论著·“乳腺癌精准靶向与转化”重点号

手术切除联合放疗降低转移性乳腺癌患者放射性皮炎风险尚无生存获益:一项回顾性队列研究

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[摘要] **目的** 转移性乳腺癌原发灶的局部干预(手术/放疗)能否改善生存仍存争议,本研究对比手术切除联合放疗(surgical resection and radiotherapy,S+R)及单纯放疗(radiotherapy,R)带来的副作用及预后探索初治转移性乳腺癌(metastatic breast cancer,MBC)患者的生存获益及安全性。**方法** 研究采用回顾性队列研究设计方案,分析2010—2025年贵州医科大学附属肿瘤医院肿瘤科89例初治诊断为MBC患者(R组42例,S+R组47例),采用倾向性评分匹配(propensity score matching,PSM,卡钳值=0.2)平衡基线特征,匹配后纳入62例(每组31例)。主要终点事件为总生存期(overall survival,OS)、无进展生存期(progression free survival,PFS);次要终点事件为毒副反应、局部控制(local control,LC)、疾病进展时间(time to disease progression,TTP)。分析患者生存预后指标:OS、PFS、TTP及毒副反应指标:放射性皮肤纤维化、放射性皮炎及患肢淋巴水肿发生率。**结果** 匹配后2组基线特征均衡(均P>0.05)。随访时间的中位数为56.2个月,S+R组与R组OS的中位数(55.4个月 *vs* 56.2个月,P=0.738)、PFS的中位数(49.2个月 *vs* 37.0个月,P=0.959)、TTP的中位数(49.2个月 *vs* 37.5个月,P=0.808)均无统计学差异,2组患者LC率均为100%。单因素及多因素Cox回归分析显示三阴性分子亚型是OS的独立危险因素(HR=15.451,95%CI:1.253~190.579,P=0.033);cN分期是PFS的独立危险因素(HR=1.489,95%CI:1.006~2.202,P=0.046)。安全性方面S+R组Ⅲ度放射性皮炎发生率显著低于R组(0 *vs* 12.9%,P=0.001),S+R组对比R组放射性皮肤纤维化发生率(3.23% *vs* 9.68%)、患肢淋巴水肿发生率(12.90% *vs* 6.45%)均无统计学差异(P>0.05)。**结论** 与单纯放疗相比,手术切除联合放疗并未显著改善MBC患者的生存结局,但术后患者放射性皮炎风险显著降低;三阴性亚型及cN分期是MBC预后差的重要因素。

[关键词] 乳腺癌;手术;放疗;预后;放射性皮炎

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Surgical resection plus radiotherapy reduces radiation dermatitis risk without survival benefit in metastatic breast cancer: a retrospective cohort study

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[Abstract] **Objective** The role of local interventions (surgery/radiotherapy) targeting the primary

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tumor in improving survival among patients with metastatic breast cancer (MBC) remains controversial. This retrospective cohort study compared two local treatment modalities—surgical resection combined with radiotherapy (S+R) versus radiotherapy alone (R)—in terms of toxicities and prognosis in treatment-naive MBC patients, to evaluate the survival benefit and safety profile of these approaches for primary tumor management in MBC. **Methods** Using a retrospective cohort design, we analyzed 89 de novo MBC patients treated at Department of Oncology, Affiliated Tumor Hospital of Guizhou Medical University, between 2010 and 2025 (42 cases in the R group and 47 cases in the S+R group). Propensity score matching (PSM) with a caliper value of 0.2 was employed to balance baseline characteristics, yielding 62 matched patients (31 per group). The primary endpoints were overall survival (OS) and progression-free survival (PFS). Secondary endpoints included treatment-related adverse events (toxicity), local control (LC), and time to disease progression (TTP). Statistical analyses were performed to evaluate survival outcomes (OS, PFS, TTP) and toxicity indicators (radiation-induced skin fibrosis, radiation dermatitis, and ipsilateral limb lymphedema). **Results** Baseline characteristics were well balanced after matching (all $P>0.05$). The median follow-up was 56.2 months. No significant differences were observed between the S+R and R groups in median OS (55.4 *vs* 56.2 month, $P=0.738$), PFS (49.2 *vs* 37.0 months, $P=0.959$), or TTP (49.2 *vs* 37.5 months, $P=0.808$). No local recurrence occurred in either group (LC: 100% *vs* 100%). Univariate and multivariate Cox regression analyses identified the triple-negative subtype as an independent risk factor for OS (*HR*=15.451, 95%*CI*: 1.253 to 190.579, $P=0.033$), and cN stage as an independent risk factor for PFS (*HR*=1.489, 95%*CI*:1.006 to 2.202, $P=0.046$). For safety outcomes, compared with R, S+R yielded a significantly lower rate of grade 3 dermatitis (0 *vs* 12.9%, $P=0.001$), with comparable rates of fibrosis (3.23% *vs* 9.68%) and lymphedema of the affected limb (12.90% *vs* 6.45%) (both $P>0.05$). **Conclusion** Compared with R, S+R does not significantly improve survival outcomes in MBC patients, but it is associated with lower risk for radiation dermatitis. Triple-negative subtype and cN stage are identified as important adverse prognostic factors in MBC.

