

基于倾向评分匹配法评估进展期胃癌合并同时性原发性食管癌综合治疗的临床疗效

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[摘要] 目的: 通过倾向评分匹配(propensity score matching, PSM)法评估进展期胃癌合并同时性原发性食管癌综合治疗的临床疗效。方法: 回顾性分析江苏省中医院2013年1月至2022年12月收治的2 551例进展期胃癌病人, 将其中45例合并同时性原发性食管癌的病人纳入观察组, 将2 506例未合并食管癌的病人纳入对照组。采用PSM法匹配, 获取组间协变量均衡样本; 统计观察组治疗方案, 对比组间的总生存(overall survival, OS)。结果: 观察组和对照组各有45例样本纳入本研究。按治疗方案将观察组分为根治性切除组($n=22$)和根治性放化疗(chemoradiotherapy, CRT)组($n=23$)。根治性切除组中有4例行近端胃切除术联合Ivor Lewis手术同时切除食管肿瘤, 18例行胃癌根治性切除联合食管癌内镜下黏膜下剥离术(endoscopic submucosal dissection, ESD)。根治性CRT组中均予以胃癌根治性切除术联合食管癌根治性CRT。生存分析显示观察组OS期明显短于对照组($P=0.042$); 根治性切除组与对照组之间OS率差异无统计学意义($P=0.799$); 根治性CRT组1、3、5年生存率明显低于对照组($P=0.003$), 而根治性切除组1、3、5年生存率与根治性CRT组相比, 差异无统计学意义($P=0.071$)。结论: 多学科综合治疗能显著改善胃癌同时性双原发癌病人的预后。胃癌根治性切除联合食管癌ESD是胃癌合并早期食管癌病人可选的治疗方法, 胃癌根治性切除联合食管癌CRT能改善进展期胃癌合并不可切除食管癌病人的预后。

关键词: 进展期胃癌; 食管癌; 同时性双原发

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Propensity score matching method evaluate the clinical efficacy of comprehensive treatment for synchronous primary advanced gastric and esophageal cancer

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[Abstract] **Objective** To evaluate the clinical efficacy of comprehensive treatment for synchronous primary advanced gastric and esophageal cancer by propensity score matching (PSM). **Methods** A total of 2 551 patients with advanced gastric cancer admitted to Jiangsu Province Hospital of Chinese Medicine from January 2013 to December 2022 were retrospectively analyzed. Among them, 45 patients with synchronous primary esophageal cancer were distributed to the observation group, and 2 506 patients without esophageal cancer were distributed to the control group. Through the PSM method, the control group was matched with the observation group and the equilibrium samples of covariates between two groups were obtained. The overall survival(OS) between the two groups were compared. **Results** Both observation and control group contained 45 patients in this study. According to the treatment regimen, the patients in the observation group was divided into radical resection treatment subgroup ($n=22$) and chemoradiotherapy (CRT) subgroup ($n=23$). In the radical resection subgroup, 4 patients underwent the simultaneous surgical resection of gastric and esophageal tumors through proximal gastrectomy with the Ivor Lewis operation. Eighteen patients underwent endoscopic submucosal dissection(ESD) of their esophageal tumors and gastric cancer radical resection. Radical resection of gastric cancer combined with

preoperative chemoradiotherapy of esophageal cancer was performed in the CRT subgroup. Survival analysis showed that OS in the observation group was significantly shorter than that in the control group ($P=0.042$) and there was no significant difference in OS between the radical resection subgroup and the control group ($P=0.799$). The 1-, 3-, and 5-year survival rates of the patients in the CRT subgroup were significantly lower than those of the control group ($P=0.003$). While the 1-, 3-, and 5-year survival rates of the patients in the radical resection subgroup were not statistically significant, compared to those of the CRT subgroup ($P=0.071$). **Conclusions** Multidisciplinary and comprehensive treatment can significantly improve the prognosis of patients with synchronous primary advanced gastric and esophageal cancer. Radical resection of gastric cancer combined with ESD of esophageal cancer is an optional treatment for patients with gastric cancer complicated with early esophageal cancer. Radical resection of gastric cancer combined with CRT of esophageal cancer can improve the prognosis of patients with advanced gastric cancer complicated with unresectable esophageal cancer.

