



· 论 著 ·

甲状腺未分化癌的预后因素分析及治疗决策

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[摘要] 背景与目的: 甲状腺未分化癌(anaplastic thyroid carcinoma, ATC)是一种临床罕见但侵袭性高的恶性肿瘤, 预后极差, 尚无标准的治疗方案。分析ATC的预后影响因素, 探讨其合理的治疗方法。方法: 回顾性分析2008年5月—2014年5月在甘肃省肿瘤医院接受诊治的37例ATC患者的社会人口学和临床病理学资料, 采用Kaplan-Meier法计算生存率, 采用log-rank检验进行比较, 通过单因素和多因素COX模型分析筛选预后因素。结果: 37例ATC患者中, 男性12例, 女性25例, 年龄42~82岁, 中位年龄为64岁; ATC占有甲状腺癌的5.3% (37/698), 29.7% (13/37)的患者合并甲状腺肿, 居住在城市的患者不足20% (7/37), 超过50% (19/37)的患者生活在地方性甲状腺肿高发地区; 全组患者平均生存期为11.5个月, 中位生存期为5.9个月, 6个月、1年和2年的生存率分别为48.6%、21.6%和13.5%。单因素分析显示, 首诊年龄、合并甲状腺肿、远处转移、手术、综合治疗、术后放疗和白细胞计数是影响ATC患者生存的预后因素。多因素分析显示, 首诊年龄 ≤ 50 岁(HR=0.21, 95% CI: 0.06~0.77, $P=0.019$)、手术(HR=0.15, 95% CI: 0.04~0.59, $P=0.007$)和综合治疗(HR=0.31, 95% CI: 0.11~0.85, $P=0.023$)是预后较好的独立预测因素。对于手术患者, R2切除(HR=7.98, 95% CI: 1.38~46.21, $P=0.020$)和远处转移(HR=6.26, 95% CI: 1.65~23.83, $P=0.007$)是预后不良的独立风险因素, 术后放疗(HR=0.18, 95% CI: 0.04~0.83, $P=0.028$)可明显改善预后。结论: 年龄、手术切除方式、手术+术后放疗是影响ATC生存的独立预测因素, 根据患者的个体情况进行以手术+术后放疗为主的综合治疗可能改善其生存。

[关键词] 甲状腺未分化癌; 预后; 因素分析; 生存; 治疗方法

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[Abstract] **Background and purpose:** Anaplastic thyroid carcinoma (ATC) is a rare but highly aggressive malignancy with poor prognosis, and there is no standardized therapeutic regimen. The aim of the study was to analyze the prognostic factors influencing survival of the patients with ATC, and to explore the reasonable treatment methods. **Methods:** The sociodemographic and clinicopathologic characteristics of 37 ATC patients at the Department of Head and Neck Surgery in Gansu Provincial Cancer Hospital between May 2008 and May 2014 were analyzed retrospectively. The Kaplan-Meier method and log-rank test were used to determine and compare the survival. Potential prognostic factors were identified by univariate and multivariate Cox regression analyses. **Results:** Females were more affected. Twenty-five cases occurred in women, and 12 in males. The age range was 42-82 years, and the median age was 64. ATC accounted for 5.3% of all thyroid cancers in this study, and goiter was present in 29.7% of patients with ATC. Less than 20% of the ATC patients lived in urban areas, and more than half lived in endemic goiter areas. Mean survival time was 11.5 months. Median survival time was 5.9 months, and half-, 1- and 2-year overall survival rates were 48.6%, 21.6% and 13.5%, respectively. Univariate analysis showed that age, goiter, distant metastasis, surgery, comprehensive therapy and