[**Key words**] breast neoplasms; surgery; radiotherapy; prognosis; radiation dermatitis

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全球乳腺癌发病率居高不下,其中转移性乳腺癌(metastatic breast cancer,MBC)威胁着乳腺癌患者的生存及生活质量。6%的新发乳腺癌患者在初次诊断时为远处MBC[1]。MBC的系统治疗是主要治疗策略[2-3],但对原发灶的局部干预(手术/放疗)能否改善生存仍存争议[4]。既往研究结论不一致,来自印度的TATA研究表明,早期局部放疗(local radiotherapy,LRT)的总生存期(overall survival,OS)没有优势[5]。Bjelic-radisic等[6]的回顾性研究提示手术或放疗可能改善生存,但缺乏高质量证据。本研究回顾性收集相关数据,通过倾向性评分匹配(propensity score matching,PSM)控制混杂偏倚,比较手术切除联合放疗(surgical resection and radiotherapy,S+R)与单纯放疗(radiotherapy,R)对初治MBC患者的生存获益及安全性,为优化MBC局部管理提供依据。

1 资料与方法

1.1 研究对象

研究采用回顾性队列研究设计方案。纳入2010—2025年贵州医科大学附属肿瘤医院肿瘤科门诊及住院的初治诊断为MBC的患者共89例,R组年龄(49.21±9.65)岁,S+R组年龄(50.60±10.70)岁。纳入标准:①组织学确诊初治转移性乳腺癌(初治转移性乳腺癌患者定义为确诊乳腺癌时即使已发生转移的Ⅳ期患者);②原发灶接受R或S+R治疗的患者(R组患者治疗顺序:接受一线治疗后4~6周接受乳腺及区域淋巴结放疗;S+R患者治疗顺序:先接受一线治疗,随即完成手术后4~6周接受乳腺及区域淋巴结放疗);③基线资料完整。排除标准:①活动性脑转移患者;②已接受多线治疗的MBC患者;③合并其他恶性

肿瘤。通过就诊记录、门诊复诊、电话沟通3种方式进行随访,随访率达100%,记录复发、转移事件和毒性反应,病例收集时间截止到2025年1月13日,随访截止日期为2025年2月10日。研究通过贵州医科大学附属肿瘤医院伦理审批(FZ2025-12-329)。

1.2 分组与匹配

共纳入MBC患者89例,R组(n=42),S+R组(n=47)。采用PSM,1∶1最近邻匹配,卡钳值0.2。协变量包括年龄、分子分型、全身治疗疗效评价、原发灶治疗疗效评价、远处转移部位、远处转移数量,匹配后62例(每组31例)。

1.3 治疗策略

所有患者经全身治疗后,接受原发灶单纯根治性放疗(中位剂量62 Gy,常规分割)作为R组;原发灶切除术(保乳/全乳切除)+术后放疗(中位剂量50.4 Gy,常规分割)作为S+R组。

