

喉癌术后放疗患者复发影响因素及与不同放疗剂量的关系

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【摘要】目的:探讨喉癌术后放疗患者复发的影响因素、各术式下不同放疗剂量与复发的关系及对生存率的影响。**方法:**回顾性分析石家庄市人民医院收治的134例喉癌术后放疗患者临床资料,先对其进行单因素分析,后采用多因素Logistic回归分析术后复发的危险因素。同时探讨不同放疗剂量与各术式的关系,利用Kaplan-meler法、Log rank检验对喉癌患者2年生存率进行分析。**结果:**134例患者中,30例术后复发者设为复发组,其余104例为未复发组。经多因素Logistic回归分析可知,临床分期(III~IV期)、T分期(T3~T4期)、N分期(N1~N3)、放疗剂量(低剂量)、甲状腺软骨受侵(是)、手术切缘(阳性)为喉癌术后复发的独立危险因素($OR>1, P<0.05$)。支撑喉镜下激光声带肿物切除/喉部分切除术、喉全切除术后接受高剂量放疗患者复发率分别低于接受低剂量放疗患者,总复发率相比具有统计学差异($P<0.05$)。截至2023年6月,134例喉癌术后放疗患者中,中位随访时间为14.23个月(1~24个月),其中低剂量组死亡8例,高剂量组死亡2例,中位生存时间估计值分别为19.13、22.13月,患者的生存曲线具有差异性(Log rank $P=0.20$),高剂量组优于低剂量组。**结论:**喉癌术后联合放疗的整体疗效较好,但临床分期、T分期、N分期、低剂量放疗、肿瘤侵及甲状腺软骨、手术切缘阳性、术后至放疗结束时间>11周等因素均可影响疾病复发,临幊上应当结合患者病情适当调高放疗剂量,以改善预后,延长生存期限。

【关键词】喉癌;术后放射治疗;放疗剂量;复发;生存曲线;影响因素

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Factors affecting laryngeal cancer relapse after postoperative radiotherapy and relationship between relapse with radiotherapy dose

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Abstract: Objective To explore the factors associated with laryngeal cancer relapse after postoperative radiotherapy, discuss the relationship between radiotherapy dose under various surgical procedures and relapse, and analyze their effects on survival rate. Methods The clinical data of 134 patients with laryngeal cancer treated with postoperative radiotherapy in Shijiazhuang People's Hospital were retrospectively analyzed. The risk factors of postoperative relapse were analyzed with univariate analysis, followed by multivariate Logistic regression analysis. The relationships between radiotherapy doses under various surgical procedures and the relapse were discussed. Kaplan-meler method and Log rank test were used to analyze the 2-year survival rate of laryngeal cancer patients. Results Thirty out of the 134 patients relapsed after treatment, and there was no recurrence in the remaining 104 patients. Multivariate Logistic regression analysis identified clinical stage (III - IV), T stage (T3-T4), N stage (N1-N3), radiotherapy dose (low-dose), thyroid cartilage invasion (yes) and surgical margin (positive) as independent risk factors for postoperative laryngeal cancer relapse ($OR>1, P<0.05$). The relapse rates of patients receiving high-dose radiotherapy after laser vocal cord mass resection/partial laryngectomy and total laryngectomy under self-retaining laryngoscope were lower than those of patients receiving low-dose radiotherapy, with a statistically significant difference in overall relapse rate ($P<0.05$). As of June 2023, the median follow-up time of 134 patients undergoing postoperative radiotherapy for laryngeal cancer was 14.23 months (1-24 months), and there were 8 deaths in low-dose group

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and 2 deaths in high-dose group. The estimated median survival times in low- and high-dose groups were 19.13 months and 22.13 months. The survival curves in two groups were different (Log rank $P=0.20$), with high-dose group outperforming low-dose group. Conclusion The overall therapeutic effect of surgery combined with postoperative radiotherapy for laryngeal cancer is favorable. However, clinical stage, T stage, N stage, low-dose radiotherapy, tumor invasion into thyroid cartilage, positive surgical margin, and >11 weeks from postoperation to radiotherapy completion were risk factors for disease relapse. In clinical practice, the radiotherapy dose should be appropriately increased based on the patient's condition to improve prognosis and extend survival duration.