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postoperative radiotherapy were independent prognostic factors of survival in all ATC patients. Multivariate analysis showed that age no more than 50 years (HR=0.21, 95% CI: 0.06-0.77, $P=0.019$), surgery (HR=0.15, 95% CI: 0.04-0.59, $P=0.007$) and comprehensive therapy (HR=0.31, 95% CI: 0.11-0.85, $P=0.023$) were independent protective factors associated with the survival of ATC patients. With regard to operated patients, macroscopic residual tumor (HR=7.98, 95% CI: 1.38-46.21, $P=0.020$) and distant metastasis (HR=6.26, 95% CI: 1.65-23.83, $P=0.007$) were independent risk factors of survival. Postoperative radiotherapy (HR=0.18, 95% CI: 0.04-0.83, $P=0.028$) was a protective factor. **Conclusion:** Age, type of surgery resection and postoperative radiotherapy influence prognosis of ATC independently. The patients with ATC may have a better prognosis by receiving multidisciplinary comprehensive therapy combining surgery and postoperative radiotherapy with or without chemotherapy based on each individual circumstance.

[Key words] Anaplastic thyroid cancer; Prognosis; Factor analysis; Survival; Treat methods

甲状腺未分化癌(anaplastic thyroid carcinoma, ATC)占甲状腺恶性肿瘤的1%~2%^[1],病死率却高达14%~39%^[2]。ATC侵袭性强、恶性程度高,目前尚无标准的治疗方法。有研究^[3]发现,年龄、手术、远处转移、白细胞计数和放疗剂量等因素影响ATC的预后,但仍存在争议。本文回顾性分析37例ATC患者的临床及随访资料,探讨其预后影响因素和各种治疗方法的效果,旨在为ATC的治疗决策提供依据。

1 资料和方法

1.1 一般资料

研究对象为2008年5月—2014年5月甘肃省肿瘤医院头颈外科收治的ATC患者,所有病例均纳入研究。病例资料包括社会人口学信息、临床病理学特征、治疗及随访情况。肿瘤TNM分期参照2010年第7版美国癌症联合会(American Joint Committee on Cancer, AJCC)分期标准,患者体力状况评估采用KPS评分法。实验室检查指标为白细胞计数、血小板计数和C反应蛋白,病理学描述包括细胞类型及合并其他甲状腺疾病。免疫组织化学染色检测指标包括细胞角蛋白5/6(cytokeratin 5/6, CK5/6)、波形蛋白(vimentin)、甲状腺球蛋白(thyroglobulin, Tg)、降钙素(calcitonin, CT)、甲状腺转录因子-1(thyroid transcription factor-1, TTF-1)、p53表达及Ki-67标记指数。随访方式为门诊和电话随访,随访截止时间至少为确诊后2年。

1.2 治疗方法

依据手术切除范围分为:①单纯甲状腺手术,包括甲状腺部分切除、腺叶切除、甲状腺

次全切和全切术;②同时切除周围部分组织的局部广泛切除术;③甲状腺癌联合根治术。依据肿瘤切除方式分为R0切除(完全切除)、R1切除(镜下残留)和R2切除(肉眼残留)。放疗包括三维适形放疗和调强放疗,每次剂量为1.7~2.1 Gy,每周5次,治疗6~7周。化疗方案包括多西他赛+铂类药物、表柔比星+铂类药物和替吉奥单药,化疗2~4个周期。开放性活检术、单纯气管切开术归于未手术治疗,接受2种或2种以上的治疗方法视为综合治疗。

1.3 随访

采用门诊复诊和电话随访的方式对所有患者进行生存状态的随访。

1.4 统计学处理

应用SPSS 22.0软件进行统计分析,单因素分析采用Kaplan-Meier法和log-rank检验,生存期自确诊日开始计算至患者死亡或末次随访,采用COX风险模型多因素分析确定影响ATC预后的独立危险因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 社会人口学特征

698例甲状腺恶性肿瘤患者中ATC共37例,约占5.3%,男女比为1.0:2.1。年龄42~82岁,中位年龄为64岁,平均年龄为(62.3±8.5)岁。约80%的患者居住在经济落后的农村地区,50%以上的患者生活在地方性甲状腺肿高发地区,且患者数与碘缺乏程度相关(表1,图1)。13例有甲状腺肿病史,最长者40年,最短者1个月,平均病程为8.5年。

2.2 临床病理学特征(表2)

