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容积弧形调强放疗同步化疗治疗晚期非小细胞肺癌患者的短期疗效 及对血清 TSGF、TK1、CA125 水平的影响 *

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摘要 目的:探讨容积弧形调强放疗同步化疗治疗晚期非小细胞肺癌患者的短期疗效及对血清肿瘤特异性生长因子(TSGF)、胸苷激酶 1(TK1)、糖类抗原 125(CA125)水平的影响。**方法:**选择 2015 年 1 月至 2018 年 1 月我院接诊的 95 例晚期非小细胞肺癌患者,按照随机数表法分为观察组 48 例和对照组 47 例。观察组使用容积弧形调强放疗,对照组使用三维适形放疗,临床靶区(CTV)剂量均为 2.0Gy/次,总剂量 50Gy,1 次/d,5 次/周,两组均使用长春瑞滨+顺铂同步化疗。比较两组的临床疗效、治疗前后血清 TSGF、TK1、CA125 水平的变化及不良反应的发生情况。**结果:**治疗后,观察组疾病总缓解率为 43.75%,明显高于对照组(23.4%, $P<0.05$),血清 TSGF、TK1、CA125 均明显低于对照组($P<0.05$)。两组治疗期间胃肠道反应、血液毒性、心脏毒性、骨髓抑制、肝功能损伤、放射性肺炎、放射性食管炎不良反应发生率比较差异均无统计学意义($P>0.05$)。**结论:**容积弧形调强放疗同步化疗治疗晚期非小细胞肺癌患者的短期效果显著优于三维适形放疗,其可更有效降低血清 TSGF、TK1、CA125 的表达水平,且安全性更高。

关键词:晚期非小细胞肺癌;容积弧形调强放疗;三维适形放疗;肿瘤特异性生长因子;胸苷激酶 1;糖类抗原 125

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Short-term Clinical Efficacy of Volume-arc Intensity Modulated Radiotherapy in the Treatment of Advanced Non-small Cell Lung Cancer and its Effects on the Serum TSGF, TK1 and CA125 Levels*

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ABSTRACT Objective: To study the short-term clinical efficacy of Volume-arc intensity modulated radiotherapy in the treatment of advanced non-small cell lung cancer and its effects on the serum tumor-specific growth factor(TSGF), Thymidine kinase 1(TK1) and Carbohydrate antigen 125(CA125) levels. **Methods:** 95 patients of advanced non-small cell lung cancer who were treated from January 2015 to January 2018 in our hospital were selected as the research objects, they were divided into the 48 cases in the observation group and 47 cases in the control group by the random number table. The observation group was treated with volume-arc intensity modulated radiotherapy, while the control group was treated with three-dimensional conformal radiotherapy, the clinical target area (CTV) dose was 2.0Gy/ times, total dose 50Gy, 1/d, 5 times/week, they were treated with chemotherapy combined with rubinbin plus cisplatin in Changchun. The clinical efficacy, changes of the serum TSGF, TK1, CA125 levels before and after treatment and incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the total remission rate of observation group was 43.75%, which was significantly higher than that in the control group (23.4%, $P<0.05$); the serum TSGF, TK1, CA125 levels were significantly lower than those in the control group($P<0.05$); there was no significant difference in the incidence of adverse reactions including gastrointestinal reaction, blood toxicity, cardiotoxicity, myelosuppression, liver function injury, radiation pneumonia and radiation esophagitis between the two groups during treatment($P>0.05$). **Conclusion:** The short-term effect of volume-arc intensity modulated radiotherapy combined with chemotherapy for advanced non-small cell lung cancer is significantly better than that of three-dimensional suitable radiotherapy, which can effectively reduce the expression of serum TSGF, TK1 and CA125 levels with higher security.

