鼻咽癌颅底破坏肿瘤靶区拆分勾画剂量学研究

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【摘 要】**目的：**探讨鼻咽癌颅底骨质破坏调强放疗中肿瘤靶区拆分勾画的可行性，为鼻咽肿瘤和颅底骨质破坏区域给予不同处方剂量提供剂量学支持。**方法：**2010年7月~2011年12月将30例具有颅底骨质破坏、无远处转移的初治鼻咽癌的GTV_{nx}拆分勾画为GTV_{np}和GTV_{bone}，分别代表为鼻咽肿瘤和颅底骨质破坏区域。在每个病人的定位CT上设计3个治疗计划，第1个计划：GTV_{np}和GTV_{bone}处方剂量相同，但相对较低，6800 cGy~7000 cGy；第2个计划：GTV_{np}和GTV_{bone}处方剂量相同，剂量相对较高，7000 cGy~7400 cGy；第3个计划：GTV_{np}和GTV_{bone}处方剂量不同，GTV_{np} 6800 cGy~7000 cGy、GTV_{bone} 7000 cGy~7400 cGy。比较鼻咽癌颅底骨质破坏调强放疗GTV拆分勾画肿瘤靶区体积变化、肿瘤靶区及正常组织的剂量变化。**结果：**3个计划95%的处方剂量均能包括各自的靶区，颅底剂量分布不均匀，尤其最上两层靶区，3个计划PTV_{bone}的D_{max}与D_{min}平均相差1231 cGy、1824 cGy、1731 cGy，PTV_{bone}的D_{mean}分别为6910 cGy、7550.1 cGy、7541.8 cGy；鼻咽剂量分布均匀，PTV_{np}的D_{max}与D_{min}平均相差429.3 cGy、571.4 cGy、926.7 cGy；PTV_{np}的D_{mean}分别为6966 cGy、7557.6 cGy、7222.7 cGy。双侧腮腺、口腔剂量与GTV_{np}剂量梯度相关，口腔平均剂量相差约341.5 cGy~513.4 cGy，双侧腮腺的平均剂量相差362.3 cGy~491.7 cGy。脑干、脊髓、双侧中耳、左右视神经、颞叶剂量分布无显著差异。**结论：**鼻咽癌颅底骨质破坏GTV拆分勾画可行，能满足鼻咽肿瘤和颅底骨质破坏区域的不同剂量要求，降低了口腔、双侧腮腺等正常组织的剂量。

【关键词】鼻咽肿瘤；颅底破坏；调强放疗；大体肿瘤靶区；剂量学
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Dosimetric study on dividing delineation of gross target volume of nasopharyngeal carcinoma with skull base destruction

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Abstract: Objective To provide dosimetric basis for delivering different prescription dose to nasopharyngeal neoplasms and areas of skull base destruction by exploring the feasibility of dividing delineation of gross target volume (GTV) in the intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC) with skull base destruction. **Methods** From July 2010 to December 2011, 30 patients with non-metastatic NPC with skull base destruction, treated by IMRT, were analyzed. Their GTV_{nx} were divided into GTV_{np} and GTV_{bone}, respectively representing the GTV of nasopharyngeal neoplasm and areas of skull base destruction. Based on the location CT, three treatment plans were designed for each patient. In the first plan, GTV_{np} and GTV_{bone} were given the same prescribed dose, 6800 cGy-7000 cGy. In the second plan, GTV_{np} and GTV_{bone} were also given the same prescribed dose, 7000 cGy-7400 cGy. While the prescribed doses to GTV_{np} and GTV_{bone} were different in the third plan, respectively 6800 cGy-7000 cGy, 7000 cGy-7400 cGy. The changes of target volume divided by GTV delineation and the dose to target volumes and normal tissues in the IMRT for NPC with skull base destruction were analyzed. **Results** The prescribed dose received by planning target volume (PTV) was more than or equal to 95% in each plan. The dose to skull base was not uniform, especially to the top two layers of target volume. The average dose differences between the maximal dose (D_{max}) and minimum dose (D_{min}) of PTV_{bone} were respectively 1231 cGy, 1824 cGy, 1731 cGy. The mean doses (D_{mean}) of PTV_{bone} were respectively 6910 cGy, 7550.1 cGy, 7541.8 cGy. The dose distribution of nasopharynx was uniform and the average dose

