

螺旋断层根治性放疗联合同步化疗治疗局部晚期下咽癌疗效分析

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摘要 目的:评价螺旋断层根治性放疗联合同步化疗和/或抗EGFR单克隆抗体治疗局部晚期下咽癌的疗效及不良反应。**方法:**回顾性分析螺旋断层根治性放疗联合同步化疗和/或抗EGFR单克隆抗体治疗局部晚期下咽癌患者30例。下咽原发病灶及转移淋巴结根治性放疗计划剂量均为70 Gy/33 F、PTV1 60 Gy/33 F、PTV2 54 Gy/33 F。**结果:**47%患者发生了3~4级急性反应,未发生≥3级的晚期反应。30例患者放疗过程中除2例死于原发部位大出血,其余28例患者中位随访时间为15.5(3~41)个月,1和2年的原发病灶控制率、淋巴结控制率、远处转移控制率和生存率分别为63%和35%、84%和61%、89%和81%、8%和50%。全组患者治疗失败11例,原发病灶进展为最常见的失败原因。**结论:**螺旋断层放疗联合同步化疗和/或抗EGFR单克隆抗体治疗局部晚期下咽癌患者能很好地耐受,临床疗效较好。

关键词 螺旋断层放疗 下咽癌 局部晚期 根治性放疗 同步化疗

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Therapeutic effect of radical helical tomotherapy combined with concurrent chemotherapy on locally advanced hypopharynx cancer

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Abstract Objective: This study aimed to evaluate the toxicity and therapeutic effect of radical helical tomotherapy (RHT) combined with concurrent chemotherapy in treating locally advanced hypopharyngeal cancer (HPC). **Methods:** Thirty patients with locally advanced HPC were treated by RHT combined with concurrent chemotherapy. The RHT dosage was as follows: 70 Gy/33 F was used in the pGTVnx+pGTVnd treatment, 60 Gy/33 F in PTV1, and 54 Gy/33 F in PTV2. Early and late radiation side effects were evaluated against the rating scales of the Radiation Therapy Oncology Group of the European Organization for Research and Treatment. **Results:** Early side effects (i. e., grades 3 and 4 acute reactions) occurred in 47% of the 30 patients. Late side effects (i. e., grade 3 and higher) were not observed. Among the 30 patients, 2 died during radiotherapy for locoregional hemorrhage. In the other 28 patients, the median of follow-up time was 15.5 months (range = 3 - 41 months); the one- and two-year local relapse-free, lymph node metastasis-free, distant metastasis-free, and overall survival rates were 63% and 35%, 84% and 61%, 89% and 81%, as well as 58% and 50%, respectively. Treatment failed in 11 cases mainly because of progression of the primary lesion. **Conclusion:** RHT combined with concurrent chemotherapy for locally advanced hypopharyngeal cancer is well tolerated and reproduces satisfactory clinical outcomes.

Keywords: helical tomotherapy, hypopharyngeal neoplasm, locally advanced stage, radical radiotherapy, concurrent chemotherapy

下咽癌临床较少见,放射治疗是无法手术切除的局部晚期下咽癌患者有效的治疗手段。本研究采用国内首台螺旋断层放疗系统根治性治疗局部晚期下咽癌30例,现就疗效和不良反应报告如下。

1 材料与方法

1.1 病例资料

解放军总医院2007年10月至2011年10月采用螺旋断层放疗技术根治性治疗局部晚期下咽癌患者30例,患者的临床和疾病特征见表1。

1.2 方法

1.2.1 放射治疗 全部病例采用螺旋断层放疗根治性外照射。均为初治患者。常规CT模拟定位,下咽原发肿瘤(GTVnx)外扩5mm命名为pGTVnx;转移淋巴结(GTVnd)外扩3mm命名为pGTVnd;CTV1为高危临床靶区包括GTVnx和GTVnd,以及颅底、咽后淋巴结区域、口咽、下咽、部分食道入口及高危颈部淋巴引流区;CTV2为低危颈部淋巴引流区;CTV1、CTV2分别外扩3mm形成PTV1及PTV2,与皮肤保持

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至少 2 mm 距离。pGTVnx 和 pGTVnd 剂量为 70 Gy/33 F, PTV1 60 Gy/33 F, PTV 2 54 Gy/33 F。邻近头颈部危及器官勾画及剂量限制参考本单位常规^[1]。