所有ATC患者均有颈部肿块,30例伴气短或

表 1 37例ATC患者的社会人口学特征

Tab. 1 The sociodemographic characteristics of 37 ATC patients

		[n (%)]	
Characteristic	Number of patients	Characteristic	Number of patients
Gender		Residential areas	
Male	12 (32.4)	Rural	30 (81.1)
Female	25 (67.6)	Urban	7 (18.9)
Age/year		Goiter	
≤50	6 (16.2)	Yes	13 (35.1)
50-70	23 (62.2)	No	24 (64.9)
>70	8 (21.6)	Degree of iodine deficiency	
Ethnicity		Severe	11 (29.7)
Han	28 (75.7)	Moderate	6 (16.2)
Minorities	9 (24.3)	Mild	2 (5.4)
Career		No	18 (48.7)
Retiree	5 (13.5)	Family history of thyroid cancer	
Staff	2 (5.4)	Yes	5 (13.5)
Peasant	29 (78.4)	No	32 (86.5)
Herders	1 (2.7)		

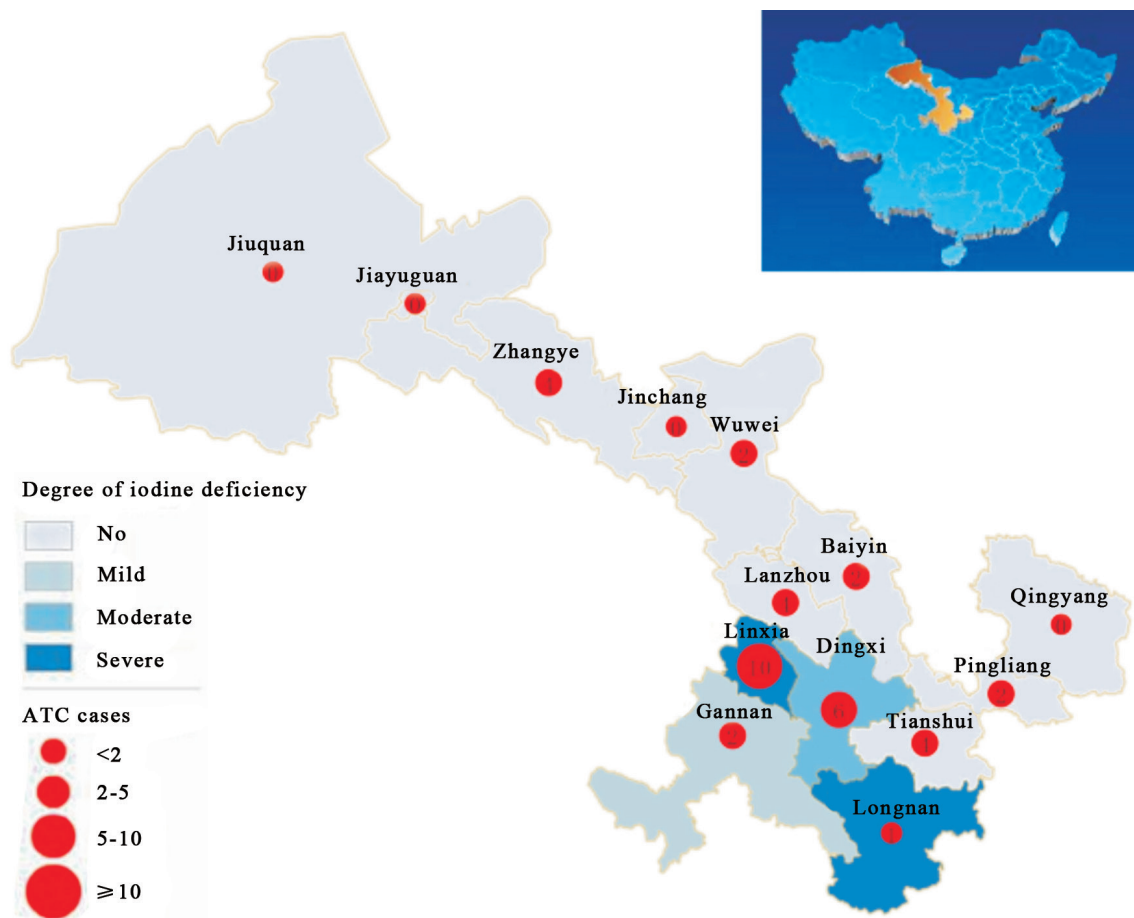


图 1 ATC患者地区分布与碘缺乏程度的关系

Fig. 1 The relationship between ATC patients' distribution and the degree of iodine deficiency