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differences between D_{max} and D_{min} of PTV_{np} were 429.3 cGy, 571.4 cGy, 926.7 cGy, respectively. The D_{mean} of PTV_{np} were 6966 cGy, 7557.6 cGy, 7222.7 cGy, respectively. The doses of bilateral parotid glands and oral cavity were related to the dose gradient of GTV_{np}. The average dose difference of oral cavity was 341.5 cGy~513.4 cGy, and that of bilateral parotid glands was 362.3 cGy~491.7 cGy. There were no statistically significant differences in dose distribution of critical regions, such as brain stems, spinal cords, bilateral middle ears, right and left optic nerves and temporal lobes. **Conclusion** Dividing delineation of GTV in the IMRT for nasopharyngeal carcinoma with skull base destruction is feasible. It can deliver different prescribed dose respectively for nasopharyngeal neoplasm and areas of skull base destruction, and decrease doses to normal tissues of oral cavity and bilateral parotid glands.

Key words: nasopharyngeal neoplasm; skull base destruction; intensity modulated radiotherapy; gross target volume; dosimetry

前　言

鼻咽癌调强放谢治疗(IMRT)靶区勾画是关键,大体肿瘤靶区(Gross Target Volume, GTV)是决定局部控制的一个重要因素,目前国内外鼻咽癌IMRT计划中,靶区定义参考ICRU第50号、62号报告原则[1],GTV的定义基本趋于一致。对于鼻咽癌并颅底骨质破坏的患者鼻咽肿瘤和被肿瘤侵犯的颅底作为一个GTV,由于肿瘤生物学行为、解剖结构等差异,可能并不合理。我科2010年7月~2011年12月,对30例鼻咽癌并颅底骨质破坏的IMRT放疗患者的GTV拆分勾画,即鼻咽肿瘤和颅底骨质破坏区域分别勾画,命名为GTV_{np}和GTV_{bone},给予不同的处方剂量,取得了较好的临床疗效,现报道其剂量学优势。

1 对象与方法

1.1 一般临床资料

具有颅底骨质破坏、无远处转移的初治鼻咽癌30例,均经病理活检证实。病理分型WHOⅡ、Ⅲ型分别为11例、17例,未分型2例,其中男性19例、女性11例,年龄32岁~65岁,中位年龄45岁;按鼻咽癌08分期[2],Ⅲ期13例、Ⅳa期17例。

1.2 CT定位

采用IMRT技术,头肩颈热塑面罩固定,CT增强定位,层厚3 mm,层距3 mm。扫描范围从头顶扫描至锁骨头下3 cm,将CT图像传入治疗计划系统。

1.3 勾画靶区

在每个病人的定位CT上勾画两组GTV。一组同传统靶区勾画,参考ICRU第50号、62号报告原则,根据临床大体所见及鼻咽MR所示的大体肿瘤靶区(鼻咽肿瘤和颅底骨质破坏区域)勾画为GTV_{nx}。另一组拆分GTV_{nx},即鼻咽肿瘤和颅底骨质破坏区域分别独立勾画为GTV_{np}和GTV_{bone}。颈部阳性淋巴结(GTV_{nd})、高危临床靶体积(CTV_1)和低危临床靶体积(CTV_2)与传统的靶区勾画基本一致[1],见图1。

