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### Effect of radiotherapy on prognosis of stage I E/ II E gastric mucosa-associated lymphoid tissue lymphoma

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### Abstract

**AIM:** To assess the effect of radiotherapy on prognosis of stage IE/II E gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

**METHODS:** The records of 35 patients treated for stage IE/II E MALT lymphoma at Sun Yat-sen University Cancer Center between June 24, 1997 and October 27, 2011 were retrospectively reviewed, including 9 cases who received radiotherapy followed by chemotherapy, 11 cases who received surgery followed by chemotherapy, and 15 cases who received chemotherapy alone. The curves of progression-free survival (PFS) and overall survival (OS) were calculated by the Kaplan-Meier method, and their significance was calculated by the log-rank tests. The curves of PFS and OS were compared among the three groups of patients.

**RESULTS:** The median follow-up time was 44.50 mo (range, 0.67 to 155.10 mo). Ten cases recurred, including 3 cases receiving surgery followed by chemotherapy, and 7 cases receiving chemotherapy alone. By multiple comparisons, the curve of PFS for cases receiving radiotherapy followed by chemotherapy had a statistical difference compared to those receiving chemotherapy alone ( $P = 0.043$ ), but showed

### ■背景资料

虽然胃相关淋巴组织(mucosa-associated lymphoid tissue, MALT)淋巴瘤对化疗高度敏感, 但化疗更易出现重度骨髓抑制和胃肠道反应。I E/ II E期胃MALT淋巴瘤长期局限于胃, 对放疗高度敏感, 可达到与手术、化疗和抗幽门螺旋杆菌(*Helicobacter pylori*, *H. pylori*)治疗相同的治疗效果; 但因发病率低, 病例数少, 国内远期疗效的报道鲜见。

### ■同行评议者

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## 应用要点

现代精确放疗手段能很好保护胃、肝、脊髓等危及器官, 放疗不良反应轻, 且可保存胃功能。因此, 局部放疗可作为是 I E/II E 期胃 MALT 淋巴瘤的一种优化治疗策略选择, 尤其是病理提示染色体异位的病例或者抗 *H. pylori* 治疗后复发者。本文中大多数病例初次治疗均在外院, 多数已行抗 *H. pylori* 治疗。

no statistical difference compared to those receiving surgery followed by chemotherapy ( $P = 0.195$ ). The curve of OS for cases receiving radiotherapy followed by chemotherapy did not differ significantly from that for cases receiving surgery followed by chemotherapy ( $P = 0.304$ ). No severe adverse reactions such as gastric hemorrhage or perforation occurred in cases receiving radiotherapy followed by chemotherapy.

**CONCLUSION:** Radiotherapy followed by chemotherapy is associated with significantly longer PFS in the treatment of stage IE/II E gastric MALT lymphoma compared to chemotherapy alone or surgery followed by chemotherapy, although OS had no significant difference in the three groups.

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**Key Words:** Gastric; MALT; Lymphoma; Surgery; Radiotherapy; Chemotherapy; Prognosis

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## 摘要

**目的:** 评价放疗在 I E/II E 期胃黏膜相关淋巴组织(mucosa-associated lymphoid tissue, MALT)淋巴瘤中的预后价值。

**方法:** 收集1997-06-24/2011-10-27中山大学肿瘤防治中心治疗的35例 I E/II E 期胃 MALT 淋巴瘤临床随访资料进行回顾性分析, 9例接受放疗+化疗, 11例接受手术+化疗, 15例接受单纯化疗, 采用Kaplan-Meier法计算无进展生存期(progression-free survival, PFS)和总生存期(overall survival, OS)生存率曲线, Log-rank统计学分析进行显著性检验, 比较放疗+化疗与手术+化疗、单纯化疗的PFS和OS生存率曲线。

**结果:** 中位随访44.50 mo(0.67-155.10 mo), 10例复发, 其中放疗+化疗组无复发, 手术+化疗组3例且均已死亡, 单纯化疗组7例。两两比较, 放疗+化疗组PFS生存率曲线与单纯化疗组比较有差异( $P = 0.043$ ), 与手术+化疗组比较无差异( $P = 0.195$ ); OS生存率曲线与手

术+化疗组比较无差异( $P = 0.304$ ), 与单纯化疗组无法进行比较。放疗+化疗组未发生胃出血、穿孔等严重不良反应。

**结论:** 在 I E/II E 期胃 MALT 淋巴瘤治疗上, 放疗+化疗PFS较单纯化疗延长, 与手术+化疗相同, OS与手术+化疗和单纯化疗均相同; 放疗不良反应小, 可保存胃功能, 推荐优先选择。

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**关键词:** 胃; 黏膜相关淋巴组织; 淋巴瘤; 手术; 放疗; 化疗; 预后

