-Modulated Radiotherapy Informed by Magnetic Resonance Imaging

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Abstract: Cervical cancer is a common gynecological malignancy, and radiotherapy plays a crucial role in its treatment. However, conventional radiotherapy for cervical cancer often leads to bone marrow damage, considerably affecting patients' quality of life and treatment outcomes. In recent years, the application of intensity-modulated radiotherapy (IMRT) and magnetic resonance imaging (MRI) technologies has provided novel solutions to this issue. IMRT optimizes dose distribution, minimizing radiation exposure to surrounding normal bone marrow tissues and thus considerably reducing damage. MRI allows for accurate tumor localization and monitoring, including organs at risk, such as the bone marrow, and providing precise guidance for radiotherapy. This article analyzes the feasibility and potential benefits of MRI-guided pelvic IMRT for bone marrow protection in cervical cancer, aiming to offer a basis for precise and effective bone marrow protection strategies in cervical cancer radiotherapy.

Key words: Cervical cancer; Magnetic resonance imaging; Intensity-modulated radiotherapy; Bone marrow protection; Dose distribution optimization

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摘　要：宫颈癌是常见的妇科恶性肿瘤，放射治疗在其综合治疗中具有重要地位。然而，传统放疗技术常难以避免骨髓损伤，严重影响患者的生活质量和治疗效果。近年来，调强放疗（IMRT）联合磁共振成像（MRI）技术为该问题提供了新的解决方案。IMRT通过优化剂量分布，可降低正常骨髓组织的照射剂量，从而减少骨髓损伤。MRI技术能更精准地定位和监测肿瘤及危及器官（包括骨髓），为放疗计划提供更精确的指导。本文探讨MRI指导下宫颈癌盆腔IMRT对骨髓功能保护的可行性及优势，旨在为宫颈癌放疗的骨髓保护策略提供依据。

关键词：宫颈癌；磁共振影像；调强放疗；骨髓功能保护；剂量分布优化

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0　引言

宫颈癌是全球女性第四大常见的恶性肿瘤，近年来其发病率和死亡率均呈上升趋势。目前，宫颈癌的主要治疗手段包括手术、放疗及化疗。对于局部晚期患者，放疗可有效提高肿瘤局部控制率[1-2]。然而，传统放疗技术由于照射野较大，常将盆腔骨髓组织纳入照射靶区，导致骨髓抑制风险显著增加[3]。放射性骨髓损伤不仅降低患者对同步放化疗的耐受性，还可能引发贫血、感染等并发症，严重影响治疗效果及患者生存质量[4-5]。近年来，调强放射治疗（Intensity-modulated radiotherapy, IMRT）通过优化剂量分布，可有效降低正常组织受照剂量，已在多种恶性肿瘤治疗中展现出显著优势[6]。与此同时，磁共振成像（Magnetic resonance imaging, MRI）凭借其卓越的软组织分辨能力，能够精准勾画肿瘤及危及器官（Organs at risk, OAR），如红骨髓，为放疗计划的制定提供重要依据。本文从骨髓损伤机制、IMRT的剂量学优势及MRI的精准指导作用等方面，对MRI引导下宫颈癌盆腔IMRT中

