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调强适形放疗联合化疗治疗局部晚期食管癌的疗效观察

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摘要 目的:观察调强适形放疗(intensity modulated radiation therapy, IMRT)联合多西他赛、奈达铂方案化疗同步治疗局部晚期食管癌的疗效及安全性。**方法:**选择 66 例局部晚期食管癌患者为研究对象,将其随机分为 2 组,其中常规放疗组(A 组)共 30 例,采用常规照射方法,6/8 MV 高能 X 线,2.0 Gy/次,5 次/周;40 Gy/20 次后再次定位剂量达 60~66 Gy,强调放疗组(B 组)共 36 例,采用强调适形性放疗,6/8MV-X 射线照射,以 95% 等剂量线包绕 PTV(计划靶区),处方剂量 GTV(肿瘤区)66 Gy/30 次,CTV(临床靶区)60 Gy/30 次,PTV 60 Gy/30 次,每天 1 次,每周 5 次。强调放疗组同期接受 IMRT 和多西他赛、奈达铂化疗,21 天 1 个周期,连续 2 个周期。治疗结束后根据实体瘤疗效评价标准(RECIST)评定临床疗效;参照 WHO 毒性反应分度标准评价毒副反应。**结果:**常规放疗组和强调放疗组的总有效率分别为 46.66%和 91.67% ($\chi^2=17.26, P<0.05$);常规放疗组的毒副反应发生率显著高于强调放疗组,包括骨髓抑制、放射性食管炎和消化道反应的发生率存在显著差异($P<0.05$)。**结论:**调强适形放疗联合多西他赛、奈达铂化疗同步治疗局部晚期食管癌疗效较好,毒副反应可耐受,具有潜在的推广应用价值,值得临床进一步研究。

关键词:局部晚期食管癌;调强适形放疗;多西他赛;奈达铂

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Observation on the Clinical Efficacy of Intensity Modulated Radiation Therapy (IMRT) Combined Chemotherapy in the Treatment of Local Advanced Esophageal Cancer

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ABSTRACT Objective: To observe the clinical effects of intensity modulated radiation therapy (IMRT) combined docetaxel and nedaplatin chemotherapy for local advanced esophageal cancer. **Methods:** Totally 66 patients with local advanced esophageal cancer were enrolled in this study. Thirty patients enrolled in group A (n=30) received conventional radiotherapy. External beam radiation of 6/8MV-X ray was given 2.0 Gy/time and 5 time / week. A total dose of 60-66 Gy was reset after 40 Gy/20 times. Thirty-six patients enrolled in group B (n=36) received IMRT with external beam radiation of 6/8MV-X ray and PTV received 95% of total dose radiation. GTV received a dose of 66 Gy/30 times, CTV received a dose of 60 Gy/30 times and PTV received a dose of 60 Gy/30 times. Patients were treated once a day and 5 times/week and combined with docetaxel and nedaplatin chemotherapy. After two cycles of chemotherapy, the clinical efficacy was evaluated according to the standards of response evaluation criteria in solid tumors (RECIST); toxic side effects were measured referring to the standards of WHO. **Results:** The clinical efficacy of all the patients could be evaluated, of which the total effective rate was 46.66% in group A and 91.67% in group B ($\chi^2=17.26, P<0.05$). The main toxic and side effects included myelosuppression, radiation esophagitis and digestive tract reactions, which were all significantly severer in group A than those in group B ($P<0.05$). **Conclusion:** IMRT combined docetaxel and nedaplatin chemotherapy has shown satisfactory efficacy and safety in treating local advanced esophageal cancer which has the potential for extensive application and is deserved further clinical research.