Keywords: laryngeal cancer; postoperative radiotherapy; radiotherapy dose; relapse; survival curve; influencing factor

前言

喉癌是源于喉黏膜上皮组织的恶性肿瘤,在全身恶性肿瘤疾病中的占比约为2.1%,在头颈部恶性肿瘤疾病中的占比为13.9%^[1-2]。临幊上以手术治疗为主,治疗该疾病的宗旨为尽可能切除病灶的前提下,重建与恢复患者发音、呼吸、吞咽功能^[3-4]。但部分患者手术时已经存在转移,致使手术治疗不彻底,术后容易出现转移或者复发,而复发正是手术治疗失败的主要原因,可直接影响喉癌患者生存率^[5-6]。长期以来,喉癌放疗采用双侧对穿野为主的常规二维照射技术,其优点在于可杀灭或者抑制较低分化肿瘤,达到降低癌细胞在术后向远处转移、扩散的风险,但由于喉解剖部位的特殊性,加之放疗的局限性,即使喉癌患者接受手术+放疗干预,术后复发率仍然居高不下,考虑与放疗干预时不同的照射剂量相关^[7-8]。本研究旨在全面了解喉癌术后复发的危险因素,并着重探讨不同术式、不同放疗剂量与复发的关系,以改进治疗策略,降低复发率,延长患者生存期限。

1 资料与方法

1.1 研究对象

回顾性分析2017年6月至2021年6月石家庄市人民医院收治的134例喉癌术后放疗患者的临床资料。患者中男89例,女45例,年龄40~80岁,平均(56.20±7.85)岁。纳入标准:①患者符合《耳鼻咽喉头颈外科学》^[9]中对该病的诊断标准,且经术后病理学检查确诊,符合2002年美国癌症联合会TNM分期标准^[10];②患者符合手术适应证,手术操作依据《临床技术操作规范耳鼻咽喉-头颈外科分册》^[11]实施;③患者首次接受治疗,术前未接受放疗或者化疗;④患者随访依从性高,随访时间至少2年。排除标准:①患者治疗前已知有远处转移、非鳞癌恶性肿瘤;②患者头颈部存在严重外伤史;③患者存在先天性咽喉部畸形或者发育不良;④患者身体状况差,不能耐受

放疗;⑤患者未行手术,直接进行放疗。134例患者,2年内复发30例,占比为22.39%,设为复发组,其余104例患者局部控制良好设为未复发组。该研究经过石家庄市人民医院伦理委员会批准,伦理批准号:2022-1064。

复发诊断^[9]:术后采用增强磁共振(MRI)或者多层螺旋CT(MSCT)增强、喉镜等检查,发现肿瘤出现区域外淋巴结或者瘤床外转移,代表远处转移;若出现颈部淋巴结或者瘤床转移,表示局部复发;若未发现淋巴结转移及局部复发,代表局部控制。

1.2 方法

所有患者治疗前均经喉镜、颈部MRI或者MSCT增强检查评估患者病情,选择合适的手术方式,包括支撑喉镜下激光声带肿物切除术/喉部分切除术、喉全切除术。

通过病历、门诊复查资料等,收集患者临床资料,包括性别、年龄、临床分期、病理分型、手术切缘、病理分级、TN分期、甲状腺软骨受侵情况、术后至放疗结束时间、放疗治疗剂量。

1.3 统计学方法

采用SPSS24.0软件处理数据,计数资料用n(%)表示,行 χ^2 检验,等级有序分类变量采用秩和检验。采用二元Logistics回归分析临床分期、T分期、N分期、放疗剂量(低剂量:50~64 Gy,高剂量:66~70 Gy)、甲状腺软骨受侵、手术切缘与喉癌术后复发的关系。生存情况组间比较利用Log-rank检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 喉癌术后复发的单因素分析

两组患者的年龄、性别、病理分型、手术方式、病理分级相比无统计学差异($P>0.05$)。经单因素分析,临床分期、T分期、N分期、放疗剂量、甲状腺软骨受侵、手术切缘、术后至放疗结束时间与喉癌术后复发相关。见表1。

表1 喉癌术后复发的单因素分析[例(%)]

Table 1 Univariate analysis of postoperative relapse of laryngeal cancer [case (%)]