1.4 观察指标

从医院信息系统(hospital information system,HIS)中收集患者的基线特征、临床和病理学诊断、治疗方案以及疗效观察指标相关数据。基线特征包括年龄、诊断时KPS评分、治疗后KPS评分、cT分期、cN分期、术前分子分型、远处转移部位、解救治疗全身疗效、解救治疗原发灶疗效、是否绝经、穿刺时ER表达、穿刺时PR表达、穿刺时Ki67、HER2表达、放疗是否加量(未做手术组残留病灶予以加量)。主要观察终点:总生存期(overall survival, OS)、无进展生存期(progression free survival, PFS)、局部控制率(local control, LC)、疾病进展时间(time to progression, TTP);次要观察终点:不良反应,包括放射性皮肤纤维化、放射性皮炎、患肢淋巴水肿,参照不良反应通用术语标准(CTCAE 5.0),根据治疗记录评估毒副反应的发生率及程度。

1.5 统计方法

统计学分析用的统计学软件为SPSS 22.0,计量资料首先进行正态性检验,符合正态分布者以$\bar{x}\pm s$表示,组间比较采用独立样本t检验;否则采用$M(P_{25}, P_{75})$表示,2组间比较采用Mann-Whitney U检验,计数资料采用频次(%)表示,组间比较采用χ^2检验;等级资料组间比较采用Mann-Whitney U检验,采用Kaplan-Meier绘制生存曲线,用Log-rank法进行组间比较,采用Cox回归分析各临床病理特征对患者生存时间的影响,P<0.05表示差异具有统计学意义。

2 结果

2.1 两组基线特征匹配效果

共纳入89例患者,经PSM后剩余62例(表1),上述特征在2组间无统计学差异(P均>0.05)。匹配后R组31例[年龄30~69(50.29±9.56)岁],S+R组31例[年龄32~70(51.16±10.53)岁]。2组患者分子分型中Luminal B型患者占比较多,R组11例(35.48%),S+R组14例(45.16%)。转移部位:单纯骨转移R组11例(35.48%),S+R组13例(41.94%);仅内脏转移R组7例(22.58%),S+R组13例(41.94%);骨合并内脏转移R组13例(41.94%),S+R组5例(16.13%)。转移部位数量:2组患者均为1~3个转移病灶,不包括转移部位数量大于3个的患者。解救治疗全身疗效评价中2组患者90%以上获得了CR/PR[R组29例(93.55%),S+R组28例(90.32%)],10%以下的患者获得SD/PD[R组2例(6.45%),S+R组3例(9.68%)]。解救治疗原发灶疗效评价中2组患者疗效获益与全身疗效一致。

2.2 生存分析

至随访截止日,中位随访时间为56.2个月。随访期间共有32例(51.16%)患者发生疾病进展,其中S+R组13例(41.94%),R组19例(61.29%)。在生存结局方面,S+R组与R组的中位OS分别为55.4个月和56.2个月,2组间差异无统计学意义(P=0.738,图1A)。中位PFS分别为49.2个月和37.0个月,差异亦无统计学意义(P=0.959,图1B)。2组均未观察到局部复发事件(局部控制率均为100%),故未绘制相应的Kaplan-Meier曲线。中位TTP分别为49.2个月和37.5个月,经Log-rank检验,组间差异无统计学意义(P=0.808,图1C)。单因素及多因素Cox回归分析显示,三阴性亚型(以Luminal A型为参照)是OS的独立危险因素(HR=15.451,P=0.033,表2);较高的cN分期是PFS的独立危险因素(HR=1.489,P=0.046,表3)。而TTP未发现独立的预后影响因素(表4)。