**核心提示:** 随着对胃相关淋巴组织(mucosa-associated lymphoid tissue, MALT)淋巴瘤发病机制的认识加深和诊断技术的进步, 胃大部切除术不再是其主要手段, 抗幽门螺杆菌治疗虽然可以抑制淋巴瘤但并不能完全消除肿瘤细胞, 尤其是伴染色体异位(11, 18)者易产生耐药。

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## 0 引言

胃黏膜相关淋巴组织(mucosa-associated lymphoid tissue, MALT)淋巴瘤幽门螺旋杆菌(*Helicobacter pylori*, *H. pylori*)感染阳性率约67%-91%<sup>[1-4]</sup>, 早期病例抗 *H. pylori* 治疗有效率约75%<sup>[5]</sup>。然而, 作为早期胃 MALT 淋巴瘤一线治疗方案的抗 *H. pylori* 治疗敏感性、消退情况 and 无病生存期个体差异性很大<sup>[6]</sup>, 清除 *H. pylori* 可以抑制淋巴瘤但并不能完全消除肿瘤细胞<sup>[7]</sup>。放疗对胃 MALT 淋巴瘤高度敏感, 是 I E/II E 期病变潜在可治愈手段<sup>[8]</sup>, 故有必要通过长期随访, 评价其在早期胃 MALT 淋巴瘤中的预后价值。现收集1997-06-24/2011-10-27中山大学肿瘤防治中心治疗的35例 I E/II E 期胃 MALT 淋巴瘤临床随访资料进行回顾性分析, 报道如下。

## 1 材料和方法

**1.1 材料 纳入标准:** 1997-06-24/2011-10-27于中山大学肿瘤防治中心接受治疗的经手术或胃镜活检病理确诊的胃 MALT 淋巴瘤患

表 1 临床病例随访资料

临床特点	n	百分比(%)
性别		
男	26	74.29
女	9	25.71
主要临床症状		
上腹痛	18	51.43
便血	9	25.71
呕吐/呕血	4	11.43
厌食/体质量下降	17	48.57
其他	10	28.57
幽门螺旋杆菌感染		
阳性	17	48.57
阴性	5	13.16
未查	13	37.14
LDH水平		
正常	25	71.43
升高	3	8.57
未查	7	20.00
Arbor分期		
I E期	27	77.14
II E期	8	22.86
累及部位		
胃窦	11	34.12
胃体	9	25.71
胃窦及胃体	25	71.43
染色体异位(11,18)		
阳性	8	22.86
阴性	2	5.71
未查	25	71.43

LDH: 乳酸脱氢酶.

者, 结合上消化道钡餐、胸/腹部计算机断层扫描(computed tomography, CT)或磁共振成像(magnetic resonance imaging, MRI)、正电子发射计算机断层显像(positron emission tomography, PET)/CT、腹部B超、胸片、骨髓穿刺等结果确定临床分期为 I E/II E期. 排除标准: 除外合并其他恶性肿瘤, 临床分期为 III/IV期者, 重要器官功能障碍不能接受手术治疗、放化疗等抗肿瘤治疗者. 分析临床病例随访资料, 35例符合入选标准, 年龄介于18-72岁之间, 中位年龄51岁, 内镜、病理及免疫组织化学手术切除活检11例, 内镜下活检24例, 胃镜下主要表现为黏膜粗糙, 水肿或浅表糜烂或溃疡或胃壁弥漫性增厚, 也可表现为黏膜隆起呈鹅卵石样特征. 病理结果均提示淋巴组织高度增生, 大多数具有边缘区B细胞和

中心样细胞的共同特征, 部分伴残余反应性滤泡; 部分病例行免疫组织化学检查, 其结果均提示B细胞淋巴瘤, 免疫组织化学: CD20(+)14例, LCA(+)21例, Bcl-2(+)11例, 弱(+)2例, (-)1例, Ki67弱(+)11例, (+)4例(表1).

1.2 方法 9例接受放疗+化疗, 11例接受手术+化疗, 15例接受单纯化疗, 手术方式为胃大部切除术, 放疗范围为全胃+胃周淋巴结, 中位放疗剂量34.2 GY(剂量范围20.0-36.0 GY/10-18 F), 化疗方案为CHOP、COP、CVP、CMOP、EPOCH, 化疗4-6周期.

**统计学处理** 全部数据采用SPSS19.0统计软件包进行统计学分析. 采用Kaplan-Meier法计算无进展生存期(progression-free survival, PFS)和总生存期(overall survival, OS)生存率曲线, Log-rank统计学分析进行显著性检验,  $P < 0.05$  为差异有统计学意义.