呼吸困难, 21例伴肿块疼痛或压痛, 19例伴哽噎感或吞咽困难, 14例伴声音嘶哑, 2例无伴随症状, 6例以声音嘶哑为首发症状。肿瘤最大径为3.5~15.0 cm, 中位直径为6.0 cm, 平均直径为(7.5±2.2) cm。初诊时颈部淋巴结转移18例, 上纵隔淋巴结转移3例, 颈部及上纵隔淋巴结转移2例, 无淋巴结转移14例。远处转移8例, 肺转移5例, 骨转移1例, 脑转移1例, 肺、骨多发性转移1例。肿瘤TNM分期: IVA期3例, IVB期26例, IVC期8例。KPS评分≥70分35例, KPS评分<70分2例。细针抽吸细胞学诊断2例, 粗针穿刺组织病理学诊断5例, 切除组织标本病理学确诊33例。Vimentin阳性16例, CK5/6阳性3例, TG灶状阳性6例, TTF-1和CT均为阴性。

2.3 治疗情况

17例行单纯甲状腺手术, 4例行局部广泛切除术, 11例行甲状腺癌联合根治术。5例仅行穿刺或开放活检术, 1例确诊后未行治疗即窒息死亡。仅行手术治疗者17例, 仅行化疗者3例, 综合治疗者16例: 手术+术后放疗+化疗6例, 手术+术后放疗4例, 手术+化疗5例, 放疗+化疗1例。11例接受放疗的患者中5例行三维适形放疗, 6例行调强放疗, 2例因局部反应较重而终止治疗; 2例剂量<40 Gy(22 Gy, 36 Gy), 9例剂量≥40 Gy(54.4~69.3 Gy)。15例患者接受化疗: 顺铂(20 mg/m², 第1~3天)+多西他赛(60~75 mg/m², 第1天)9例, 洛铂(50 mg/m², 第1天)+多西他赛(60~75 mg/m², 第1天)2例, 奈达铂(80~100 mg/m², 第1天)+多西他赛(60~75 mg/m², 第1天)1例, 顺铂(30 mg/m², 第1~3天)+表柔比星(60~120 mg/m², 第1天)2例, 口服替吉奥单药(80 mg/m², 每天2次, 第1~14天)1例。

2.4 生存及预后分析

截至末次随访日期2016年5月, 仍有3例患者存活, 2例失访。死亡32例, 10例死于远处转移(治疗后肺转移2例), 21例死于肿瘤局部进展, 1例为非肿瘤相关性死亡。全组平均生存期为11.5个月, 中位生存期为5.9个月, 6个月、1年和2年生存率分别为48.6%、21.6%和13.5%。单因素分析结果显示, 年龄、合并甲状腺肿、远处转移、白

表2 37例ATC患者的临床病理特征

Tab. 2 The clinicopathologic characteristics of 37 ATC patients

Characteristic	Number of patients
[n(%)]	
Tumor size D/cm	
>6	25 (67.6)
≤6	12 (32.4)
Extrathyroidal extension	
Yes	34 (91.9)
No	3 (8.1)
Lymph node metastasis	
Yes	23 (62.2)
No	14 (37.8)
Distant metastasis	
Yes	8 (21.6)
No	29 (78.4)
White blood cell count	
≤10.0×10 ⁹ /L	27 (73.0)
>10.0×10 ⁹ /L	10 (27.0)
Platelet count	
≤300×10 ⁹ /L	28 (75.7)
>300×10 ⁹ /L	9 (24.3)
C-reactive protein ρ _B /(mg·L ⁻¹)	
≤3.0	8 (21.6)
>3.0	29 (78.4)
Concomitant thyroid nodule type	
Papillary thyroid carcinoma	5 (13.5)
Nodular goiter	11 (29.7)
Follicular adenoma	2 (5.4)
p53	
Positive	18 (48.6)
Negative	19 (51.4)
Ki-67	
Positive	21 (56.8)
Negative	16 (43.2)