2.3 毒副反应

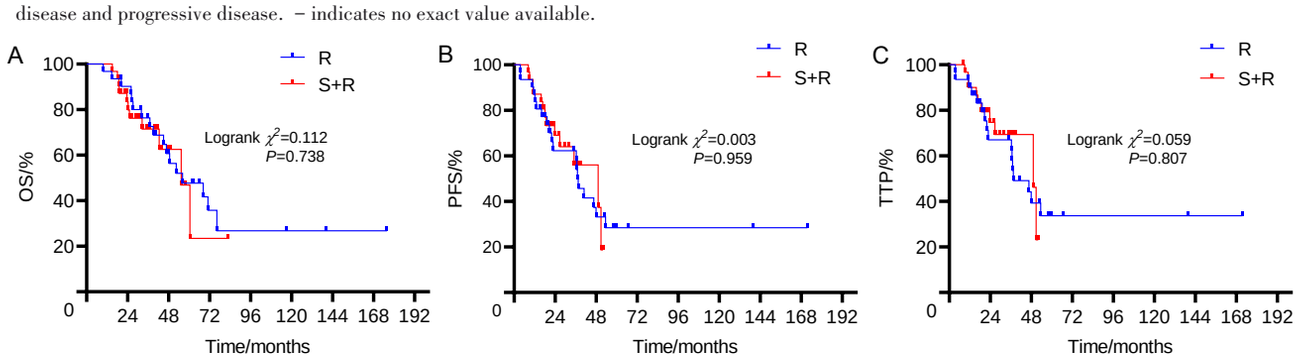
所有患者毒副反应根据CTCAE v5.0分级标准进行分级并记录,R组有2名(6.46%)患者出现Ⅱ度放射性皮肤纤维化,1名(3.23%)患者出现Ⅰ度纤维化表现,S+R组仅有1名(3.23%)患者出现Ⅰ皮肤纤维化,2组患者放射性皮肤纤维化无显著性差异(P=0.605)。S+R组放射性皮炎严重程度显著低于R组(P=0.001),

表1 初治转移性乳腺癌(MBC)患者倾向性评分匹配后基线资料比较 [例(%), $\bar{x}\pm s$]

Table 1 Comparison of baseline characteristics in the metastatic breast cancer (MBC) patients before and after propensity score matching [n(%), $\bar{x}\pm s$]

	Before matching				After matching			
	R (n=42)	S+R (n=47)	χ^2/z	P	R (n=31)	S+R (n=31)	χ^2/z	P
Age/years	49.21±9.65	50.60±10.70	0.637	0.526	50.29±9.56	51.16±10.53	0.341	0.734
Preoperative molecular subtype			9.337	0.096			9.022	0.108
Luminal A	3(7.14)	4(8.51)			3(9.68)	2(6.45)		
Luminal B	14(33.33)	24(51.06)			11(35.48)	14(45.16)		
Triple-negative	2(4.76)	4(8.51)			1(3.23)	2(6.45)		
HER2 positive(HR^+)	11(26.19)	11(23.4)			6(19.35)	11(35.48)		
HER2 positive(HR^-)	9(21.43)	4(8.51)			8(25.81)	2(6.45)		
Unknown	3(7.14)	0			2(6.45)	0		
Metastasis site			20.222	<0.01			5.522	0.063
Bone only	11(26.19)	27(57.45)			11(35.48)	13(41.94)		
Visceral only	8(19.05)	15(31.91)			7(22.58)	13(41.94)		
Bone and visceral	23(54.76)	5(10.64)			13(41.94)	5(16.13)		
Number of metastatic sites			5.107	0.024			–	–
1 to 3	36(85.71)	47(100)			31(100)	31(100)		
>3	6(14.29)	0			0	0		
Systemic response to salvage therapy			0.272	0.602			0	1.000
CR+PR	36(85.71)	42(89.36)			29(93.55)	28(90.32)		
SD+PD	6(14.29)	5(10.64)			2(6.45)	3(9.68)		
Primary tumor response to salvage therapy			0.272	0.602			0	1.000
CR+PR	36(85.71)	42(89.36)			29(93.55)	28(90.32)		
SD+PD	6(14.29)	5(10.64)			2(6.45)	3(9.68)		

S+R: Surgical resection combined with radiotherapy; R: Radiotherapy alone; CR+PR: Complete response and partial response; SD+PD: Stable disease and progressive disease. – indicates no exact value available.



A: Overall survival (OS) curves of MBC patients treated with primary lesion S+R group versus R group; B: Progression-free survival (PFS) curves of the 2 groups; C: Time to progression (TTP) curves of the 2 groups

图1 转移性乳腺癌原发灶行手术联合放疗与单纯放疗组患者随访期间预后曲线

Figure 1 Survival curves of MBC patients who received primary lesion S+R versus R during follow-up

S+R组无患者出现Ⅲ度以上放射性皮炎,R组有4名(12.90%)患者出现Ⅲ度以上放射性皮炎;患肢淋巴水肿无差异(P=0.668),S+R组有4名患者出现患肢淋巴水肿,R组有2名(6.45%)患者出现患肢淋巴水肿,2组患者的淋巴水肿均为轻度,不影响患者日常生活(表5)。