相关因素	n	复发组(n=30)	未复发组(n=104)	Z/χ ² 值	P值
年龄/岁				0.216	0.642
<60	72	15(50.00)	57(54.81)		
≥60	62	15(50.00)	47(45.18)		
性别				0.165	0.685
男	89	19(63.33)	70(67.31)		
女	45	11(36.67)	34(32.69)		
临床分期				5.690	0.017
I~II期	91	15(50.00)	76(73.08)		
III~IV期	43	15(50.00)	28(26.92)		
病理分型				1.611	0.447
声门上	48	9(30.00)	39(37.50)		
声门	68	15(50.00)	53(50.96)		
声门下	18	6(20.00)	12(11.54)		
T分期				4.684	0.030
T1~T2	85	14(46.67)	71(68.27)		
T3~T4	49	16(53.33)	33(31.73)		
N分期				5.193	0.023
N0期	82	13(43.33)	69(66.65)		
N1~N3期	52	17(56.67)	35(33.65)		
病理分期				0.703	0.704
高分化	36	7(23.33)	29(27.88)		
中分化	41	11(36.67)	30(28.85)		
低分化	57	12(40.00)	45(43.27)		
放疗剂量				11.886	0.001
低剂量	53	20(66.67)	33(31.73)		
高剂量	81	10(33.33)	71(68.27)		
甲状腺软骨受侵				4.176	0.041
是	27	10(33.33)	17(16.35)		
否	107	20(66.67)	87(83.65)		
手术切缘				4.701	0.030
阳性	41	14(46.67)	27(25.96)		
阴性	93	16(53.33)	77(74.04)		
术后至放疗结束时间				15.077	0.001
≤11周	76	12(40.00)	64(61.54)		
>11周	58	18(60.00)	40(38.46)		
手术方式				1.512	0.219
喉全切除术	54	15(50.00)	39(37.50)		
喉部分切除术	80	15(50.00)	65(62.50)		

2.2 喉癌术后复发的Logistic回归分析

经多因素Logistic回归分析可知,临床分期(III~IV期)、T分期(T3~T4期)、N分期(N1~N3)、放疗剂量(低剂量)、甲状腺软骨受侵(是)、手术切缘(阳性)、术后至放疗结束时间>11周为喉癌术后复发的独立危险因素($P<0.05$),表2。

2.3 不同术式下不同放射剂量复发率

支撑喉镜下激光声带肿物切除/喉部分切除术、喉全切除术后接受高剂量放疗患者复发率分别低于接受低剂量放疗患者,总复发率相比具有统计学差异($P<0.05$)。见表3。

表2 喉癌术后复发的 Logistic 回归分析
Table 2 Logistic regression analysis of postoperative relapse of laryngeal cancer

因素	回归系数	标准误	χ^2 值	P值	OR	95% CI
常量	-1.624	0.292	30.827	0.000	0.197	-
临床分期(参照:I-II期)						
III~IV期	0.999	0.427	5.472	0.019	2.714	(1.176, 5.266)
T分期(参照:T1~T2)						
T3~T4	0.900	0.422	4.540	0.033	2.459	(1.075, 5.626)
N分期(参照:N0)						
N1~N3	0.947	0.423	5.016	0.025	5.578	(1.126, 5.905)
放疗剂量(参照:高剂量)						
低剂量	1.043	0.435	10.734	0.001	2.837	(1.208, 6.662)
甲状腺软骨受侵(参照:否)						
是	0.940	0.469	4.007	0.045	2.559	(1.020, 6.421)
手术切缘(参照:阴性)						
阳性	0.914	0.429	4.546	0.033	2.495	(1.077, 5.784)
术后至放疗结束时间(参照:<=11周)						
>11周	1.020	0.041	5.011	0.031	5.332	(1.011, 6.101)

表3 不同术式下不同放射剂量复发率[例(%)]

Table 3 Relapse rates of different radiotherapy doses under various surgical procedures [case (%)]

放疗剂量	不同术式		合计
	喉全切除术	喉部分切除术	
低剂量(n=53)	10(18.87)	10(18.87)	20(37.74)
高剂量(n=81)	6(7.41)	4(4.94)	10(12.35)
χ^2 值			11.886
P值			0.001