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的骨髓功能保护策略进行综述与分析。

1 骨髓损伤机制及其与放射剂量相关性

成人骨髓可分为造血活跃的红骨髓和脂肪化的黄骨髓。红骨髓富含具有自我更新能力的造血干细胞（Hematopoietic stem cells, HSCs），是维持造血功能的主要场所，其中50%以上分布于髂骨、骶骨、下段腰椎及股骨近端。两者分布比例受年龄、生理状态及疾病等因素影响，放化疗可导致红骨髓含量减少、红/黄骨髓比例降低[7]。常规宫颈癌放疗照射野通常包括大范围骨盆结构，使大量骨髓组织受到照射。其损伤机制主要包括：（1）红骨髓在放射线、化疗药物等损伤因子作用下向黄骨髓转化，直接影响造血功能[8]；（2）放射线直接损伤对辐射高度敏感的HSCs，通过诱导细胞衰老、凋亡及分化障碍导致骨髓抑制[9]。具体而言，骨髓放射损伤的核心机制涉及：（1）电离辐射（Ionizing radiation, IR）诱导DNA双链断裂（Double strand break, DSB），激活DNA损伤应答（DNA damage response, DDR）通路，其关键在于共济失调毛细血管扩张突变（Ataxia telangiectasia-mutated, ATM）激酶等核心调控因子的活化，触发了全局性的DNA修复、细胞周期停滞、凋亡及衰老等生物学过程[10]；（2）IR通过粒细胞集落刺激因子（G-CSF）/信号转导和转录激活因子（STAT3）通路干扰HSCs分化，同时激活p53-PUMA凋亡通路；（3）辐射可增强NADPH氧化酶4（NOX4）活性，促进活性氧（Reactive oxygen species, ROS）的过量生成，通过p38丝裂原活化蛋白激酶（p38-MAPK）信号通路介导的氧化应激与炎性反应，抑制HSCs的增殖与分化能力[11]。

多项回顾性研究及正常组织并发症概率模型证实，盆腔骨髓低剂量照射与血液毒性显著相关[12-13]。此外，采用顺铂/吉西他滨同步放化疗（Concurrent chemoradiotherapy, CCRT）时，治疗期间3级或4级血液毒性反应发生率可达80%以上。严重血液学毒性（如重度血小板减少）不仅需要增加辅助用药，还可能导致治疗中断、住院时间延长，最终影响治疗效果和患者生活质量[14-15]。临床研究认为，放射性骨髓损伤的发生率和严重程度与骨髓组织受照的体积和剂量相关[16]。多项研究指出盆腔骨髓V20、V30等参数与骨髓抑制程度相关。Tang等[17]发现盆腔骨髓的V20≥76%与3级及以上血液学毒性风险显著相关。Zhang等[18]研究证实，在盆腔骨髓接受中低剂量照射体积（如V5、V10、V20、V30）较大的患者中，≥2级淋巴细胞减少症的发生风险显著升高，且毒性出现时间更早。Qin等[19]研究结果显示，盆腔骨髓平均剂量每增加1 Gy，中性粒细胞和白细胞每周分别减少9.6/μl和7.8/μl，证实了急性骨髓损伤的剂量—效应关系。

2 调强放疗对盆腔骨髓保护的优势

IMRT通过优化算法可生成高度适形于肿瘤靶区的剂量分布，在保证靶区剂量的同时降低周围正常组织的受照剂量。目前临床主要应用的IMRT主要包括两大类：一类是传统意义上的IMRT，其通过多叶准直器（Multi-leaf collimator, MLC）调节射野内不同区域的剂量强度，以实现对肿瘤靶区的精确照射；另一类是容积调强放疗（Volume modulated arc therapy, VMAT），其通过在单次或多次连续旋转中动态调整剂量分布，进一步提高放疗的效率和精度。两类都具备高度精确的剂量调节能力，但传统IMRT在剂量分布的精细控制上可能更具优势，尤其是在复杂形状的肿瘤和需要高度个体化治疗的情况下。而VMAT在治疗时间上相对较短，对于减少患者整体辐射暴露时间进而保护骨髓等敏感组织是有益的。在剂量分布层面，VMAT通过旋转照射实现更均匀的剂量分布，有助于减少高剂量“热点”区域，而传统IMRT则更侧重于在三维空间内的精确剂量调节[20]。