表2 初治转移性乳腺癌患者总生存期的单因素和多因素Cox回归分析

Table 2 Univariate and multivariate Cox regression analysis of overall survival in metastatic breast cancer patients

	Univariate		Multivariate	
	HR(95%*CI*)	*P*	*HR*(95%*CI*)	*P*
Treatment modality	1.144(0.520—2.519)	0.738		
Age	0.989(0.952—1.028)	0.576		
KPS score at diagnosis	1.035(0.987—1.085)	0.156		
KPS score after treatment	0.994(0.939—1.052)	0.823		
cT stage	0.918(0.616—1.368)	0.673		
cN stage	1.235(0.840—1.816)	0.282		
Preoperative molecular subtype				
Luminal A	1.000		1.000	
Luminal B	4.470(0.564—35.407)	0.156	3.128(0.365—26.799)	0.298
Triple-negative	24.723(2.370—257.943)	0.007	15.451(1.253—190.579)	0.033
HER2 positive(HR^+)	3.746(0.453—31.005)	0.221	2.510(0.273—23.103)	0.416
HER2 positive(HR^-)	6.284(0.700—56.379)	0.101	3.853(0.375—39.627)	0.257
Unknown	2.043(0.127—32.894)	0.614	1.394(0.081—23.934)	0.819
Metastasis site				
Bone only	1.000			
Visceral only	0.719(0.297—1.739)	0.464		
Bone and visceral	0.574(0.227—1.449)	0.240		
Systemic response to salvage therapy	0.570(0.076—4.260)	0.584		
Primary tumor response to salvage therapy	0.570(0.076—4.260)	0.584		
Menopausal status	0.518(0.210—1.279)	0.154		
ER at biopsy	0.994(0.984—1.004)	0.216		
PR at biopsy	0.998(0.987—1.01)	0.765		
Ki67 at biopsy	1.020(1.002—1.039)	0.028	1.012(0.993-1.031)	0.213
HER2 at biopsy	1.056(0.496—2.247)	0.888		
Radiotherapy boost	0.980(0.441—2.181)	0.961		

Univariate and multivariate Cox regression analyses show that preoperative molecular subtype is an independent prognostic factor for overall survival (OS). Compared with the Luminal A subtype, the triple-negative subtype is associated with significantly shorter OS. KPS: Karnofsky performance status; ER: estrogen; PR: progesterone receptors

3 讨论

本研究基于回顾性数据分析,采用PSM方法,系统比较S+R与R在初治MBC原发灶处理中的疗效与安全性。2组生存结局等效,在OS、PFS、TTP及LC上均无统计学差异,2组的中位OS仅相差0.8个月(55.4 *vs* 56.2个月)。2组局部控制情况良好,LC均达100%,高于既往文献报道的80%~90%,可能与根治性放疗剂量(中位50.4 Gy)及现代全身治疗迭代有关。2组毒性差异显著,S+R组Ⅲ度放射性皮炎发生率降至0(R组12.9%,*P*=0.001),提示手术介入可间接优化放疗安全性。上述结论通过PSM平衡了年龄、分子分型、转移负荷等混杂因素,增强了结果的可信度,为MBC原发灶管理的"去手术化"提供了回顾性研究数据及对其临床管理策略具有一定的启示意义。

3.1 生存获益等效性与治疗模式优化

与既往研究对比,本研究展现了生存获益的"非手术依赖"现象,即原发灶局部干预方式(S+R和R)不影响患者OS及PFS,该结论与Yoshimura等[7]纳入308例MBC患者的回顾性研究高度一致。然而,在这一等效性背后,2种放疗模式的剂量学差异及其与全身治疗迭代的交互作用,值得深入探讨。

全身治疗的持续进步可能是弱化局部干预价值的核心原因。本研究入组患者均为1~3个转移灶,且接近100%接受了一线全身治疗,其中HR^+/$HER2^-$患者接受内分泌治疗联合CDK4/6抑制剂,$HER2^+$患者接受抗HER2双靶向治疗,三阴性乳腺癌患者接受化疗或卡培他滨维持治疗。这类现代全身治疗方案相比

表3 初治转移性乳腺癌患者无进展生存期的单因素和多因素Cox回归分析

Table 3 Univariate and multivariate Cox regression analysis of progression-free survival in metastatic breast cancer pations