细胞计数、手术治疗、手术方式、术后放疗和综合治疗是影响ATC患者生存的预后因素(表3)。年龄≤50岁患者的生存率显著增加(图2), 无远处转移的患者预后明显好于有远处转移者(log-rank $\chi^2=14.126$, $P=0.000$), 1年生存率分别为31.0%和0.0%(图3)。手术患者的生存率明显高于未手术患者(log-rank $\chi^2=10.819$, $P=0.001$)。手术切除方式与长期生存显著相关(log-rank $\chi^2=8.857$, $P=0.012$), R0、R1和R2切除患者的2年生存率分别为75.0%、16.7%和4.5%(图4)。术后未行放疗的患者和术后放疗者1年生存率分别为7.4%和70.0%(图5)。

表 3 ATC患者生存影响的单因素分析

Tab. 3 Univariate analysis of the prognostic factors and survival of patients with ATC

Characteristic	Number of patients	Number of deaths	Number of survivals	Log-rank χ^2	<i>P</i> value
Age/year				6.804	0.033
≤ 50	6	3	3		
50-70	23	21	2		
> 70	8	8	0		
Gender				0.090	0.770
Male	12	10	2		
Female	25	22	3		
Ethnicity				3.836	0.050
Han	9	9	0		
Minorities	28	23	5		
Residential areas				1.355	0.244
Rural	7	6	1		
Urban	30	26	4		
Goiter				3.975	0.046
Yes	13	10	3		
No	24	22	2		
Tumor size <i>D</i> /cm				3.075	0.080
> 6	12	9	3		
≤ 6	25	23	2		
Extrathyroidal extension				2.749	0.097
Yes	8	8	0		
No	29	24	5		
Lymph node metastasis				2.115	0.146
Yes	6	4	2		
No	31	28	3		
Distant metastasis				14.126	0.000
Yes	8	8	0		
No	29	24	5		
Surgery				10.819	0.001
Yes	32	27	5		
No	5	5	0		
Resection type				8.857	0.012
R0	4	2	2		
R1	6	4	2		
R2	22	21	1		
Radiotherapy				15.562	0.000
Yes	11	6	5		
No	26	26	0		
Chemotherapy				2.674	0.102
Yes	13	10	3		
No	24	22	2		
Surgery+radiotherapy				16.885	0.000
Yes	10	5	5		
No	27	27	0		
Comprehensive therapy				11.163	0.001
Yes	16	11	5		
No	21	21	0		

续表3

Characteristic	Number of patients	Number of deaths	Number of survivals	Log-rank χ^2	P value
White blood cell count				6.500	0.011
$\leq 10.0 \times 10^9/L$	10	10	0		
$> 10.0 \times 10^9/L$	27	22	5		
Platelet count				0.854	0.356
$\leq 300 \times 10^9/L$	11	10	1		
$> 300 \times 10^9/L$	26	22	4		
C-reactive protein $\rho_B/(mg \cdot L^{-1})$				2.053	1.052
≤ 3.0	7	5	2		
> 3.0	30	27	3		
p53				2.006	0.157
Positive	22	18	4		
Negative	15	14	1		
Ki-67				0.680	0.410
Positive	21	19	2		
Negative	16	13	3		