## 2 结果

2.1 重度不良反应 治疗期间放疗+化疗组3例出现III/IV度骨髓抑制, 2例发生于化疗期间, 1例发生于放疗期间, 未发生胃出血、穿孔等严重不良反应. 手术+化疗组1例出现III/IV度骨髓抑制、便血及发热, 1例强的松反应大停用. 单纯化疗组出现5例III/IV度骨髓抑制, 1例出现左腰背部带状疱疹, 予抗病毒、镇痛等对症处理. 骨髓抑制主要表现为白细胞或血小板下降, 予升白细胞、血小板等对症处理后恢复.

2.2 随访与预后 随访至2013-01, 中位随访时间44.50 mo(0.67-155.10 mo), 无失访病例, 10例复发, 放疗+化疗组无复发, 3例为手术+化疗组均已死亡, 7例为单纯化疗组. 4例行挽救放疗肿瘤消退, 继续随访无复发; 3例行挽救化疗, 其中2例分别于6 mo和12 mo后死于肿瘤, 1例带瘤生存; 1例行抗*H. pylori*治疗后病变控制, 随访未见复发; 1例拟行挽救放疗合并肝炎时予对症支持治疗后带瘤生存; 1例治疗情况不明并死亡. 生存曲线Log-rank法显著性检验结果如下: 放疗+化疗组与单纯化疗组PFS比较, 差异有统计学意义( $\chi^2 = 4.090$ ,  $P = 0.043$ ); 放疗+化疗组与手术+化疗组PFS、OS比较, 差异均无统计学意义( $\chi^2 = 1.676$ ,  $1.055$ ;  $P = 0.195$ ,  $0.304$ ); 放疗+化疗组与单纯化疗组OS比较, 无法进行差异性计算. 提示放疗+化疗较单纯化

## 同符评价

胃黏膜相关淋巴组织淋巴瘤发病率较低, 临床进行随机分组研究几无可能, 本文回顾性分析可以为临床提供参考.

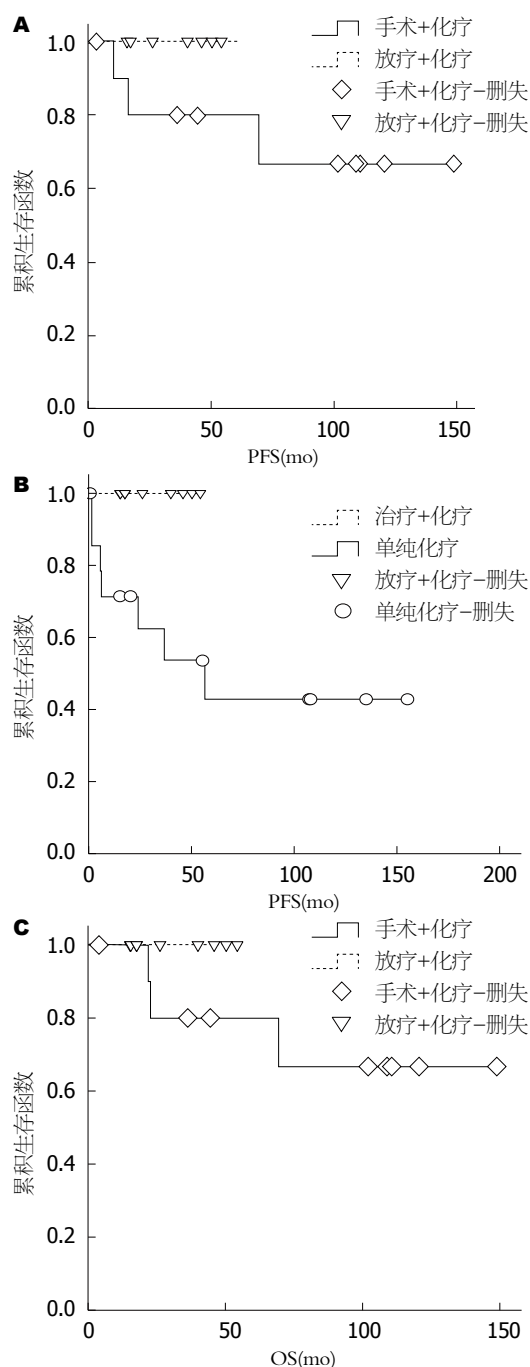


图1 Kaplan-Meier法计算患者PFS和OS生存率曲线。A: 手术+化疗和放疗+化疗PFS生存曲线; B: 放疗+化疗和单纯化疗PFS生存曲线; C: 手术+化疗和放疗+化疗患者OS生存曲线。PFS: 无进展生存期; OS: 总生存期。