	Univariate		Multivariate	
	HR(95%*CI*)	*P*	HR(95%*CI*)	*P*
Treatment modality	0.981(0.470—2.046)	0.959		
Age	0.994(0.958—1.032)	0.762		
KPS score at diagnosis	1.016(0.973—1.062)	0.473		
KPS score after treatment	0.995(0.942—1.052)	0.873		
cT stage	1.025(0.702—1.495)	0.899		
cN stage	1.319(0.926—1.88)	0.125	1.489(1.006—2.202)	0.046
Preoperative molecular subtype				
Luminal A	1.000		1.000	
Luminal B	1.629(0.359—7.393)	0.528	1.883(0.358—9.909)	0.455
Triple-negative	7.344(1.170—46.082)	0.033	6.118(0.56—66.826)	0.138
HER2 positive(HR^+)	1.928(0.407—9.121)	0.408	1.492(0.256—8.699)	0.657
HER2 positive(HR^-)	2.878(0.566—14.621)	0.202	1.690(0.187—15.247)	0.640
Unknown	0.828(0.075—9.171)	0.878	0.385(0.024—6.256)	0.503
Metastasis site				
Bone only	1.000			
Visceral only	0.902(0.385—2.116)	0.813		
Bone and visceral	0.939(0.410—2.150)	0.882		
Systemic response to salvage therapy	0.487(0.065—3.626)	0.482		
Primary tumor response to salvage therapy	0.487(0.065—3.626)	0.482		
Menopausal status	0.662(0.297—1.479)	0.315		
ER at biopsy	0.993(0.984—1.002)	0.123	0.994(0.976—1.012)	0.500
PR at biopsy	0.996(0.986—1.007)	0.504		
Ki67 at biopsy	1.012(0.994—1.029)	0.188	1.003(0.984—1.022)	0.778
HER2 at biopsy	1.246(0.613—2.533)	0.543		
Radiotherapy boost	1.108(0.528—2.323)	0.787		

TATA研究[5]所处的传统化疗时代,对微转移灶的系统性控制能力已显著提升,从而可能削弱了原发灶局部干预对生存的相对贡献。关于MBC原发灶的处理价值,现有文献报道尚存分歧:部分研究支持手术获益,如TATA研究显示,手术延长OS长达8个月[5],中国老年仅骨转移或内脏转移患者亦可从原发灶手术中获得明显生存获益[8],但合并脑转移的三阳性患者未能从中获益[9];另有一些研究持否定观点,如奥地利的POSYTIV试验未能证明手术切除可改善新发Ⅳ期乳腺癌患者的OS[10],SCO 2020公布的初步数据同样显示手术对OS无显著影响[11]。上述研究结果的不一致性提示,临床医生需结合患者个体情况制定个体化局部治疗方案[12]。

本研究的多因素分析显示,三阴性亚型是OS的独立危险因素(*HR*=15.451),这一发现与Liu等[13]的荟萃分析结论(TNBC手术获益*HR*=0.93,Luminal型*HR*=0.72)相互印证,亦符合三阴性乳腺癌侵袭性强的固有生物学特性[14]。激素受体阴性患者长期生存较差的真实世界证据[15],进一步支持了本研究的核心推论:三阴性乳腺癌(trip-negative breast cancer, TNBC)患者因肿瘤侵袭性强、全身治疗反应差,局部干预难以改变其不良预后格局;而Luminal型患者(本研究中占比>45%)无论接受S+R还是R,OS均无显著差异。提示此类患者通过强化全身治疗即可实现生存获益。

关于放疗模式选择,本研究R组采用了“根治性剂量”策略,针对未切除的原发灶进行全程照射;而S+R组采用“术后辅助”模式,主要覆盖术后胸壁及区域淋巴引流区。2种放疗模式的剂量和靶区差异,正是生存等效性背景下探讨“最低有效干预”的关键切入点。本研究观察到局部控制率达100%的潜在机制可能与剂量学优势有关:R组放疗剂量中位数为60.2 Gy(剂量范围:50~70 Gy),达到了根治性放疗的剂量阈

表4 初治转移性乳腺癌患者疾病进展时间的单因素和多因素Cox回归分析

Table 4 Univariate and multivariate Cox regression analyses of TTP in metastatic breast cancer pations