Key words: Local advanced esophageal cancer; Intensity modulated radiation therapy; Docetaxel; Nedaplatin

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前言

食管癌是我国常见的消化道恶性肿瘤之一,具有高度侵袭性,预后极差且生存率低^[1]。手术治疗是目前公认食道癌的治疗手段,但其存在手术风险及对患者术后生活质量的长期负面影响^[2,3]。同时临床调查发现,大多数食管癌患者确诊时已属晚期,局部病灶早已远处转移,发生了广泛的浸润,给治疗带来

极大的困难,失去了切除治疗和彻底根治的最佳时机^[4]。研究发现,同步放化疗可以有效的治疗局部中晚期食管癌,显著提高近期治疗疗效和生存率^[5]。但对放疗患者的跟踪调查发现,一般放疗技术的疗效并不理想,局部复发和远处转移是导致生存率低的主要原因^[6]。调强适形放疗是一项治疗癌症的精确放疗技术,已被广泛应用在癌症治疗领域。临床研究表明强适形放疗通过提高放射的准确性和控制照射靶体积的来达到理想的处方剂量,从而有效的提高治疗食管癌的疗效^[6]。近年来的研究发现,多西他赛和奈达铂可以有效的治疗食道癌^[7,9]。因此,本研究应用调强适形放疗同时给予多西他赛、奈达铂药物的化疗治疗

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局部晚期食管癌,分析其近期疗效和不良反应及其对患者生活质量的影响。

1 资料与方法

1.1 临床资料

入组患者 66 例,所有病例均行电子胃镜检查取活检,明确组织学诊断,且均未经放疗、化疗和手术及其他特殊治疗。其中男性 28 例,女性 8 例,平均年龄 56 岁(44-70 岁);病理类型:鳞癌 34 例,腺癌 2 例。病变部位:颈段 8 例,胸中上段 22 例,胸下段 6 例,病变长度 3 cm-8 cm。经过严格地体检,所有病例没有食管活动性出血和穿孔前征象,也没有远处淋巴结或其它脏器转移,仅含有区域淋巴结转移;血常规、肝肾功能及心电图均正常;无其他恶性肿瘤病史及严重内科疾患,KPS 评分 ≥ 70 。

1.2 研究方法

1.2.1 放射治疗 两组患者均取仰卧位,双手交叉置头顶,真空袋固定体位。常规放疗组在普通模拟机下定位射野。采用三野等中心照射,长度为模拟机下病变长度上下各加 3 cm。野宽一前野 6 cm,二后野宽 5 cm,8 MV 直线加速器照射,2.0 Gy/次,5 次/周。40 Gy/20 次后再次定位剂量达 60~66 Gy。调强放疗组在模拟机下参考移动激光灯标出患者体模及治疗床的相对位置,保证患者体模及床的位置相对固定。以治疗体位行定位 CT 扫描。扫描层厚 5 mm,扫描范围自环状软骨至腹腔干,颈段病变还应包括全颈。将定位 CT 重建图像通过局域网络传输入 TPS 治疗计划系统,设计放疗计划。肿瘤区(GTV)、临床靶区(CTV)、计划靶区(PTV)等靶区按照国际辐射单位和测定委员会(ICRU)50 号及 62 号文件规定标准定义,结合 CT 扫描图像、消化道造影片及胃镜检查结果勾画靶区,并勾画体表轮廓及肺、心脏、脊髓等危及器官。其中 GTV 包及影像可见的原发灶及转移的区域淋巴结;CTV 为 GTV 上下各放 3 cm、前后左右各放 0.8 cm,另包括相应的淋巴引流区;PTV 在 CTV 的基础上再外放 0.5 cm。8 MV-X 射线照射,照射野为 5 野或 7 野。以 PTV 几何中心为射野中心,并定义其为剂量归一点。根据靶区剂量、适形度、剂量体积直方图(DVH)对治疗计划进行评估和优化,给出处方剂量并对危及器官限量要求。以 95%等剂量线包绕 PTV,处方剂量 GTV 66 Gy/30 次;CTV 60 Gy/30 次,PTV 60 Gy/30 次。每天 1 次,每周 5 次。脊髓受量在 40 Gy

以下,肺受量满足 $V_{20}<25\%$,心脏 $V_{40}<45\%$ 。通过 TPS 计划系统计算结果,在模拟机下定出摆位参考点并验证各照射野的正确性,通过多叶光栅技术实施放疗。治疗过程中每周查血常规 1-2 次,每 2 周复查食管吞钡 X 线摄片,根据病情定期检查肝肾功能。