1.4 计划设计

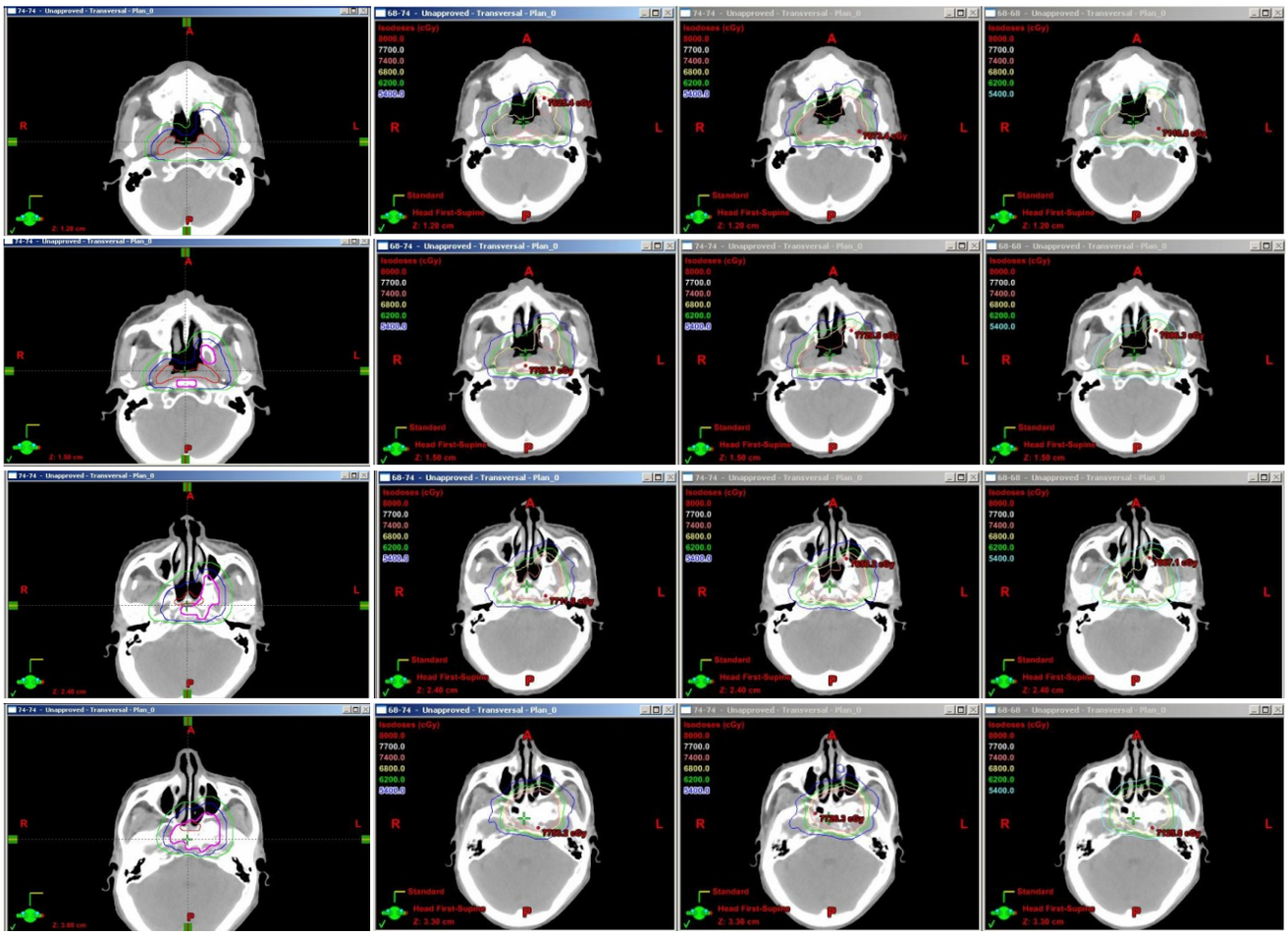
靶区勾画后设计3个治疗计划,第1个:GTV_{np}和GTV_{bone}处方剂量相同,但相对较低,6800 cGy~7000 cGy(GTV_{np}+GTV_{bone}相当于GTV_{nx});第2个:GTV_{np}和GTV_{bone}处方剂量相同,剂量相对较高,7000 cGy~7400 cGy;第3个:GTV_{np}和GTV_{bone}处方剂量不同,GTV_{np} 6800 cGy~7000 cGy、GTV_{bone} 7000 cGy~7400 cGy。PTV_{nd}、CTV_1、CTV_2处方剂量分别为6600 cGy~7200 cGy、6000 cGy~6600 cGy、5200 cGy~5600 cGy,30次~33次。治疗计划设计采用瓦里安Eclipse(8.6版)治疗计划系统,射线质选用瓦里安Trilogy 6 MV X线。剂量算法选用AAA算法(Anisotropie Analytical Algorithm, AAA),计算网格边长为2.5 mm。3个计划的优化约束条件基本一致,颞叶、脑干最大剂量(D_{max})<5500 cGy,脊髓D_{max}<4000 cGy,中耳D_{max} 5500 cGy,50%腮腺受到的剂量(Dose Received by 50% of Volume, D_{50})<3000 cGy,口腔D_{max} 5000 cGy,优化时选取正常组织优化目标。3个计划的归一方式为95% PTV_{nx}、PTV_{np}、PTV_{bone}达到处方剂量,并保证其他靶区95%的靶体积满足处方要求。