	Univariate		Multivariate	
	HR(95%*CI*)	*P*	*HR*(95%*CI*)	*P*
Treatment modality	0.903(0.396—2.058)	0.808		
Age	0.981(0.941—1.023)	0.376		
KPS score at diagnosis	1.027(0.978—1.080)	0.286		
KPS score after treatment	1.015(0.952—1.081)	0.654		
cT stage	0.996(0.655—1.515)	0.986		
cN stage	1.246(0.841—1.846)	0.272		
Preoperative molecular subtype				
Luminal A	1.000			
Luminal B	1.080(0.223—5.238)	0.924		
Triple-negative	5.408(0.716—40.826)	0.102		
HER-2 positive(HR^+)	1.818(0.373—8.872)	0.460		
HER-2 positive(HR^-)	3.055(0.593—15.731)	0.182		
Unknown	0.851(0.077—9.423)	0.895		
Metastasis site	0.043(0—62.955)	0.397		
Bone only	0.043(0—62.955)	0.397		
Visceral only	0.477(0.179—1.268)	0.138	0.563(0.210—1.512)	0.255
Bone and visceral	0.989(0.979—0.999)	0.029	0.991(0.980—1.002)	0.103
Systemic response to salvage therapy	0.993(0.981—1.006)	0.295		
Primary tumor response to salvage therapy	1.011(0.992—1.030)	0.274		
Menopausal status	1.690(0.762—3.746)	0.196	1.274(0.548—2.960)	0.574
ER at biopsy	1.248(0.540—2.880)	0.604		

As shown in the table above, univariate and multivariate Cox regression analyses indicate that none of the variables are independent prognostic factors for time to progressive disease (TTP). Since only one variable had a $P<0.05$, the inclusion criterion for multivariate analysis is extended to $P<0.2$

表5 初治转移性乳腺癌患者匹配后行手术联合放疗与单纯放疗毒副反应比较[例(%)]

Table 5 Comparison of toxic effects between surgical resection plus radiotherapy and radiotherapy alone in metastatic breast cancer patients after propensity socre matching[*n*(%)]

	R (*n*=31)	S+R (*n*=31)	z/χ^2	*P*
Radiation-induced skin fibrosis				
No	28(90.32)	30(96.77)	0.267	0.605
Yes	3(9.68)	1(3.23)		
Radiation dermatitis			3.373	0.001
Grade 0	0	9(29.03)		
Grade Ⅰ	18(58.06)	17(54.84)		
Grade Ⅱ	9(29.03)	5(16.13)		
Grade Ⅲ	4(12.90)	0		
Grade Ⅳ	0	0		
Lymphedema of the affected limb			0.185	0.668
No	29(93.55)	27(87.10)		
Yes	2(6.45)	4(12.90)		

值;S+R组术后照射剂量为50.4 Gy,符合“低剂量、高足量”的放射治疗原则[11-12]。全身系统治疗可实现协同抗肿瘤:包括抗HER-2药物(曲妥珠单抗、帕妥珠单抗)[16]、小分子酪氨酸激酶抑制剂[17-19],内分泌联合CDK4/6抑制剂[20-22],抗血管生成药物[23],以及近年来临床应用日益广泛的PD-1/PD-L1免疫检查点抑制剂[24]与抗体药物偶联物[25-27]。上述药物联合使用可协同抑制局部残留病灶与微小转移灶,有效提升局部病灶控制率。

虽然本研究结果显示,S+R组与R组的PFS及TTP在统计学上并无显著性差异,但从数值层面可见,S+R组PFS中位数为49.2个月,R组为37.0个月;S+R组TTP的中位数为49.2个月,R组为37.5个月,2组中位时间相差约12个月,这在MBC的临床背景下是一个不可忽视的数值差异。出现这种差异的原因可能是匹配后样本量较小,统计检验效能不足难以捕捉到2组间真实存在的细微差异。本研究2组间PFS、TTP存在12个月绝对差值的趋势,提示可能在特定MBC