2.4 喉癌术后放疗不同剂量生存时间比较

截至2023年6月,134例喉癌术后放疗患者中,中位随访时间为14.23个月(1~24个月),其中低剂量组死亡8例,高剂量组死亡2例,中位生存时间估计值分别为19.13、22.13月,患者的生存曲线具有差异性(Log rank P=0.20),高剂量放疗优于低剂量放疗。

3 讨论

喉癌属于临床中常见的头颈部恶性肿瘤,仅次于鼻咽癌,患者主要表现为声音嘶哑、吞咽困难、喉鸣、呼吸困难等,对其生命质量有着不同程度影响^[12]。喉癌的发病原因尚未明确,其发生、发展可能与多种因素长期协同作用于敏感的个体有关^[13]。由于喉癌患者多为鳞癌,对放射线的敏感度较高,故而术后常联合放疗干预,以提高治疗效果^[14-15]。即便如此,喉癌术后复发的情况也较为常见。相关研究显示有10%~50%的患者治疗后复发,预后差,这也成为

临床工作者及研究者重点关注的问题^[16-17]。本研究得出喉癌术后放疗患者的复发率为22.39%,与张亚亚等^[18]报道的复发率相似,但略低于其他研究中喉癌术后的复发率^[19],原因可能与本研究中纳入的患者均接受手术联合放疗干预有关,这也说明综合疗法有利于降低喉癌患者术后复发率。进一步通过多因素Logistic回归分析可知,临床分期、T分期、N分期、放疗剂量、甲状腺软骨受侵、手术切缘、术后至放疗结束时间为喉癌术后复发的独立危险因素,分析原因:①临床分期晚、病变范围广的患者,即使术后通过放疗干预复发的几率仍然较高,一般而言声门、声门下型喉癌5 mm切缘相对安全,也可在此基础上扩大安全切缘利于彻底清除病灶,减少术后复发,但肿瘤黏膜下浸润程度深、有转移,加之肿瘤部位影响,放疗照射体积、剂量因人而异,也是部分患者预后效果不佳的主要因素^[20]。②手术切缘阳性,提示术后残留有肿瘤细胞,则发生颈部淋巴结转移及复发的风险明显增加,因此术前通过影像学检查确诊病灶范围,尽可能做到切缘阴性,对降低术后复发率有着十分重要的作用^[21-22]。③本研究中发现喉癌术后患者在短期内接受放疗能够获得较高的生存效益,提示术后坚持放疗有利于提高局部控制性,保持高度的耐受性与依从性,进而利于生存率的提升。

放疗可通过高能量的射线将肿瘤细胞加以破坏,使其生长受到阻碍,但放疗也会破坏正常细胞,使之受到刺激而出现各种并发症,并随着放射剂量的增大而受损严重,相对而言低剂量放疗对机体的

损伤小,但一味地追求低剂量,不能达到治疗目的,疾病复发率高^[23-24]。本研究对不同术式后不同剂量放疗患者进行对比,结果显示:喉癌术后接受高剂量放疗患者的复发率低于接受低剂量放疗患者,总复发率相比具有统计学差异,提示患者身体耐受好、喉全切术后患者,可控制放疗剂量在66~70 Gy,有利于降低复发率。但本研究并未得出高低放疗剂量在各术式患者中有差异性,考虑与纳入样本量较少有关。本研究进一步对高低剂量放疗患者2年内生存率进行对比,结果显示:患者的生存曲线不同(Log rank P=0.20),高剂量组优于低剂量组,喉全切术的复发率整体较高,原因与该类患者多有淋巴结转移情况,且并发症多,提高放疗剂量虽然能够杀灭癌细胞,促进生存率提高,但并不能无限制增大,放射剂量增大可相应增加并发症发生率,故而不能单纯通过增加照射剂量提高生存率,还应当结合影响因素,选择合适患者的综合治疗方案,以保障生活质量^[25]。

综上所述,喉癌术后联合放疗干预的整体疗效较好,但临床分期、T分期、N分期高、低剂量放疗、肿瘤侵及甲状腺软骨、手术切缘阳性、术后至放疗结束时间>11周因素均可影响疾病复发,临幊上应当结合患者病情适当调高放疗剂量,以改善预后,提高生存率。

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