1.5 比较指标

靶区比较指标有D_{95},D_{max},最小剂量(D_{min}),平均剂量(D_{mean})和105%剂量占靶区体积的百分比(Target Volume Percentage Receiving at Least of 105% of The Prescribed Dose, $V_{105\%}$)。对脊髓、脑干、视神经评估D_{max},对腮腺评估D_{mean}、D_{50},对颞叶评估D_{mean}、D_5。

1.6 统计学方法

采用SPSS 13.0统计软件进行数据分析,计量资料以均数±标准差表示,3个计划剂量学的比较采用配对t检验,P<0.05为差异有统计学意义。



a b c d

图1 鼻咽癌颅底骨质破坏GTV拆分勾画的靶区及3个计划剂量分布曲线对比

Fig.1 Target volumes of dividing delineation of gross target volume (GTV) in nasopharyngeal carcinoma with skull base destruction and dose distributions of three plans

Note: a: The GTV_{nx} was divided into GTV_{np} and GTV_{bone}. The red line represented GTV_{np}, while the light line represented GTV_{bone}; b: The prescribed doses were respectively 6800 cGy–7000 cGy and 7000 cGy–7400 cGy for GTV_{np} and GTV_{bone}, and the image showed the dose distribution of transverse plane at the corresponding plane; c: The prescribed dose was 7000 cGy–7400 cGy for GTV_{np} and GTV_{bone}, and the image showed the dose distribution of transverse plane at the corresponding plane; d: The prescribed dose was 6800 cGy–7000 cGy for GTV_{np} and GTV_{bone}, and the image showed the dose distribution of transverse plane at the corresponding plane

2 结 果

2.1 靶区体积的变化

GTV_{nx}拆分勾画为GTV_{np}和GTV_{bone}，大体肿瘤体积无变化。

2.2 靶区剂量分布

3个计划95%的处方剂量均能包括各自的靶区，颅底剂量分布不均匀，尤其最上两层靶区，PTV_{bone}的D_{max}与D_{min}平均相差分别为1231 cGy、1824 cGy、1731 cGy，PTV_{bone}的D_{mean}分别为6910 cGy、7550.1 cGy、7541.8 cGy；鼻咽剂量分布均匀，PTV_{np} D_{max}与D_{min}平均相差429.3 cGy、571.4 cGy、926.7 cGy；PTV_{np}的D_{mean}分别为6966 cGy、7557.6 cGy、7222.7 cGy。见图1和表1。

2.3 正常组织剂量分布

3个计划双侧腮腺、口腔剂量与GTV_{np}剂量梯度相关，口腔D_{mean}相差约341.5 cGy~513.4 cGy，双侧腮腺的D_{mean}相差362.3 cGy~491.7 cGy。脑干、脊髓、双侧中耳、左右视神经、颞叶剂量分布无显著差异，见表2。

3 讨 论

IMRT是目前恶性肿瘤放疗中的一项比较成熟的照射技术，尤其在鼻咽癌放疗中疗效确切，提高了患者的生存质量，是鼻咽癌放疗发展的方向[1-4]。

鼻咽癌IMRT最佳的分次剂量、总剂量、靶区勾画决定其治疗效果，其中靶区勾画是关键，鼻咽癌

表1 3个治疗计划靶区剂量参数比较(n=30, $\bar{x}\pm s$, cGy)