IMRT技术因其精准的剂量调控优势，现已广泛应用于妇科肿瘤的临床治疗[21]。研究表明，IMRT可通过有目的地降低盆腔放疗中OAR的受照剂量和体积，提高患者对同步放化疗（CCRT）的耐受性，这一优势在宫颈癌、肛管癌及前列腺癌等盆腔肿瘤中均得到验证[22-24]。目前，涉及宫颈癌及子宫内膜癌盆腔放疗正常组织反应的临床试验主要有RTOG的两大重要研究，即RTOG 1203[25]和RTOG 0418[26]。前者是一项前瞻性的Ⅲ期随机临床研究，主要目的在于比较标准放疗与IMRT在两大妇科肿瘤中的疗效差别。但因入组困难提前终止，未能提供有效数据。而RTOG 0418则是一项多中心的Ⅱ期临床试验，其研究结果提示骨髓受照剂量与骨髓抑制的发生有关，而盆腔IMRT可降低血液学毒性并提高同步化疗完成率，但由于研究同时纳入宫颈癌和子宫内膜癌患者，在放疗实施过程中两种肿瘤之间存在同步化疗条件的不均衡。同时，该研究采用CT值自动勾画技术（以骨质体积替代真实骨髓腔）而未设定骨髓保护性剂量限制，仅给予观察性研究，对于骨髓保护缺乏保护的干预措施，其结论

存在一定局限性。

需要注意的是，传统IMRT在盆腔肿瘤治疗中通常仅限制膀胱、小肠和直肠等正常器官的剂量。骨髓保护调强放疗（Bone marrow sparing-intensity modulated radiation therapy, BMS-IMRT）则是在IMRT基础上，将骨盆骨髓作为需要保护的重要器官，在放疗计划制定过程实施精确的靶区勾画、剂量限制和优化[27]。这种方法可以在确保肿瘤靶区治疗效果的同时，有效保护其他正常组织，并额外提供对骨髓的保护措施。Sun等[28]对40例宫颈癌术后有辅助放化疗指征的患者进行随机对照研究，结果显示BMS-IMRT组盆腔骨髓的V10~V50剂量参数显著低于常规IMRT组，且将治疗中断率从40%降至5%。在剂量限制策略方面，选择性强化髋骨（Os coxae, OC）及腰骶椎（Lumbosacral spine, LS）的剂量-体积限制可显著降低骨髓受照剂量及高剂量体积分布[29]。研究显示，与常规骨髓保护方案（IMRT-BM）相比，联合约束OC与LS（IMRT-LS+OC）能使OC和LS的V20分别降低11.5%和11.2%，骨髓（Bone marrow, BM）、OC及LS平均剂量分别减少8.2、7.7及9.0 Gy（P<0.05），同时V10~V40 Gy受照体积缩减6.23%~30.09%（P<0.01），且靶区覆盖及其他OARs剂量未受显著影响。

IMRT技术相较于传统放疗计划系统更为复杂，需要更精细的治疗规划过程及较长的计划制定时间，并常伴随治疗次数的增加及剂量分布的复杂化。需要注意的是，由于MLC的机械结构特性，相邻叶片间及叶片与叶片槽之间易产生剂量分布的不均匀现象，即舌槽效应，这种不均匀性会导致剂量分布图中出现热点（剂量高于预期的区域）与冷点（剂量低于预期的区域），进而直接影响治疗精确性[30-31]。针对这些问题，当前研究主要聚焦于通过剂量学发展、算法优化、物联网与人工智能技术的深度参与、机架角度选择策略以及智能剂量规划系统的开发等手段，以进一步推动IMRT技术的发展与完善[32-34]。

3　MRI对盆腔骨髓保护的优势

传统宫颈癌盆腔放疗计划主要基于CT影像进行靶区勾画，但由于CT成像的局限性，难以准确区分红骨髓与黄骨髓的分布差异，导致基于CT的放疗计划在骨髓保护方面存在不足[19]。相比之下，MRI技术具有显著的软组织分辨优势，能够清晰显示红骨髓的分布特征，且无额外辐射损伤。虽然PET和骨髓淋巴显像也可用于骨髓功能评估，但由于其成本较高且伴随辐射暴露等问题，在常规临床应用中受到限制[35-36]。