疗可延长PFS(图1)。

### 3 讨论

研究表明, 抗*H. pylori*治疗后即便病理组织学提示完全缓解(complete response, CR), 通过PCR技术仍能检测出克隆性瘤细胞, 说明清除*H. pylori*可以抑制淋巴瘤但并不能完全消除肿瘤细胞<sup>[7]</sup>。放疗对胃MALT淋巴瘤高度敏感, 是

I E/II E期病变潜在可治愈手段<sup>[8]</sup>, 故有必要通过长期随访, 评价其在早期胃MALT淋巴瘤中的预后价值。

胃大部切除术曾经是胃MALT淋巴瘤诊断和治疗的必要手段, 术后5年生存率超过90%<sup>[9,10]</sup>。然而, 随着发病机制认识加深和诊断技术进步, 尤其是可通过内镜活检、胸/腹部CT、B超、PET/CT等非侵入性手段进行病理活检和临床分期, 加之影响胃功能和围手术期死亡缺点, 手术不再是首选治疗手段。德国一项多中心、非随机临床试验, 对比放疗±化疗和手术+放疗±化疗, 二者5年生存率并无区别<sup>[11]</sup>。放疗敏感性高, 胃组织相对耐受, 可保存胃功能, 提高生活质量。本研究提示, 放疗+化疗和手术+化疗PFS和OS生存率曲线无差异( $\chi^2 = 1.055$ ,  $P = 0.304$ ;  $\chi^2 = 1.676$ ,  $P = 0.195$ ), 同样证明局部放疗可取得与胃大部切除术相同的治疗效果。手术+化疗组3例复发, 2例经挽救化疗后未控死亡, 1例治疗情况不明死于肿瘤, 手术不能清除*H. pylori*抗原对胃黏膜组织的持续刺激可能是肿瘤复发的原因之一。而放疗+化疗组未见复发, 虽有3例重度骨髓抑制, 但其中2例发生于化疗期间, 说明局部放疗患者耐受性好; 即便同期放化疗, 胃出血和穿孔率亦仅约1%-4%<sup>[12,13]</sup>。如今精确放疗技术已能很好保护肝、肾、胃、脊髓等危及器官, 故放疗是I E/II E期胃MALT淋巴瘤理想局部治疗手段之一。

放疗和化疗均对胃MALT淋巴瘤高度敏感, 二者疗效预后研究结论不一致。Avilés等<sup>[14]</sup>针对241例患者进行随机研究, 中位随访7.5年, 化疗组5年生存率略优于手术组和放疗组(87% vs 80%, 75%,  $P = 0.04$ )。而Tsai等<sup>[15]</sup>对77例患者进行回顾性研究, 中位随访61 mo, 接受放疗患者与未接受放疗患者比较, 5年PFS率(79% vs 50%,  $P = 0.002$ )和FFTF率(81% vs 50%,  $P = 0.0004$ )较高。本研究中, 放疗+化疗PFS生存率曲线优于单纯化疗, OS生存率曲线一致, 放疗+化疗组无复发, 而单纯化疗组7例复发, 其中4例行挽救放疗后无复发, 1例行挽救化疗后带瘤生存, 1例行抗HP治疗后无复发, 1例行挽救放疗合并肝炎时予对症支持治疗后带瘤生存。单纯化疗组III/IV度骨髓抑制5例, 左腰背部带状疱疹1例; 而放疗+化疗组织化学治疗期间III/IV度骨髓抑制2例, 放疗期间仅1例。无论一线放疗还是挽救放疗患者长期缓解率均达100%, 未

发生胃出血、穿孔等严重不良反应。I E/II E期胃MALT淋巴瘤病变进展缓慢, 较长时间局限于胃, 放疗+化疗较单纯化疗PFS延长, 即便单纯放疗长期缓解率也达到100%<sup>[12,16]</sup>, 而化疗较放疗更易出现重度骨髓抑制, 故局部放疗可能是早期病例的一种优化治疗策略选择。

通过对本研究35例 I E/II E期胃MALT淋巴瘤临床随访资料进行回顾性分析发现, 放疗+化疗PFS较单纯化疗延长, 与手术+化疗相同, OS与手术+化疗和单纯化疗均相同。早期病变较长时间局限于胃, 局部放疗可保存胃功能, 不良反应小, 推荐优先选择。当然, 本研究系回顾性分析, 样本量小, 尚需扩大样本量进行前瞻性随机临床试验, 评价其预后价值。

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