人群中,手术联合放疗仍值得进一步验证。Yoshimura等[7]专门探讨了术后放疗(postoperative radiotherapy,PORT)在初诊转移性乳腺癌中的价值,其核心发现是PORT的生存获益并非普适,而是严格局限于特定高风险亚组,包括年龄≤45岁、TNBC、原发肿瘤>5 cm以及区域淋巴结阳性(cN+)的患者。值得注意的是,本研究证实高cN分期为PFS的独立不良预后因素(*HR*=1.489),该基线特征与上述研究中可从PORT获益的高危亚组人群高度吻合。

3.2 联合治疗降低放射性皮炎风险的机制探讨

尽管S+R未显示生存优势,但其在安全性指标上表现突出,S+R组Ⅲ度放射性皮炎发生率为0,显著低于R组的12.9%(*P*=0.001)。这一现象的核心机制在于手术切除原发灶消除了对瘤床加量的必要性。①R组因原发灶存在,必须对初始肿瘤体积给予60~70 Gy的根治性剂量,且常需对残留灶进行同步推量或序贯加量,导致皮肤及皮下组织受照总剂量显著升高;而S+R组术后仅需给予50 Gy左右的预防/辅助剂量,皮肤受照剂量直接降低10~20 Gy。②手术切除原发灶后,放疗靶区从完整的乳腺/胸壁肿瘤缩小为术后胸壁平面,高剂量区体积显著减小。③术后胸壁结构平坦,更利于调强放疗技术实现剂量均匀性,避免未手术患者因乳腺形态不规则或肿瘤偏心导致的皮肤剂量热点。④手术移除乏氧的肿瘤组织后,局部组织氧分压升高,可能减轻放射诱导的过度炎症反应。放射性皮炎是干扰乳腺癌放疗依从性、损害患者生活质量的主要治疗相关毒性反应。严重皮炎可导致治疗中断、继发感染及长期皮肤损伤,而S+R对此风险的有效控制具有明确的临床收益。

3.3 研究局限性

尽管采用PSM平衡基线,未测量的混杂因素(如各种分子分型的具体全身治疗方案)仍可能影响结果。虽然本研究按乳腺癌的分子分型规定了标准全身治疗方案,但具体用药时长、剂量调整及后续治疗情况的实际差异未能完全记录,可能引入偏倚。亚组分析(如不同分子分型,尤其是三阴性亚型样本量少)效力不足,需扩大队列验证。仅重点关注放射性皮肤纤维化、放射性皮炎、上肢淋巴水肿,未纳入具体放疗天数等的系统比较。由于研究采用Cox回归分析,纳入变量较多,而匹配后样本量及事件数有限,可能存在过拟合风险,从而导致*HR*不稳定,因此结果稳定性有限,后续需扩大样本量进一步研究。

本研究比较了R组与S+R组患者的结局,但实际治疗过程中2组间差异可能受到其他重要临床因素的影响。首先,虽然2组患者全身治疗方案按乳腺癌分子分型给予标准治疗解救方案且后续系统治疗一致(HR阳性患者继续使用CDK4/6抑制剂,HER2阳性患者继续抗HER2治疗、TNBC患者虽然没有接受免疫治疗但都给予卡培他滨维持治疗),但2组放疗剂量存在差异(R组中位剂量62 Gy,S+R组因患者已行手术,放疗作为辅助手段仅给予50.4 Gy的剂量);未手术患者的原发灶负荷可能更大或存在不可切除情况。此外,保乳术后与全乳切除术后患者在放疗靶区范围及剂量设计上亦可能存在差异。上述因素均可能对生存结局及毒性结果产生影响。通过以上的局限性分析,本研究也确定了我们下一步研究方向:初治转移性乳腺癌原发灶局部处理的前瞻性随机对照试验及相关生物标志物探索。

3.4 总结

本研究证实,在转移性乳腺癌原发灶管理中,单纯放疗在生存获益上与手术联合放疗对于初治转移性乳腺癌患者的预后无统计学差异,同时规避了手术创伤并降低医疗成本。在本研究队列中,经过PSM平衡后,未发现S+R相比R能显著改善MBC患者的OS、PFS或TTP。但观察到的近12个月的PFS/TTP数值差异具有潜在的临床重要性,且S+R显著降低放射性皮炎发生率的优势为特定人群提供了额外保护。未来需通过前瞻性研究进一步明确不同生物学亚型患者的最佳局部干预模式,推动治疗策略的精准化与人性化。

利益冲突 本文所有作者声明不存在利益冲突

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