表 1 30 例患者和疾病特征 例(%)

Table 1 Demographic information and clinicopathologic characteristics of the assessed cohort (30 cases)

Characteristic	No(%)
Age(y)	
≤60	20(67)
>60	10(33)
Gender	
Male	27(90)
Female	3(10)
Smoking status	
Non-smoker	4(13)
Smoker	26(87)
Primary tumor site	
Piriform sinus	17(57)
Posterioricoid area	4(13)
Retropharyngeal area	5(17)
Other*	4(13)
Concurrent therapy	
Cisplatin-based	13(43)
Cetuximab	4(13)
Nimotuzumab	1(3)
Cisplatin-based chemotherapy and cetuximab	7(23)
Cisplatin-based chemotherapy and nimotuzumab	5(17)
Pathological classification	
Well-differentiated squamous cell carcinoma	10(33)
Moderately-differentiated squamous cell carcinoma	16(54)
Poorly-differentiated squamous cell carcinoma	4(13)
T stage	
T ₁	2(7)
T ₂	8(27)
T ₃	7(23)
T ₄	13(43)
N stage	
N ₀	2(7)
N ₁	14(47)
N ₂	14(47)
N ₃	0(0)
M stage	
M ₀	30(100)
UICC 2002 Staging	
III	11(37)
IVa	10(33)
IVb	9(30)

*Primary location could not be discriminated for the huge mass

1.2.2 同步药物治疗 所有病例均同步联合含顺铂的化疗和/或抗表皮生长因子单抗靶向治疗。同步化疗方案为 TP 方案(顺铂+多西他赛),单药顺铂, PF 方案(顺铂+5-氟尿嘧啶),均每 21 天重复。靶向药物为西妥昔单抗和尼妥珠单抗,按说明书给药。

1.2.3 观察指标及随访 治疗期间至少每周对患者进行 1 次检查,据 RTOG/EORTC 标准评价急性反应。治疗结束后 1 个月首次复查,评价近期疗效。之后 1 年内每 3 个月复查,1 年后每 6 个月复查。

1.3 统计分析

采用原发病灶控制率、淋巴结控制率、远处转移控制率和生存率评价患者的局部控制和远期生存情况。采用 Kaplan-Meier 生存曲线进行生存分析,以 $\alpha=0.05$ 为检验水准。

2 结果

2.1 靶区和正常器官的照射剂量

靶区覆盖满足 ICRU 50 号和 62 号报告要求。本组 30 例患者 GTVnx、GTVnd 的平均体积分别为 48.73 (9.61 ~ 167.07) cm³、8.97 (0.83 ~ 37.17) cm³,靶区和正常组织的剂量分布特征见表 2。

表 2 肿瘤靶区及正常组织剂量分布 Gy

Table 2 Dose distribution in target area and normal tissues

Target/OAR	Mean dose	Maximal dose	Minimal dose
pGTVnx	72.37 ± 0.64	76.04 ± 1.64	68.15 ± 2.10
pGTVnd	72.39 ± 0.61	76.13 ± 1.27	68.74 ± 1.40
CTV1	64.82 ± 0.83	76.46 ± 1.68	48.80 ± 7.07
CTV2	58.38 ± 0.48	65.01 ± 6.06	51.82 ± 7.69
Ipsilateral parotid	26.42 ± 3.19	-	-
Contralateral parotid	26.17 ± 4.23*	-	-
Parotid	26.50 ± 4.10	-	-
Spinal cord	23.81 ± 3.18	40.15 ± 2.97	-
Oral cavity	28.63 ± 5.20	-	-

*No statistical significance comparing with ipsilateral parotid ($P>0.05$)

2.2 近期疗效

放疗结束后 1 个月影像学结果显示原发肿瘤完全缓解 11 例,部分缓解 13 例,稳定 4 例,无患者发生疾病进展。30 例患者中 2 例分别于放射治疗 20 次及 26 次时死于肿瘤原发部位大出血。

2.3 远期疗效

剔除放疗过程中死亡的 2 例患者,本组患者完成根治剂量放疗 28 例,中位随访时间 15.5 (3 ~ 41) 个月。1 和 2 年的原发病灶控制率、淋巴结控制率、远处转移控制率和生存率分别为 63% 和 35%、84% 和 61%、89% 和 81%、58% 和 50%。全组患者的生存率曲线见图 1。全组患者治疗失败 11 例,其特征见表 3。