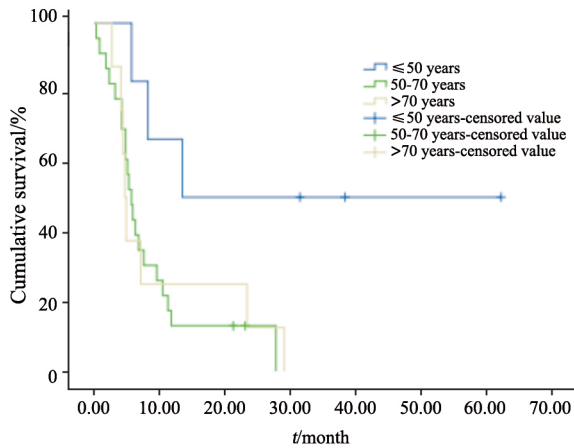


图2 不同年龄对ATC患者预后的影响

Fig. 2 The influence of age on the prognosis of ATC patients

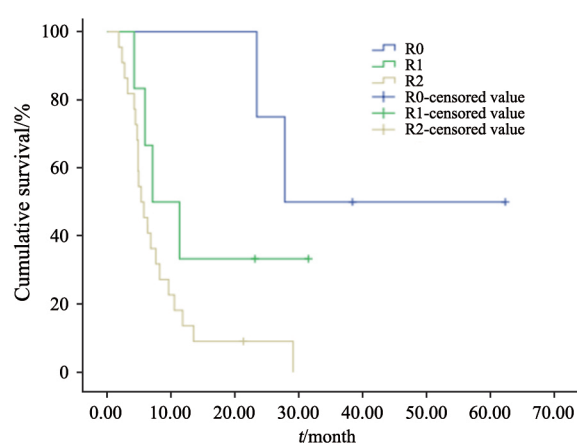


图4 手术切除方式对ATC患者预后的影响

Fig. 4 The influence of surgical resection on prognosis of ATC patients

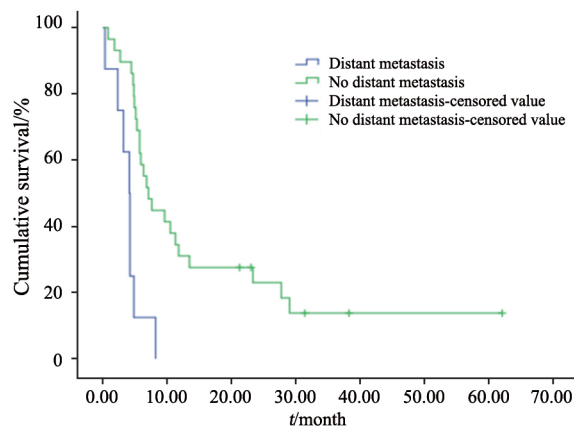


图3 远处转移对ATC患者预后的影响

Fig. 3 The influence of distant metastasis on the prognosis of ATC patients

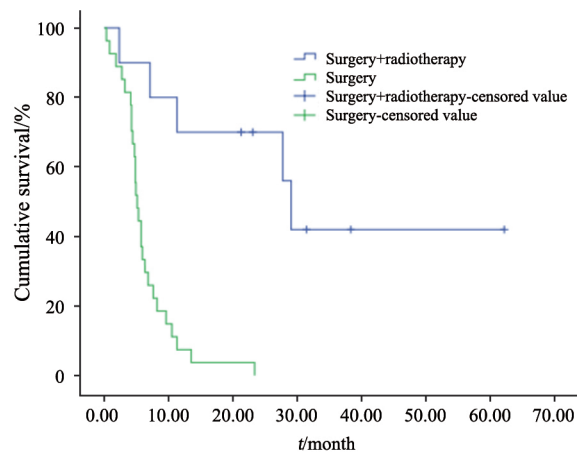


图5 手术+术后放疗对ATC患者预后的影响

Fig. 5 The influence of surgery and postoperative radiotherapy on the prognosis of ATC patients