1.2.2 化疗方法 多西他赛(希存,深圳万乐药业有限公司)75 mg/m² 静脉滴注(1 h),第一天给药;奈达铂(奥先达,江苏奥赛康药业有限公司)25 mg/m² 静脉滴注,第 1~3 天给药。21 d 为一个周期。多西他赛治疗前一天服用地塞米松 8 mg,每日 2 次,持续 3 d;每次化疗前常规给予托烷司琼预防呕吐。

1.2.3 疗效及毒性反应的判定标准 治疗期间详细记录早期反应(按照美国肿瘤放射治疗协作组织标准 RTOG)。同步放化疗结束后 3 个月,根据治疗前后 X 线食管钡餐片、纵隔 CT 的改变评价肿瘤灶退缩情况进行近期疗效评价。根据美国临床肿瘤学会 2000 年公布的实体瘤疗效评价标准(RECIST)评定临床疗效,分为完全缓解(CR)、部分缓解(PR)、稳定(SD)和进展(PD),有效率(RR)为 CR+PR。毒副反应评价参照 WHO 毒性反应标准^[9],分为 0-IV 度,食管放射性损伤分级按 RTOG 急性放射损伤分级标准确定。

1.2.4 统计学方法 采用统计学软件 SPSS13.0 进行统计学分析,两组治疗有效率、毒副反应发生率的差异采用 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组近期疗效的比较

根据实体瘤疗效评价标准(RECIST)评定患者治疗后的临床疗效,结果显示常规放疗组 CR 4 例(13.33%),PR 10 例(33.33%),SD 12 例(40.00%),PD 4(13.33%),治疗总有效率为 46.66%;而强调放疗联合化疗组 CR 15 例(41.67%),PR 18 例(50.00%),SD 2 例(5.56%),PD 1(2.77%),治疗总有效率为 91.67%,显著高于常规放疗组($\chi^2=17.26, P<0.05$)。

2.2 两组毒副反应的比较

治疗后,对所有患者的毒副反应进行了分析和比较,结果显示两组患者的主要毒副反应包括骨髓抑制、放射性食管炎、口腔粘膜炎症、放射性肺炎和消化道反应,强调放疗联合化疗组各种毒副反应的发生率均显著低于常规放疗组($P<0.05$)(表1)。

表 1 两组毒副反应的比较(例)

Table 1 Comparison of the toxic and side effects between two groups (case)

Toxic and side effects	Group A					Group B					x ²	P
	0	I	II	III	IV	0	I	II	III	IV		
Radiation esophagitis	1	5	8	9	7	1	14	17	4	0	16.1	<0.05
Leukopenia	0	2	5	18	5	1	9	19	6	1	21.92	<0.05
Thrombocytopenia	3	4	14	6	3	12	12	8	3	1	12.60	<0.05
Decrease of hemoglobin	3	6	15	4	2	8	16	12	0	0	12.71	<0.05
Oral mucositis	8	18	4	0	0	26	8	2	0	0	13.61	<0.05
Nausea and vomiting	8	13	9	0	0	7	23	6	0	0	12.13	<0.05
Diarrhea	10	16	4	0	0	29	7	0	0	0	16.34	<0.05
Radiation pneumonitis	10	12	8	0	0	28	8	0	0	0	16.92	<0.05

* 注: Group A 表示常规放疗组;Group B 表示强调放疗联合化疗组;P <0.05 表示显著差异。

*Notes: Group A indicates patients received conventional radiotherapy, Group B indicates patients received IMRT combined chemotherapy, P < 0.05 denotes significant difference.