Key words: Advanced non-small cell lung cancer; Volume-arc intensity modulated radiotherapy; Three-dimensional conformal radiotherapy; Tumor-specific growth factor; Thymidine kinase 1; Carbohydrate antigen 125

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前言

非小细胞肺癌是临床上常见的恶性肿瘤,多数晚期非小细胞肺癌患者已丧失根治手术的机会,同步放化疗已成为此类患

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者的治疗标准手段,但大部分患者无进展生存率仍较低,3年总生存率不足24%^[1,2]。容积弧形调强放疗是一种新型的放射疗法,在加速器进行弧形照射的同时,多叶光栏的叶片位置会随着机架旋转,并根据靶区的形状变化而变化,令照射束和接受照射的靶体积始终保持一致,达到提高靶区剂量的目的,但目前关于其用于晚期非小细胞肺癌的报道仍较少^[3,4]。

肿瘤标志物在恶性肿瘤诊疗过程中具有重要价值,国内外均有报道显示检测血清肿瘤特异性生长因子(TSGF)、胸苷激酶1(TK1)、糖类抗原125(CA125)的表达对于判断非小细胞肺癌患者疗效及预后具有重要的参考价值^[4,5]。本研究通过检测血清TSGF、TK1、CA125水平的变化,主要探讨了容积弧形调强放疗治疗晚期非小细胞肺癌的短期疗效。

1 资料与方法

表1 两组一般资料的比较($\bar{x} \pm s, n(\%)$)

Table 1 Comparison of the general data between two groups($\bar{x} \pm s, n(\%)$)

Groups	n	Sex(Male)	Age(years)	Pathological type			Pathological stage		
				Adenocarcinoma	Squamous cell carcinoma	adenosquamous carcinoma	III ^a	III ^b	IV
Observation group	48	25(52.08)	67.85 $\pm$ 8.41	8(16.67)	36(75.00)	4(8.33)	19(39.58)	21(43.75)	8(16.67)
Control group	47	26(55.32)	68.14 $\pm$ 8.26	9(19.15)	34(72.34)	4(8.51)	17(36.17)	23(48.94)	7(14.89)
χ^2/t		0.100	0.170		0.106			0.258	
<i>P</i>		0.752	0.866		0.949			0.879	

1.2 治疗方法

所有患者均使用负压袋将身体固定,在治疗体位下进行螺旋CT平扫加增强扫描,层厚5mm,图像传输至TPS工作站,由同一位医师进行勾画放射靶区,并和同一位物理医师使用Eclipse TPS设计进行放疗计划;观察组使用容积弧形调强放疗,每2°给予1个照射野,共计划1~2个弧,每弧360°旋转,分别沿顺时针、逆时针方向扫描;对照组使用三维适形放疗,使用3~5个照射野,以多叶光栅适形,并经过反复调整各射野的权重进行优化选取计划。两组临床靶区(CTV)剂量均为2.0 Gy/次,总剂量50 Gy,1次/d,5次/周。两组化疗方案均选择长春瑞滨(规格1 mL: 10 mg,厂家:海南齐鲁制药有限公司,国药准字H20093078)25 mg/m²静脉滴注,d1、d8,顺铂(规格20 mL: 20 mg,厂家:江苏豪森药业股份有限公司,国药准字H20010743)75 mg/m²静脉滴注,d1~d3;以3周为1个周期,第1个周期和放疗同步,之后3个周期进行序贯。

1.3 观察指标

于治疗前后,采集3 mL空腹静脉血,离心后,留取上层血清液置于冷冻箱内待检,血清TSGF的检测使用比色法试剂盒(福建新大陆生物技术股份有限公司),血清TK1的检测使用化学发光法试剂盒(深圳华瑞同康生物技术有限公司),血清CA125的检测使用酶联免疫吸附法试剂盒(上海晶抗生物工程有限公司);记录治疗期间不良反应的发生情况。