Key words: Advanced gastric cancer; Esophageal cancer; Synchronous

近年来,随着内镜诊疗技术的发展,胃癌合并多原发癌的病例逐渐增加^[1],常见合并食管癌、结肠直肠癌、肺癌等,占同期胃癌发病率的4.3%~6.7%^[2]。对于进展期胃癌合并同时性原发食管癌,临床治疗较棘手。随着内镜下切除术、根治性放化疗(chemoradiotherapy, CRT)等治疗技术及临床疗效的提高,多学科综合治疗的理念被广泛接受。但进展期胃癌合并同时性原发食管癌的发病率较低^[3],很难进行大样本的临床研究,相关治疗方法的安全性和有效性仍缺乏一定样本量的临床证据支持。因此,本研究回顾性分析了本院进展期胃癌合并同时性原发食管癌的病人临床资料,总结如下。

1 资料与方法

1.1 一般资料

对江苏省中医院2013年1月至2022年12月收治的2551例接受根治性切除的进展期胃癌病人进行回顾性分析,将其中合并同时性原发食管癌的45例纳入观察组。将未合并食管癌的2506例进展期胃癌病人纳入对照组,按照1:1倾向性评分匹配(propensity score matching, PSM)后,两组各有45例样本纳入本研究。

1.2 纳入及排除标准

纳入标准:①同时性多原发癌的诊断符合Warren诊断标准^[4];②均采用胃癌根治性切除术。

排除标准:①合并肝肾功能异常;②合并严重内分泌系统疾病;③精神疾病。

1.3 研究方法

1.3.1 治疗方法

经消化肿瘤外科、放疗科、消化内镜科、病理科和肿瘤内科医师评估,根据肿瘤位置、大小、活检病理以及肿瘤分期制定个体化治疗方案如下:①合并

早期食管癌的病人(肿瘤临床分期包括cTis期、cT1期和cT1a期),先在内镜中心行内镜下黏膜下剥离术(endoscopic mucosal dissection, ESD)治疗食管癌。2周后,针对进展期胃癌采用新辅助化疗(neoadjuvant chemotherapy, NAC)方案,包括每2周重复1次的FLOT(氟尿嘧啶、多西他赛、奥沙利铂、亚叶酸钙)方案和每3周重复1次的EOX(表柔比星、卡培他滨、奥沙利铂)方案。2个治疗周期结束后2~3周进行胃癌根治性切除术。具体手术方式由术前分期和肿瘤位置决定。胃癌根治性切除术后继续辅助化疗。②经评估为可切除的食管癌病人,采用胃癌NAC联合食管癌CRT后进行同时性胃癌、食管癌根治性切除。具体如下,接受胃癌NAC 1~2个疗程后,采用三维适形放疗或常规分割6~8 MV光子束调强放射治疗食管癌,共40 Gy辐射剂量(2 Gy/d,分20次,每周5 d);放疗期间化疗方案包括单药多西他赛或氟尿嘧啶。放疗结束后4~6周行食管胃癌同期根治性切除手术。术后行辅助化疗。③合并晚期不可切除的食管癌病人,予胃癌NAC联合根治性CRT方案,放疗总辐射剂量为60 Gy(2 Gy/d,分30次,每周5 d),在CRT结束4~6周后行胃癌根治性切除术,术后予辅助化疗。

1.3.2 随访

生存期从病理明确诊断后开始计算,随访截至2022年12月31日。所有病人都在我院接受标准随访检查,即术后2年内每3个月进行1次血常规、血生化、体格检查和腹部超声或CT检查等,之后每6个月1次。通过体格检查以及超声、胸片、内镜、MRI、CT、PET-CT检查或组织学活检来评估复发情况。CRT不良反应分级依据WHO标准进行评估。