3 讨论

食管癌是一种常见的消化道恶性肿瘤。调查显示,食管癌患者主要集中在40岁以上,有肿瘤家族史或癌前疾病并且吸烟和过度饮酒是引起食管癌的高发因素^[11-13]。由于食管的结构及位置比较特殊,食管癌侵入外膜时可累及邻近器官;且食管富含淋巴毛细血管,易出现淋巴转移,给治疗带来了极大的困难。临床研究显示,食管癌的最佳治疗时期是在癌症发生的早期^[14]。但是由于大多患者缺乏早期检查的意识及现阶段诊断技术的限制,大多数食管癌患者临床确诊时,已发生了远处转移和广泛的浸润,失去了可以彻底根治的最佳机会。

放射治疗是食管癌的主要治疗手段之一。尽管在照射技术、分割方式和多学科综合治疗方面已取得明显进展,但食管癌常规放疗的疗效多年来无明显提高,主要的失败原因仍为肿瘤的局部未控或复发约60-70%,肺损伤、脊髓及心脏耐受量妨碍了局部肿瘤剂量的提高。调强适形放疗(IMRT)是近年来开展的新技术,该技术可以通过保持高剂量的等剂量线面与靶区在三维空间上形态上高度一致给予靶区充足的剂量照射并可以减少对其他器官和组织的照射,因此该技术不但可以最大限度的杀灭癌细胞,同时确保周围的组织和器官不受伤害,实现了在不增加组织并发症概率(NTCP)的前提下提高肿瘤局部照射剂量和局部控制率^[15,16]。临床治疗中发现,常规放射治疗技术不能实现肿瘤靶体积足够的剂量照射,是导致食管癌局部复发的主要原因^[17]。IMRT与常规放射治疗相比,可以保持肿瘤靶体积和正常组织理想的照射剂量分布,在治疗食道癌中根据有独特的优势。

放射治疗作为一种局部治疗手段,也存在着一定的缺陷,可以治疗肿瘤局部和周围的浸润但不能控制肿瘤的转移。药物的化疗不仅可以有效的抑制癌细胞的增殖和扩散,并可以增加癌细胞对放疗的敏感性,因此在实施放射治疗的时候同时给予药物的化疗可以取得理想的治疗效果。国内外大量研究发现,同期化放疗较单纯放疗可降低局部复发率,延长了生存时间。目前,同期化放疗已成为美国和欧洲等国家的局部非手术治疗食管鳞癌的标准方案。

研究表明多西他赛是细胞周期特异性抑制的是植物碱类抗肿瘤药物。多西他赛不仅可以引起和加快微管的合成通常抑制微管解聚,导致细胞有丝分裂期纺锤体功能异常,从而达到抑制细胞分裂和增殖的目的;另一方面还可以同化所有肿瘤细胞处于放疗敏感的G2/M期,有利于和放疗联合治疗肿瘤。采用多西他赛行全身化疗不仅可以控制肿瘤病灶的转移而且还可以抑制微小转移灶和肿瘤细胞的增殖^[18]。奈达铂为顺铂类似物,作用机制同顺铂,与肿瘤细胞的DNA碱基结合,抑制DNA复制而发挥抗肿瘤效果。研究发现,食管癌同步放化疗时用多西他赛、奈达铂分别作为单药增敏化疗,可提高中晚期食管癌的近期疗效,且不良反应相对较轻^[19]。

本研究发现IMRT联合多西他赛、奈达铂化疗同步治疗局部晚期食管癌可以取得较好的近期疗效,有效率高达91.67%。骨髓抑制及放射性食管炎是本组最常见的毒副反应。其中,骨髓抑制中白细胞的减少最为显著。一般情况下,白细胞在用药10d左右时,数量降至最低。但是,该毒副反应在经G-CSF治疗后很快减轻,一般持续3~5d,并不耽误下周期的治疗。由于

多西他赛和奈达铂均有骨髓抑制作用,两药物联合使用并与放疗同期进行,可加重骨髓抑制。因此,治疗期间要严密检测患者的生命体征,及时处理。放射性食管炎明显考虑与采用调强治疗后肿瘤局部高剂量有关。

总之,本研究结果显示,调强适形放疗联合多西他赛、奈达铂化疗治疗局部晚期食管癌,和常规治疗方法相比,不仅可以显著的提高临床疗效,而且具有明显的安全性,值得临床进一步的研究和推广应用。在今后的工作中,我们将作进一步随访,以了解患者的远期生存率及安全性。

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