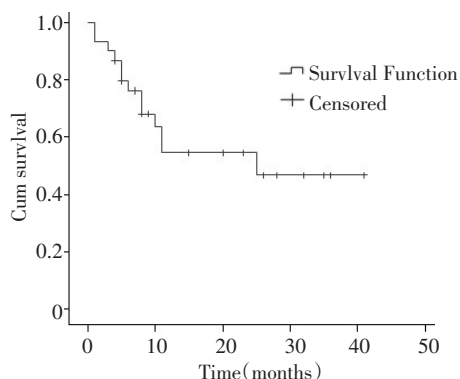


图1 全组局部晚期下咽癌螺旋断层根治性放疗生存情况

Figure 1 Survival rate after radical helical tomotherapy for locally advanced hypopharyngeal cancer of the entire cohort

2.4 不良反应

本组47%患者产生了3~4级急性放射反应。其中3~4级白细胞减少9例;3级咽食管反应3例;3级口腔黏膜反应1例;3级腹泻2例;3级皮肤反应1例。随访超过6个月的患者共24例,未观察到3级及以上的晚期不良反应。

2.5 本研究治疗疗效与同期其他研究结果的比较

本组共研究30例Ⅲ~Ⅳ期下咽癌患者,28例完成螺旋断层根治性调强放疗并同步化疗和/或单克隆抗体靶向治疗。通过中位随访15.5个月,2年局部区域控制率63%,2年总生存率50%。与同期国外其他临床研究的相关参数及结果的比较见表4。

表3 治疗失败患者的疾病特征

Table 3 Disease characteristics of treatment failure cases

Patients	Tumor site	GTV volume(cm ³)	Staging	Treatment	Effect	Location of failure	TTF(m)	Salvage treatment
1	Piriform sinus	9.61	T ₁ N ₁ M ₀ (Ⅲ)	R+T	CR	Nasopharynx metastasis	7	R+C
2	Piriform sinus	113.59	T _{4b} N ₁ M ₀ (Ⅳa)	R+T	SD	Locoregional progression	0	AT
3	Hypopharynx*	153.19	T _{4b} N _{2b} M ₀ (Ⅳb)	R+C	SD	Locoregional progression	4	C
4	Piriform sinus	52.02	T ₃ N ₁ M ₀ (Ⅲ)	R+T	PR	In-field recurrence	6	C+T
5	Posterioricoid area	56.72	T _{4b} N ₁ M ₀ (Ⅳa)	R+C+T	PR	Locoregional progression	0	C
6	Posterioricoid area	145.23	T _{4b} N _{2b} M ₀ (Ⅳb)	R+C	SD	Oral floor metastasis, gastric cancer	6	AT
7	Retropharyngeal area	16.75	T ₂ N ₁ M ₀ (Ⅲ)	R+C+T	PR	Locoregional progression	0	C
8	Piriform sinus	134.32	T _{4b} N _{2b} M ₀ (Ⅳb)	R+C	SD	Locoregional progression	0	AT
9	Piriform sinus	57.52	T ₃ N ₁ M ₀ (Ⅲ)	R+T	CR	In-field recurrence	8	C+S
10	Retropharyngeal area	26.14	T ₂ N ₁ M ₀ (Ⅲ)	R+C+T	SD	Locoregional progression	0	AT
11	Retropharyngeal area	141.08	T _{4b} N _{2b} M ₀ (Ⅳb)	R+C+T	PR	Lymph node persistence	0	S

Abbreviations: R: radiation therapy, C: chemotherapy, T: anti-EGFR Mab target treatment, AT: alleviative treatment, S: surgery; * primary location could not be discriminated for the huge mass

表4 本研究下咽癌调强放疗与其他头颈部肿瘤放疗研究结果的比较

Table 4 Intensity modulation radiation therapy in hypopharyngeal cancer: comparison with other radiotherapy findings on head and neck neoplasms