相较之下，MRI凭借T1加权序列在脂肪信号的高度特异性，能够精确区分骨髓腔内红骨髓与黄骨髓的分布特征及比例关系，这一特性使其在宫颈癌盆腔放疗的骨髓保护研究中具有独特价值。研究显示，基于MRI勾画的靶区体积、三维径线均显著小于CT图像，为剂量优化提供了更精确的解剖基础[37-38]。李萍等[39]的研究显示，MRI勾画的红骨髓体积（219.38±9.73 cm^3）较CT定位的骨盆体积（600.32±6.88 cm^3）减少了63.4%，有效避免了非活性骨髓区域的不必要照射。此外，通过定量非对称回波的最小二乘估算法迭代水脂分离序列（Iterative decomposition of water and fat with echo asymmetry and least-squares estimation quantitation sequence, IDEAL-IQ）影像技术，MRI结合可评估的参数进一步提供与解剖位置相结合的定量诊断，实现对红/黄骨髓的空间分布及含量变化的精准评估[40]。在临床实践中，MRI常与CT进行多模态融合。孙丽等[41]发现，相较于CT图像，CT/MRI融合图像使高危临床靶区体积（HR CTV）缩小了22.6%，同时显著降低膀胱等正常组织的单位体积内接收到的最高剂量（D1cc），显著提升了靶区界定的精确性。

值得注意到的是，MRI引导调强放疗（Magnetic resonance imaging guided intensity-modulated radiotherapy, MRgIMRT）技术（如MRI-Linac系统[42]等）在宫颈癌治疗中展现出显著优势。该技术基于实时MRI影像引导的动态照射野调控，可有效补偿因解剖结构位移导致的剂量偏差[43]。Portelance等[44]通过MRI实时监测患者解剖变化动态调整照射野，将传统指南推荐的1.5 cm均匀靶区外放范围优化为方向特异性非对称外放，使计划靶区体积（Planning target volume, PTV）平均减少38%，并精准识别骨髓富集区域显著降低骨髓组织受照剂量，为骨髓功能保护开辟新路径。此外，与MRgIMRT相比，自适应调强放疗（Adaptive radiation therapy, ART）的技术核心在于构建动态治疗体系：不仅通过影像引导实时追踪解剖变化，还能动态调整治疗计划（包括靶区勾画和剂量分布）。当ART技术融合MRI后，凭借卓越的软组织分辨能力，其靶区勾画精度和治疗验证效能得到实质性提升[45]。相较于锥形束CT，MRI引导的ART可减少高达30%的再计划需求，同时显著降低敏感器官的剂量，并提高靶区剂量精度[46]。海盼盼等[47]通过

MRI/CT多模态成像策略，精确界定ART计划靶区，使患者客观缓解率从57.5%提升至85%，病情控制率从80%增至95%，并显著降低血清癌胚抗原、血清鳞癌抗原等血清肿瘤标志物水平，进一步印证了其在肿瘤控制方面的优越性。在安全性评估方面，ART组未出现血小板减少，白细胞减少率从15%降至2.5%，这一结果提示ART在减少骨髓抑制、保护患者造血功能方面具有潜在的临床应用价值。

现有研究已初步证实了MRI用于骨髓保护的可行性，但要全面验证其优越性仍需开展更多前瞻性的研究，以确保MRI参与的IMRT能够更有效地降低对骨髓组织的潜在损伤[48]。目前主要存在两个关键问题：一是红骨髓与黄骨髓的MRI信号值缺乏统一的量化标准，导致成像质量不稳定和医师勾画的主观差异，其可能成为影响骨髓轮廓勾画准确性的重要因素；二是红骨髓限量参数尚未形成国际共识，增加了技术应用的复杂性和不确定性[49]。在这一背景下，基于U-net的深度学习自动勾画系统展现出重要价值，其股骨头骨髓勾画的Dice相似性系数（Dice similarity coefficient, DSC）值可达0.894~0.896，能够有效识别骨髓组织的细微信号差异，避免高剂量照射对造血功能的损害。这类系统通过标准化算法统一红骨髓与黄骨髓的信号阈值，降低成像质量波动对勾画的影响，提高放疗计划中骨髓保护的可重复性[50]。未来研究应聚焦于开发自动或半自动MRI勾画系统，构建标准化的骨髓MRI信号解析体系，明确红骨髓的量化标准及辐射限量参数，以推动MRI在骨髓保护领域的深入应用。目前基于MRI指导的主要骨髓保护技术的临床效果与优化策略比较见表1。