1.4 统计学方法

相关数据运用SPSS 19.0软件处理。对病人的年龄、性别、NAC方案以及肿瘤位置和大小和分期

等混杂协变量以 1:1 的比例进行 PSM 法匹配,卡钳值设置为 0.01。符合正态分布的计量资料用均数±标准差表示,使用 student *t* 检验。计数资料的统计比较使用卡方检验和 Fisher 精确检验。生存分析使用 Kaplan-Meier 曲线和 Log-rank 检验比较各组间的 OS 结果。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 一般资料

观察组纳入 45 例,中位年龄 66(52~84)岁。食管癌临床 TNM 分期 I 期 20 例,II 期 0 例,III 期 19 例,IV 期 6 例;其中上段食管癌 5 例,中段食管癌 15 例,下段食管癌 25 例。胃癌临床 TNM 分期 I 期 0 例,II 期 13 例,III 期 21 例,IV 期 11 例;肿瘤位于贲门 26 例,胃体 8 例,胃窦 11 例。18 例(40.0%)早期食管癌行 ESD 联合胃癌根治性切除术,4 例(8.9%)接受食管胃肿瘤同时根治性切除手术,为根治性切除组。23 例(51.1%)晚期不可切除食管癌行食管癌根治性 CRT 联合胃癌根治性切除术,为根治性 CRT 组。

2.2 治疗结果

18 例成功行 ESD 切除食管恶性肿瘤,其中 1 例因术后病理检查提示黏膜下肿瘤浸润行补救 CRT 治疗,1 例术后出现食管狭窄,行食管扩张术后症状缓解。4 例采用 Ivor Lewis 术式切除食管和近端胃肿瘤。无术中死亡病例,4 例发生手术并发症,其中肺炎 2 例,肠梗阻 1 例,切口感染 1 例。

23 例不可切除食管癌病人中,22 例(95.7%)完成了 CRT 疗程,1 例因出现食管炎停止 CRT。行 CRT 治疗后 2 个月,其中 6 例(26.1%)完全缓解,15 例(65.2%)部分缓解。2 例(8.7%)病情稳定,缓解率 91.3% (21/23)。10 例(43.5%)发生 3~4 级急性不良反应,其中骨髓抑制 8 例(34.8%),食管炎 6 例(26.1%),重度黏膜炎 4 例(17.4%),重度肺炎 2 例(8.7%)。所有病人均未出现严重的晚期不良反应。

22 例食管癌根治性切除术病人中,8 例(36.4%)出现术后复发。复发部位多位于腹膜(4/22, 18.2%),其次为淋巴结(3/22, 13.6%)。23 例行 CRT 的病人中,有 18 例(78.3%)出现疾病进展,其中局部进展 6 例(26.1%),远处进展 9 例(39.1%),两者均有的有 3 例(13.0%)。

2.3 PSM 法匹配结果

45 例合并同时性原发食管癌的进展期胃癌病人与 2 506 例未合并食管癌的进展期胃癌病人胃癌

肿瘤部位、胃癌病理细胞类型、胃癌临床 TNM 分期、是否接受 NAC 方面差异均有统计学意义(见表 1)。经 PSM 匹配后,纳入未合并食管癌的进展期胃癌病人 45 例作为对照组,两组年龄、性别、NAC 方案以及肿瘤位置、大小和分期等基线资料比较,差异无统计学意义($P > 0.05$)(见表 1)。

2.4 总生存期比较

观察组 1、3 和 5 年总体生存(overall survival, OS)率分别为 100%、58% 和 23%,对照组 OS 率分别为 95%、67% 和 52%。对照组的总 OS 期明显长于观察组($P = 0.042$)(见图 1A)。

根据治疗方案不同,将观察组分为根治性切除组($n = 22$)和根治性 CRT 组($n = 23$)。生存分析提示根治性切除组的 1、3、5 年生存率分别为 100%、62% 和 48%,与对照组 OS 率差异无统计学意义($P = 0.799$)(见图 1B);根治性 CRT 组的 1、3、5 年生存率分别为 100%、53% 和 0,与对照组 OS 率差异有统计学意义($P = 0.003$)(见图 1C)。根治性切除组 1、3、5 年生存率与根治性 CRT 组相比,差异无统计学意义($P = 0.071$)(见图 1D)。