Study	Time(y)	No. of patients (Hypopharynx/All)	Percentage of III-IV stage (%)	Treatment	Median follow-up time(m)	GTV dose	Local relapse-free survival (%)	Overall survival(%)
Miah et al ^[2]	2012	12/29	100	IC+CCRT	51.0	63 Gy/28 F	64.2(2 y)	NA
		15/31	100	IC+CCRT	36.2	67.2 Gy/28 F	78.4(2 y)	NA
Loimu et al ^[3]	2011	31/83	91	CCRT	51.0	70 Gy/35 F	84(2 y)	82(2 y)
Daly et al ^[4]	2011	23/42	98	CCRT	30.0	66 Gy/30 F	70(3 y)hypo	45(3 y)hypo
Studer et al ^[5]	2010	65/117	64	CCRT	21.0	66-72.6 Gy/30-33 F	77(2 y)	83(2 y)
Liu et al ^[6]	2010	27 hypo	81	CCRT	53.0	72.6-76.8 Gy/35-37 F	63.3(5 y)	34.8(5 y)
Lee et al ^[7]	2007	11/33	100	CCRT	26.0	70 Gy/33 F	73(2 y)hypo	63(2 y)
our study	2012	28 hypo	100	CCRT/RT+Mab	15.5	70 Gy/33 F	35/61*(2 y)	50(2 y)

Abbreviations: IC: induction chemotherapy, CCRT: concurrent chemoradiotherapy, CT: chemotherapy, RT: radiotherapy, hypo: hypopharynx, NA: not applicable, Mab: anti-EGFR monoclonal antibody, *Local control 35%, regional control 61%

3 讨论

下咽癌是临床较少见的头颈部肿瘤,发病率约占所有头颈部恶性肿瘤的0.8%~1.5%,放疗是局部晚期下咽癌的主要治疗手段,Krstevska等^[8]认为采用

调强放疗、同步化疗、序贯化疗和靶向治疗是局部晚期下咽癌明确预后因素。螺旋断层放疗是一种新兴的调强放疗技术,Wiezorek等^[9]研究后发现螺旋断层放疗的总体治疗计划质量优于静态调强、动态调

强及旋转调强。在肺癌、前列腺癌等肿瘤的治疗中也观察到螺旋断层放疗较常规调强放疗靶区剂量分布更适形、正常器官不良反应更轻微^[10-13]。本单位自2007年引进螺旋断层放疗以来已治疗头颈部肿瘤300余例,在鼻咽癌病例分析中也观察到类似剂量分布优势^[1,14]。

本研究采用螺旋断层放疗根治性治疗局部晚期下咽癌患者的靶区剂量分布和不良反应分析显示,靶区内剂量分布均匀,靶区形状和剂量适形度好,正常器官受照剂量较低。与Studer等^[15]对29例下咽癌常规IMRT治疗的剂量学指标进行比较,脊髓的平均剂量和最大剂量分别为23.81 Gy vs. 26 Gy和40.15 Gy vs. 44.4 Gy,3级咽食管不良反应发生率为10% vs. 21%。在原发肿瘤体积较大(48.73 cm³ vs. 36.2 cm³)、T₃₋₄分级患者较多(67% vs. 45%)的基线背景下,证实了在正常器官受量和急性不良反应方面螺旋断层放疗均较常规IMRT有明显的优势。在其他头颈部肿瘤也发现类似情况^[4,7]。

本组28例患者均接受了根治性螺旋断层调强放疗同步化疗和/或抗EGFR单抗靶向治疗,2年各项生存指标均低于表4中列举的近期头颈部肿瘤放疗联合同步化疗的临床研究结果。分析患者肿瘤类别构成情况后,除Liu等^[6]研究的27例单纯下咽癌患者以外均为包含下咽癌在内的头颈部肿瘤患者,下咽癌所占比例为33%~55%,Ⅲ~Ⅳ期患者所占比例为64%~100%。下咽癌的预后是所有头颈部肿瘤中最差的,尤以Ⅲ~Ⅳ期患者预后更差,因此肿瘤类别构成差异可能是造成疗效差异的主要原因。此外,复习近期国外文献报道后发现,放疗后考虑原发病灶残留的患者大多进行挽救性手术^[16]。而本研究中患者临床和影像学提示原发病灶残留或复发后55%采用化疗,36%采用单纯姑息治疗,仅18%采用挽救性手术。行化疗和姑息治疗患者的肿瘤进展至死亡的平均时间为2.3个月,显示非手术挽救性治疗的效果较差。未能在更多的失败患者中及时采用挽救性手术可能也是生存率较低的原因之一,提示下咽癌应尽量遵循综合治疗模式。由于发病率的限制,目前尚缺少下咽癌,尤其是局部晚期下咽癌单病种的大宗病例临床研究,故对其临床疗效评估和预后分析的研究资料很匮乏,有待继续积累病例进行深入研究。