Tab.1 Dosimetric comparison of target volumes (n=30, *Mean±SD*, cGy)

Item	Plan 1	Plan 2	Plan 3	t	P value
PTV_{nx}					
D_{95}	6722.3±113.2	7433.1±116.9	7024.5±199.2	1.330	0.356
D_{mean}	6964.9±77.3	7742.0±204.5	7270.8±66.2	-2.370	0.003
D_{min}	6754.0±169.3	6887.1±188.3	6748.2±132.1	1.220	0.136
D_{max}	7288.6±110.2	7976.9±328.1	7752.4±264.4	4.050	0.059
PTV_{np}					
D_{95}	6753.4±87.1	7412.1±147.6	6993.2±99.3	-0.823	0.127
D_{mean}	6951.1±127.1	7782.3±165.1	7155.1±147.1	-2.790	0.015
D_{min}	6697.0±235.6	6717.1±303.0	6697.8±128.0	1.350	0.322
D_{max}	7187.4±131.3	7896.9±361.1	7533.0±202.7	3.519	0.027
PTV_{bone}					
D_{95}	6799.3±95.3	7336.2±168.6	7321.4±152.7	1.750	0.433
D_{mean}	6956.2±121.8	7550.1±99.1	7539.0±117.2	4.101	0.000
D_{min}	6593.0±177.6	6659.7±245.3	6547.8±269.8	-1.330	0.724
D_{max}	7242.8±239.4	7838.1±301.0	7813.2±255.9	2.430	0.317

Note: PTV: Planning target volume; D_{max}: Maximal dose; D_{min}: Minimum dose; D_{mean}: Mean dose

表2 3个治疗计划危及器官剂量参数比较 (n=30, $\bar{x}\pm s$, cGy)

Tab.2 Dosimetric comparison of organs at risk (n=30, *Mean±SD*, cGy)

Organ	Plan 1	Plan 2	Plan 3	t	P value
Left parotid gland					
D_{mean}	3325.3±424.3	3828.9±338.7	3579.6±217.0	-4.550	0.033
D_{50}	3101.1±274.8	3498.3±217.8	3201.6±310.3	-3.460	0.017
Right parotid gland					
D_{mean}	3202.6±259.6	3786.2±310.3	3443.9±243.8	-5.350	0.041
D_{50}	3093.4±389.9	3181.5±332.6	3063.7±256.8	-3.610	0.000
Left middle ear					
D_{mean}	4288.1±258.2	4877.9±312.8	4762.4±215.4	0.899	0.850
Right middle ear					
D_{mean}	4453.6±291.3	4828.0±318.3	4669.9±248.1	1.221	0.361
Oral cavity					
D_{mean}	4021.2±171.2	4531.7±119.8	4231.2±220.7	4.330	0.024
Brainstem					
D_{max}	5459.1±463.2	5876.7±410.3	5718.4±332.1	1.113	0.553
Spinal cord					
D_{max}	3795.1±69.2	3977.2±173.6	3886.9±125.4	-0.916	0.224
Left optic nerve					
D_{max}	5215.8±244.2	5783.3±547.3	5550.3±113.5	-0.791	0.215
Right optic nerve					
D_{max}	5137.7±227.6	5698.8±307.9	5614.6±226.3	1.040	0.216
Left temporal lobe					
D_5	4237.6±152.9	4403.6±227.5	4476.9±204.1	1.084	0.501
D_{mean}	2202.2±71.3	2254.8±177.3	2163.3±88.6	-0.951	0.440
Right temporal lobe					
D_5	4342.8±139.4	4538.1±101.0	4583.2±155.9	1.321	0.271
D_{mean}	1967.1±66.2	2174.6±99.3	2271.2±111.6	-1.884	0.146