1.4 疗效评价标准

使用《实体瘤疗效评价标准RECIST》^[7]评价疗效:完全缓解:所有目标肿瘤病灶完全消失,时间>1个月;部分缓解:肿

1.1 一般资料

选择2015年1月至2018年1月我院接诊的95例晚期非小细胞肺癌患者,研究已通过我院伦理委员会批准。纳入标准:①符合非小细胞肺癌诊断标准^[6],临床分期III~IV期,并通过细胞学、纤维支气管镜活检查确诊;②拒绝接受手术或不宜实施手术;③既往进行过放化疗;④预计生存期>3个月;⑤患者及家属签署本研究知情同意书。排除标准:⑥血常规、心肝肾功能、生化指标等检查存在异常;⑦合并其余恶性肿瘤;⑧合并严重感染;⑨合并恶性胸水;⑩对本研究治疗方案有禁忌症。通过随机数表法将所有患者分为观察组48例,对照组47例,两组一般资料比较差异均无统计学意义($P>0.05$),具有可比性,具体见表1。

瘤最大径和最大垂直径乘积缩小 $\geq 30\%$,时间>1个月;疾病稳定:肿瘤最大径和最大垂直径乘积缩小 $<30\%$,或增大 $<20\%$;疾病进展:肿瘤最大径和最大垂直径 $\geq 20\%$,或死亡。总缓解率=(完全缓解+部分缓解)/总例数 $\times 100\%$ 。

1.5 统计学分析

以SPSS18.0软件包处理数据,正态分布的计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较使用独立样本t检验,组内比较使用配对样本t检验,计数资料以率表示,组间比较采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组近期疗效的比较

治疗后,观察组疾病总缓解率为43.75%,明显高于对照组(23.4%, $P<0.05$),见表2。

2.2 两组治疗前后血清TSGF、TK1、CA125水平的比较

治疗后,两组血清TSGF、TK1、CA125水平均较治疗前均显著降低,且观察组血清TSGF、TK1、CA125水平均明显低于对照组($P<0.05$),见表3。

2.3 两组不良反应发生情况的比较

两组治疗期间的不良反应包括胃肠道反应、血液毒性、心脏毒性、骨髓抑制、肝功能损伤、放射性肺炎、放射性食管炎不良反应,主要集中于I~II级,其发生率比较差异无统计学意义($P>0.05$),见表4。

3 讨论

表 2 两组近期疗效的比较[例(%)]

Table 2 Comparison of the short-term effects between two groups[n(%)]

Groups	n	Complete remission	Partial remission	Disease stabilization	Disease progression	Total remission rate
Observation group	48	0(0.00)	21(43.75)	14(29.17)	13(27.08)	21(43.75)
Control group	47	0(0.00)	11(23.40)	17(36.17)	19(40.43)	11(23.40)
χ^2						4.401
<i>P</i>						0.036

表 3 两组治疗前后血清 TSGF、TK1、CA125 水平的比较($\bar{x} \pm s$)

Table 3 Comparison of the serum TSGF, TK1 and CA125 levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	n	Time	TSGF(U/ml)	TK1(pmol/L)	CA125(U/ml)
Observation group	48	Before treatment	68.92 $\pm$ 7.45	3.75 $\pm$ 0.41	38.56 $\pm$ 3.41
		After treatment	44.50 $\pm$ 5.08 ^⓪	1.99 $\pm$ 0.15 ^⓪	15.02 $\pm$ 2.12 ^⓪
Control group	47	Before treatment	69.08 $\pm$ 7.34	3.69 $\pm$ 0.46	38.33 $\pm$ 3.60
		After treatment	53.19 $\pm$ 6.42 ^⓪	2.58 $\pm$ 0.24 ^⓪	24.03 $\pm$ 2.88 ^⓪

Note: Comparison with the same group before treatment, ⓪ $P < 0.05$; Comparison with control group after treatment, ⓪ $P < 0.05$.