3 讨论

胃食管同时性双原发癌是临床少见病例,与单纯胃癌、食管癌相比,其预后较差^[5]。本研究合并同时性原发食管癌的进展期胃癌病人与单纯进展期胃癌病人相比,OS 率明显下降,这与其他研究报道^[6]一致。胃食管同时性双原发癌的治疗目前尚无指南可循,临床上对于胃食管同时性双原发癌的治疗方案多根据病人病情及接诊医师个人经验制定。

同时性根治性切除手术是早期胃食管双原发癌病人的首选方案,但手术治疗的选择常受到肿瘤分期、部位以及病人心、肺功能等因素限制。此外,合并进展期胃癌的病人往往需行根治性全胃切除,消化道重建常需用结肠代食管^[7]。该手术方式创伤大,术后并发症多、生活质量差^[8-9]。本研究也仅 4 例(8.9%)接受了胃食管同时性根治性切除术。

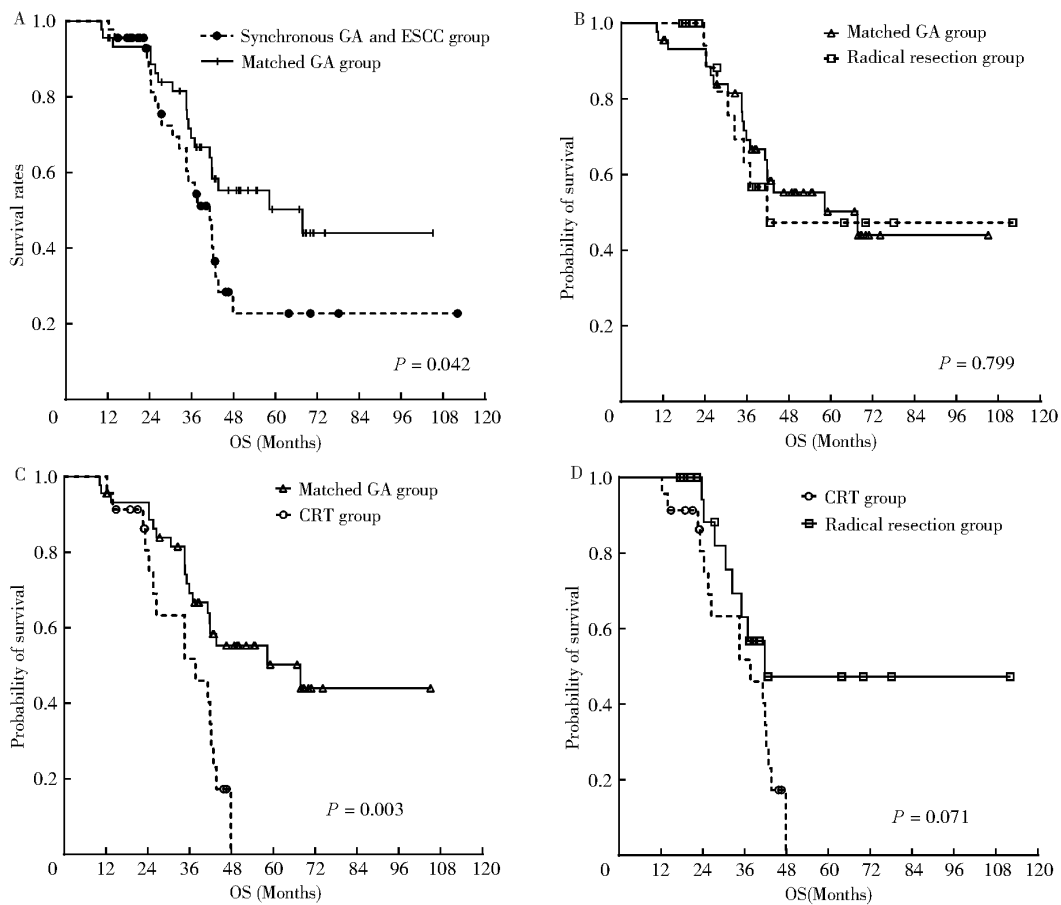
与传统手术相比,早期食管癌内镜下切除具有创伤小、整体切除率高、局部复发风险低、术后生活质量好等优势^[10],因此被广泛接受。ESD 作为内镜下治疗的主要方法,也逐渐成为早期食管癌的主要手术方案^[11]。Watanabe 等^[12]的研究也提示内镜治疗改善早期食管癌的预后。本研究对比根治性切除组与对照组发现,两组的 OS 差异无统计学意义,