4 总结

现有研究表明，宫颈癌患者骨髓抑制的发生与盆腔骨髓受照剂量和体积存在显著的剂量—体积效应关系。通过整合MRI引导的精准靶区勾画与IMRT技术，能够有效降低活性骨髓的受照体积和剂量，从而改善血液学毒性反应。然而，该技术仍面临诸多挑战：首先，MRI与CT的配准误差及设备依赖性限制了基层医院的广泛应用；其次，红骨髓与靶区的解剖重叠使剂量覆盖与保护间的平衡难度增加；此外，深度学习自动分割模型虽能缩短大量勾画时间，但其泛化性受限于不同MRI设备的参数差异。未来需制定标准化的红骨髓定量协议，并通过多中心临床试验验证长期疗效。

当前剂量学优化与影像引导技术的协同应用不仅提高了同步放化疗的完成率，还减少了辅助治疗需求与住院时间，为患者带来多维获益。然而，现

表 1 宫颈癌盆腔调强放疗中骨髓保护技术的临床效果与优化策略比较

Table 1 Comparison of clinical effects and optimization strategies of bone marrow protection techniques in intensity modulated radiation therapy for cervical cancer

Technique	Optimization strategy	Chemoradiotherapy regimen	Dosimetric parameters	Clinical outcomes	Challenges/Limitations	Ref.
BMS-IMRT	CT/MRI image registration	Cisplatin	BMS-IMRT group: Lower V10-V50 in active BM	Reduced incidence of ≥Grade 2 myelosuppression	Long-term efficacy not validated	[49]
BMS-IMRT	MRI T1WI-CT fusion	Postoperative cisplatin	Reduced BM V5, V10, V20 *vs*. IMRT	Significantly lower hematologic toxicity (33.3% *vs*. 62.1%);	High precision required; Individual BM distribution variability	[51]
Non-coplanar IMRT	MRI-based BM delineation	Cisplatin or 5-FU/MMC	63.4% reduction in BM volume *vs*. CT	Reduced pelvic or femoral head dose; Enhanced BM sparing	Complex implementation; Increased time	[39]
ART	CT/MRI replanning during therapy	Cisplatin	Significant OAR dose reduction	ORR increased to 85%; No thrombocytopenia; Leukopenia rate reduced to 2.5%	Technical complexity; Advanced equipment dependency	[47]
IMRT + ABT	CT/MRI/PET multimodal fusion	Cisplatin + gemcitabine	Femoral head V50 ≤ 10%	Improved anemia, neutropenia, thrombocytopenia; 3/5-year OS: 75.4%/66.3%	Small sample size; Short follow-up	[52]

Notes: 5-FU: 5-fluorouracil; ABT: adaptive brachytherapy; ART: adaptive radiation therapy; BM: bone marrow; BMS-IMRT: bone marrow sparing intensity-modulated radiation therapy; CT: computed tomography; IMRT: intensity-modulated radiation therapy; MMC: mitomycin C; MRI: magnetic resonance imaging; OAR: organs at risk; ORR: objective response rate; OS: overall survival; PET: positron emission tomography.

有证据仍以单中心和小样本研究为主，亟需基于大样本队列的前瞻性研究（如NRG-GY006试验）进一步验证骨髓保护策略对生存结局的影响。尽管国内研究取得了一定进展，仍需加强多中心协作以提升数据的普适性和临床转化价值。

利益冲突声明：

所有作者均声明不存在利益冲突。

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