IMRT计划中,参考ICRU第50号、62号报告原则,靶区定义基本趋于一致,但是对于鼻咽癌并颅底骨质破坏,由于肿瘤生物学行为、解剖结构的差异,放疗后容易复发,提示鼻咽肿瘤和颅底骨质对剂量要求可能不同,提高颅底放疗剂量,颅底控制率明显提高[5]。Teo等[6-9]回顾性分析了T4期鼻咽癌常规放疗颅底补量,5年生存率比对照组提高12.1%,中位生存期比对照组延长13个月,颅底放疗补量可减少蝶窦、海绵窦的复发,对提高无瘤生存率有一定的益处。Hunt等[10]研究了IMRT技术治疗鼻咽癌对靶区和正常组织结构的剂量分布差异,PTV平均所接受的剂量为处方剂量的110.4%,GTV的实际处方剂量基本上都超过7000 cGy,且单次分割剂量都大于常规分割,等效生物剂量接近甚至高于8000 cGy。Wong等[11]报道了175例鼻咽癌患者的IMRT,D_{mean}和D_{max}分别为7190 cGy(5880 cGy~7790 cGy)、7550 cGy(6140 cGy~8120 cGy)。赵充等[12]研究了419例鼻咽癌患者IMRT疗效,GTV_{nx}的D_{mean}达7342 cGy,平均生物剂量达8335 cGy。中科院肿瘤医院给予T_1、T_2期鼻咽癌病变大体肿瘤体积的剂量分割模式为6996 cGy/3次,T_3、T_4期病变为7400 cGy~7800 cGy/33次~34次[13]。因此,颅底骨质破坏区域较鼻咽可能需要更高的剂量。

基于以上研究及临床实际工作,我们提出了拆分勾画GTV的设想,通过对30例患者的研究,鼻咽癌颅底骨质破坏IMRT GTV拆分勾画在技术上容易实现。GTV_{nx}拆分勾画,总的靶区体积无明显变化,不存在遗漏靶区。GTV_{nx}拆分勾画后,可给予PTV_{np}和PTV_{bone}不同的处方剂量,符合生物学IMRT的要求。通过对每个病人的3个治疗计划比较,95%的处方剂量均能包括各自的靶区,但颅底剂量分布不均匀,尤其最上两层靶区,PTV_{bone}的D_{max}与D_{min}平均相差1231 cGy、1824 cGy、1731 cGy,PTV_{bone}的D_{mean}分别为6910 cGy、7550.1 cGy、7541.8cGy;鼻咽剂量分布均匀,PTV_{np}的D_{max}与D_{min}平均相差429.3 cGy、571.4 cGy、926.7 cGy;PTV_{np}的D_{mean}分别为6966 cGy、7557.6 cGy、7222.7 cGy。颅底剂量分布不均匀而鼻咽剂量分布相对均匀,说明颅底骨质和窦腔对剂量存在一定的影响,如果给予颅底较低的处方剂量,可能导致颅底肿瘤复发[14]。但鼻咽和颅底均给予相对较高的处方剂量(7000 cGy~7400 cGy),鼻咽D_{mean}高达7557.6 cGy,D_{max}达8241.3 cGy,临床上可能导致鼻咽粘膜及周围正常组织坏死,大血管破裂出血,从而危及患者的生命。3个计划显示双侧腮腺、口腔剂量与GTV_{np}剂量梯度相关,口腔D_{mean}相差341.5 cGy~513.4 cGy、双侧腮腺的D_{mean}相差362.3 cGy~491.7 cGy。双侧中耳、左右视神经受照射的体积和剂量无明显差异,主要因为中耳耳蜗位于颅底,接近肿瘤区,高剂量区基本相同。脑干、脊髓、双侧颞叶受照射的体积和剂量并未增加,可能与计划时约束条件较严有关。

鼻咽癌鼻咽肿瘤和颅底骨质破坏区域分别给予不同处方剂量,理论上提高了颅底的剂量,降低了鼻咽肿瘤的剂量,具有明显的剂量优势,鼻咽癌颅底骨质破坏IMRT放疗GTV拆分勾画可行,需在实践中进一步观察和验证。

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