表 1 PSM 匹配前后胃癌合并与不合并同时性食管鳞状细胞癌病人的人口学和临床特征比较

Tab 1 Demographic and clinical characteristics of the gastric cancer patients with and without synchronous esophageal squamous cell carcinoma were compared before and after propensity score matching

Characteristics	Unmatched			Matched		
	Synchronous GA and ESCC (n=45)	GA (n=2 506)	P value	Synchronous GA and ESCC(n=45)	GA (n=45)	P value
Age (years)	66.09±7.9	63.19±11.0		66.09±7.9	63.29±10.2	0.149
Gender			0.065			0.535
Male	38	1 805		38	40	
Female	7	701		7	5	
Tumor location			<0.001			0.514
Upper	26	1 356		26	31	
Middle	8	566		8	5	
Lower	11	584		11	9	
Histology of cancer			<0.001			0.126
Differentiated	32	639		32	25	
Undifferentiated	13	1 867		13	20	
cStage (TNM)			<0.001			0.959
II	13	1 073		13	12	
III	21	1 216		21	21	
IV	11	217		11	12	
NAC			<0.001			1.000
Yes	45	1 752		45	45	
No	0	754		0	0	

GA: gastric cancer; ESCC: esophageal squamous cell carcinoma; NAC: neoadjuvant chemotherapy; PSM: propensity score matching.



A: OS curve of the 45 advanced GA patients with synchronous ESCC and 45 matched GA patients; B: OS curve of curative resection group and matched GA group; C: OS curve of CRT group and matched GA group; D: OS curve of curative resection group and CRT group. OS: overall survival; GA: gastric cancer; CRT: chemoradiotherapy.

图 1 组间生存对比曲线

Fig 1 Overall survival curve of different groups

提示胃癌根治性切除联合食管癌 ESD 是进展期胃癌合并早期食管癌的可选治疗方法。

同步 CRT 是目前不可切除的中晚期食管癌之标准治疗方案^[13], 临床分期为 III 期的食管癌病人 CRT 的疗效与手术相似^[14]。食管癌根治性 CRT 的完全缓解率达到 40%^[15], 但进展期胃癌接受 NAC 后的完全病理缓解率只有 15%~20%^[16-17]。因此, 合并不可切除食管癌的进展期胃癌病人在接受食管癌根治性 CRT 后行胃癌根治性切除能否改善其预后是临床医师关注的问题, 但目前尚无相关研究报道。本研究发现, 根治性 CRT 组 1、3、5 年生存率与根治性切除组相比, 差异无统计学意义 ($P=0.071$), 提示食管癌根治性 CRT 联合胃癌根治性切除术是进展期胃癌合并不可切除食管癌病人可行的治疗方案。

本研究虽然采用 PSM 法匹配降低组间基线水平差异性, 但回顾性分析中还有很多因素未纳入匹配范围, 对研究结果产生一定影响。未来需增加临床样本量或行前瞻性研究提供更直观的临床证据。

综上所述, 多学科综合治疗显著改善胃食管同时性双原发癌病人的预后。胃癌根治性切除联合食管癌 ESD 是胃癌合并早期食管癌的可选治疗方法, 胃癌根治性切除联合食管癌 CRT 改善进展期胃癌合并不可切除食管癌病人的预后。

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