通过本研究发现,螺旋断层放疗联合同步化疗和/或抗EGFR单抗根治性治疗局部晚期下咽癌,大多数患者均能很好耐受,2年总生存率为50%,治疗失败后及时采取包括外科治疗在内的综合治疗模式有助于改善患者的长期生存质量。

参考文献

1 杜 镭,马 林,周桂霞,等.螺旋断层放疗45例鼻咽癌近期临床观

- 察[J].军医进修学院学报,2009,30(3):311-314.
- 2 Miah AB, Bhide SA, Guerrero-Urbano MT, et al. Dose-escalated intensity-modulated radiotherapy is feasible and may improve locoregional control and laryngeal preservation in laryngo-hypopharyngeal cancers[J]. *Int J Radiat Oncol Biol Phys*, 2012, 82(2):539-547.
 - 3 Loimu V, Collan J, Vaalavirta L, et al. Patterns of relapse following definitive treatment of head and neck squamous cell cancer by intensity modulated radiotherapy and weekly cisplatin[J]. *Radiother Oncol*, 2011, 98(1):34-37.
 - 4 Daly ME, Le QT, Jain AK, et al. Intensity-modulated radiotherapy for locally advanced cancers of the larynx and hypopharynx[J]. *Head Neck*, 2011, 33(1):103-111.
 - 5 Studer G, Peponi E, Kloeck S, et al. Surviving hypopharynx-larynx carcinoma in the era of IMRT[J]. *Int J Radiat Oncol Biol Phys*, 2010, 77(5):1391-1396.
 - 6 Liu WS, Hsin CH, Chou YH, et al. Long-term results of intensity-modulated radiotherapy concomitant with chemotherapy for hypopharyngeal carcinoma aimed at laryngeal preservation[J]. *BMC Cancer*, 2010, 10:102-112.
 - 7 Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers[J]. *Int J Radiat Oncol Biol Phys*, 2007, 69(2):459-468.
 - 8 Krstevska V, Stojkovski I, Zafirova-Ivanovska B, et al. Prognostic factors in patients with advanced hypopharyngeal squamous cell carcinoma treated with concurrent chemoradiotherapy[J]. *J BUON*, 2012, 17(2):327-336.
 - 9 Wiezorek T, Brachwitz T, Georg D, et al. Rotational IMRT techniques compared to fixed gantry IMRT and tomotherapy: multi-institutional planning study for head-and-neck cases[J]. *Radiat Oncol*, 2011, 6:20-30.
 - 10 Kron T, Grigorov G, Yu E, et al. Planning evaluation of radiotherapy for complex lung cancer cases using helical tomotherapy [J]. *Phys Med Biol*, 2004, 49(16):3675-3690.
 - 11 Aoyama H, Wesely DC, Mackie TR, et al. Integral radiation dose to normal structures with conformal external beam radiation [J]. *Int J Radiat Oncol Biol Phys*, 2006, 64(3):962-967.
 - 12 Madsen BL, Hsi RA, Pham HT, et al. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results[J]. *Int J Radiat Oncol Biol Phys*, 2007, 67(4):1099-1105.
 - 13 Murthy V, Master Z, Gupta T, et al. Helical tomotherapy for head and neck squamous cell carcinoma: dosimetric comparison with linear accelerator-based step-and-shoot IMRT[J]. *J Cancer Res Ther*, 2010, 6(2):194-198.
 - 14 崔 迪,戴相昆,马 林,等.鼻咽癌螺旋断层放疗与常规加速器调强放疗的剂量学比较[J].*中华放射肿瘤学杂志*,2008,17(3):169-173.
 - 15 Studer G, Lütolf UM, Davis JB, et al. IMRT in hypopharyngeal tumors[J]. *Strahlenther Onkol*, 2006, 182(6):331-335.
 - 16 Chen AM, Jennelle RL, Sreeraman R, et al. Initial clinical experience with helical tomotherapy for head and neck cancer[J]. *Head Neck*, 2009, 31(12):1571-1578.

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