表 4 两组不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	n	Grade	Gastrointestinal reaction	Hematotoxicity	Cardiotoxicity	Myelosuppression	Liver function damage	Radiation pneumonia	Radioactive esophagitis
Observation group	48	I-II	19(39.58)	5(10.42)	2(4.17)	3(6.25)	4(8.33)	2(4.17)	2(4.17)
		III-IV	2(4.17)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Control group	47	I-II	18(38.30)	7(14.89)	6(12.77)	8(17.02)	5(8.51)	3(6.38)	1(2.13)
		III-IV	1(2.13)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

同步化疗是目前不能实施手术的晚期非小细胞肺癌患者的首选治疗方案,二者有明显的协同及增敏效果,但仍有较多患者预后较差^[8,9]。三维适形放疗是近年来较为常用的放疗方案,主要是利用 CT 图像重建三维肿瘤结构,该方式定位准确,可提高计划靶体积和治疗剂量,但较多报道显示该方式用于晚期非小细胞肺癌患者的局部控制率不足 35%,5 年生存率也较低^[10,11]。

有学者提出通过提高放疗剂量可帮助肿瘤局部控制率、总生存率的提高^[12,13]。但随着剂量的提高,也会增加放射性肺损伤的机率,放射性肺损伤是胸部肿瘤放疗剂量提高的重要限制性因素^[14,15]。容积弧形调强放疗是基于固定野调强放疗所优化的一种新型放疗基础,该方式集精密三维和两维的剂量验证、新型高精尖加速器、逆向优化治疗计划软件为一体,近年来开始在较多恶性肿瘤中得以应用^[16,17]。Sudha SP 等^[18]在乳腺癌术后分别使用容积弧形调强放疗和三维适形放疗后,发现容积弧形调强放疗具有更高的靶区适形性。Joseph D 等^[19]报道也发现容积弧形调强放疗在不增加放射治疗不良反应的同时提高了靶区剂量,在提高肿瘤患者远期生存率上有积极意义。

TSGF 中肿瘤细胞所生成的特殊物质,在非小细胞肺癌病灶生成及进展过程中发挥着重要作用^[20,21]。有研究证实 TSGF 可通过促周边毛细血管生成,促使肿瘤增长,且其在疾病早期时便在血液中释放并达到较高浓度,对其的检测有助于评价非小细胞肺癌的发生和发展状况^[22,23]。TK1 在胸腺嘧啶核苷转化为单磷酸胸腺嘧啶中发挥着关键作用^[24,25]。其作为一种修复酶

在 DNA 的合成和修复过程中均有所参与,且和细胞增殖获得密切相关,随着肿瘤细胞增值能力的加强、肿瘤负荷的不断过大,TK1 的表达也会随之升高^[26,27]。CA125 属糖类抗原,既往是诊断子宫内膜癌、卵巢癌的特异性标志物,近年来的研究也证实其升高程度和非小细胞肺癌的病理分期呈正相关^[28,29]。

本研究结果显示使用容积弧形调强放疗的患者治疗后血清 TSGF、TK1、CA125 的降低程度更明显,且疾病总缓解率为 43.75%,比三维适形放疗的患者高,考虑和容积弧形调强放疗具有旋转治疗特点,可提高靶区适形性相关。且本研究中两组治疗期间不良反应如胃肠道反应、血液毒性、心脏毒性、骨髓抑制、肝功能损伤、放射性肺炎、放射性食管炎主要集中于 I-II 级,发生率比较差异均无统计学意义,提示容积弧形调强放疗并未增加相关放射性损伤。但在骨髓抑制方面,使用容积弧形调强放疗的患者稍低于使用三维适形放疗的患者。骨髓属于串联器官,其放射损伤和照射最大剂量相关。Jiang J 等^[30]报道也发现较三维适形相比,容积弧形调强放疗骨髓最大靶区剂量较低,具有更明显的剂量学优势,更适用于靠近脊髓的肿瘤患者治疗。本研究中,两组骨髓抑制差异无统计学意义考虑和样本量过少相关,此部分结论仍需扩大样本量进一步研究。本研究仅观察了近期疗效,对于该方式对患者远期无进展生存率也需再进行深入探讨。

综上所述,容积弧形调强放疗同步化疗治疗晚期非小细胞肺癌患者的短期效果显著优于三维适形放疗,其可更有效降低血清 TSGF、TK1、CA125 的表达水平,且安全性更高。

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