多因素分析结果显示, 影响ATC患者生存的独立性保护因素是年龄 ≤ 50 岁、接受手术及综合治疗(图6)。ATC手术患者预后不良的独立风

险因素是手术切除方式(R2)和远处转移, 而手术+术后放疗是与生存显著相关的独立性保护因素(图7)。

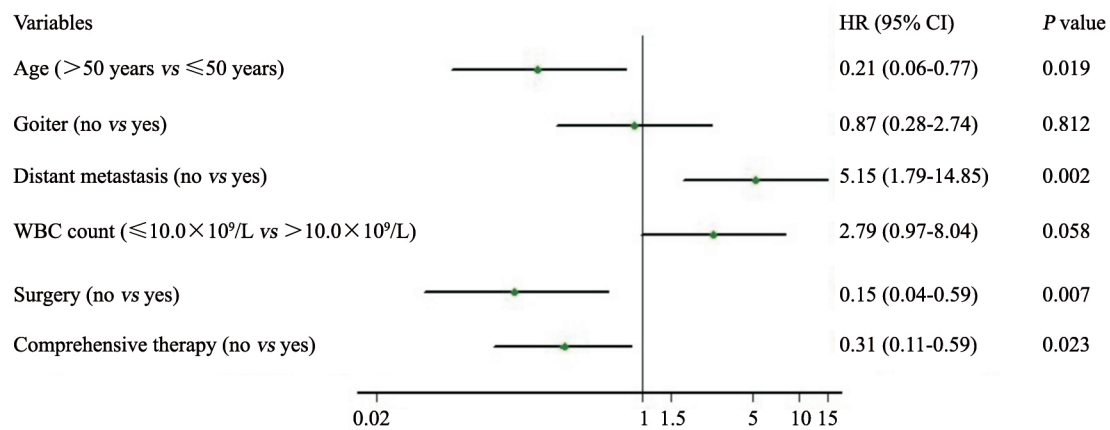


图6 ATC患者生存COX模型多因素分析

Fig. 6 COX multivariate regression model was used to analyze prognostic factors and survival of patients with ATC

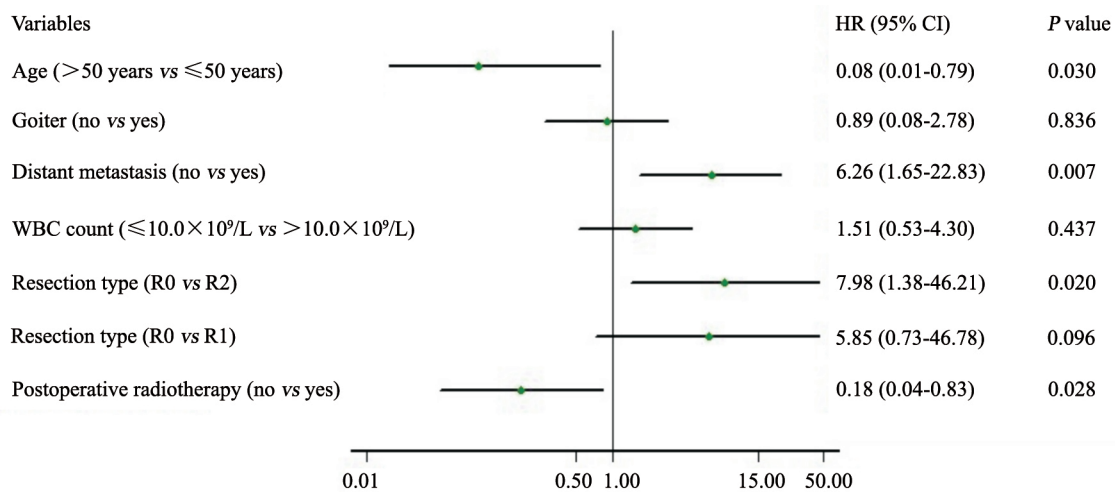


图7 ATC手术患者COX模型多因素分析

Fig. 7 COX multivariate regression model was used to analyze prognostic factors and survival of ATC patients undergoing surgery

3 讨 论

ATC临床罕见, 大多数医师对其认识不足, 容易忽视。本研究中ATC发病率占甲状腺恶性肿瘤的5.3%, 明显高于欧美国家报道的1.0%~3.8%^[1, 4], 且80%的患者生活在经济落后的农村或山区, 表明ATC发病可能与当地的经济和卫生水平相关。据文献报道, 地方性甲状腺肿高发地区ATC的发病率可增加2~3倍^[5], 甲状腺肿病史超过10年的老年人患病风险明显增加^[6]。本研究中约半数患者生活在地方性甲状腺肿地区,

并且碘缺乏程度与ATC患者数相关, 超过1/3的患者在确诊前有长期的甲状腺肿病史。本组患者颈部淋巴结转移率和远处转移率分别为62.2%和21.6%, 与文献报道^[7]相近。Paunovic等^[8]研究发现, 57.6%的患者合并甲状腺乳头状癌, 这一数据在本研究中只有13.5%, 可能与样本量不足有关。

既往研究报道, ATC的平均生存期为3~6个月^[9-11], 1年生存率为10%~15%^[12]。一项大样本回顾性研究^[8]显示, 1和5年生存率为17%和8%, 平均生存期为14个月。Sun等^[13]研究报

道, 1和3年生存率为28.6%和18.5%, 中位生存期为7个月。分析这些差异的原因可能与ATC的深入研究、重视程度、治疗方法改进及研究样本量大小有关。本组患者1和2年生存率为21.6%和13.5%, 平均生存期为11.5个月, 中位生存期为5.9个月。总体而言, ATC患者的预后不容乐观, 1年生存率在20%左右, 中位生存期小于6个月^[14]。

本研究中初诊年龄≤50岁的患者预后较好, 这与年龄越大、预后越差的结论相符^[15]。有研究^[8]发现, 合并甲状腺肿是影响ATC预后的独立因素, 但多数研究者认为两者无明显相关性^[11], 本研究结果与后者相同。以往的报道^[16]与本研究均表明局部淋巴结转移对生存无影响。远处转移是影响ATC患者生存的独立因素, 以往研究^[9]也表明这是最重要的预后因素。本研究中未发现其他影响ATC预后的独立因素。

单因素和多因素分析结果均显示, 手术是显著影响生存的独立预后因素。手术患者的平均生存期是未手术患者的5倍, 提示手术可改善ATC患者的预后。根治性手术对ATC预后的影响仍有争议^[17-19], 手术范围过大会降低患者的生活质量。本研究中R0切除患者的生存率明显高于R1和R2切除患者, 表明手术切除方式才是真正影响预后的独立因素。手术固然重要, 但对于ATC患者实现长期生存的目标来说远远不够。大多数ATC常伴有腺外侵犯, 很难达到R0切除, 单纯放疗对生存期亦无明显改善。而接受综合治疗的患者平均生存期延长, 预后较好。本研究发现, 手术+术后放疗可明显提高ATC患者的生存期, 有文献^[20]也支持术后行高剂量放疗(>40 Gy)与长期生存显著相关的结论。

有研究^[21]报道, ATC对化疗的有效率达50%, 系统化疗配合放疗可改善ATC预后^[22]。但该研究病例数较少, 且未能排除远处转移、手术及放疗等因素对疗效的影响。对于无远处转移的患者, 化疗可能会延误病情。因此, 化疗对ATC预后的影响仍有待研究证实, 应根据患者情况酌情选用。

结合本研究结果及临床经验, 笔者认为多学科协作的综合治疗是ATC最佳的治疗方法: ①腺体内ATC确诊后应行根治性手术, R0切除者可综合患者年龄及体力状况进行术后放疗, R1或R2切除者积极行术后放疗, 推荐调强放疗。②腺外侵犯的ATC患者可行局部广泛切除术, 术后2~3周内行根治性放疗, 如治疗过程中出现远处转移, 可综合患者年龄及体力状况行同步放化疗。③初诊时即有远处转移者, 年轻且体力状况较好者, 可行最大限度减瘤术, 术后行化疗或同步放化疗, 年龄大或体力状况较差者, 可考虑姑息性治疗或参加临床试验。④肿瘤侵犯气管或喉返神经出现严重呼吸窘迫危及生命者, 应紧急行气管切开防止窒息, 同时给予最佳支持治疗, 不建议行单纯预防性气管切开。由于本研究病例数较少, 且为回顾性研究, 结果尚需大样本的临床试验进一步验证。

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