

doi: 10.13241/j.cnki.pmb.2021.02.031

PF 化疗同步联合时辰放疗与常规放疗治疗局部晚期鼻咽癌的随机对照研究 *

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摘要 目的:比较局部晚期鼻咽癌分别接受顺铂联合氟尿嘧啶方案(PF)化疗联合时辰放疗以及 PF 化疗联合常规放疗时的疗效和毒副反应。**方法:**将我科 45 例初治局部晚期鼻咽癌患者随机分为时辰放疗组和常规放疗组,分别为 22 例和 23 例。两组均采用相同放射治疗方法和治疗剂量,同步给予 PF 方案化疗。时辰放疗组放疗时间在 20:00-22:00,而常规放疗组在 8:00-10:00。**结果:**两组患者在放疗结束 3 个月和 6 个月进行时比较发现,时辰放疗组患者的鼻咽部及颈部的肿瘤完全消退率(CR 率)均比常规放疗组高($P<0.05$)。而时辰放疗组的各种急性副作用发生率较常规放疗组低,但无统计学差异。治疗后时辰组 CD4/CD8 升高,常规组 CD4/CD8 降低($P<0.05$)。**结论:**时辰放疗联合 PF 同步化疗针对局部晚期鼻咽癌患者疗效好,毒副作用轻,同时可能有利于改善患者的免疫功能。

关键词:鼻咽癌;时辰放疗;常规放疗**中图分类号:**R739.6 **文献标识码:**A **文章编号:**1673-6273(2021)02-342-05

Randomized Controlled Trial of PF Chemotherapy Combined with Chronomodulated Radiation Therapy and Conventional Radiotherapy for Locally Advanced Nasopharyngeal Carcinoma*

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ABSTRACT Objective: Compared the efficacy and side effects of PF chemotherapy combined with chronomodulated radiation therapy and PF chemotherapy combined with conventional radiotherapy in locally advanced nasopharyngeal carcinoma. **Methods:** Forty-five patients with locally advanced nasopharyngeal carcinoma were randomly divided into chronomodulated radiation therapy group and conventional radiotherapy group, 22 cases and 23 cases respectively. The same radiotherapy method and therapeutic dose were used in both groups, and PF regimen was given simultaneously. The radiotherapy time of the chronomodulated radiation therapy group is between 20:00 and 22:00, while the conventional radiotherapy group is between 8:00 and 10:00. **Results:** At the time of 3 months and 6 months after the radiotherapy, the complete regression rate (CR rate) of the nasopharynx and neck of the patients in the chronomodulated radiation therapy group was higher than that of the conventional radiotherapy group ($P<0.05$). The incidence of various acute side effects in the chronomodulated radiation therapy group was lower than that in the conventional radiotherapy group, but there was no statistical difference. The level of CD4/CD8 was elevated in the chronomodulated radiation therapy group after treatment, while it was decreased in the conventional group ($P<0.05$). **Conclusion:** PF chemotherapy combined with chronomodulated radiation therapy is effective in patients with locally advanced nasopharyngeal carcinoma, with mild toxic and side effects, and may be beneficial to improve the immune function of patients.

Key words: Nasopharyngeal carcinoma; Chronomodulated radiation therapy; Conventional radiotherapy**Chinese Library Classification(CLC):** R739.6 **Document code:** A**Article ID:** 1673-6273(2021)02-342-05

前言

肿瘤与时间节律有着紧密的关系,其中癌细胞的增殖过程中有着明显的时间节律,相对于正常组织细胞的增殖节律,差

异较大^[1-3]。通过选择最适宜的治疗时间有望达到最大程度杀伤肿瘤细胞达到增效并减少副作用的目的^[4,5]。近年来,肿瘤诊疗研究进展明显,其中的热点之一就是遵循各瘤种细胞的增殖时辰节律探索其最佳的治疗方案,但大部分研究者关注点都在时

* 基金项目:四川省卫生厅科研项目(1200141);德阳市科技局应用技术与开发项目(2017SZ074)

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(收稿日期:2020-06-08 接受日期:2020-06-30)

晨化疗上,而有关时辰放疗的研究极少^[6]。时辰放疗的基础和临床研究中关于时间的选择也并非一致,多数选取了与常规放疗治疗时间不同的夜间时间段作为时辰放疗的时间,其主要原因在于多个基础研究和动物研究表明肿瘤细胞和移植于哺乳动物的肿瘤细胞的 DNA 合成均存在光周期昼夜变化节律^[10-12],部分研究明确 G1 期、S 期、G2/M 期细胞的相对比例在不同时间段变化存在着统计学差异,特别是 G1 期、G2/M 期细胞高峰均出现在光照后的休息相^[13,14]。另一方面,局部晚期鼻咽癌的治疗目前仍以同步放化疗为主^[15-17],疗效已取得令人满意的结果,其中 PF 方案化疗是鼻咽癌同步放化疗中经典的标准方案^[18-23]。但研究者们并未就此停止追求的脚步,近年来靶向、免疫等治疗也先后在鼻咽癌的治疗中不断尝试^[24-29],但治疗费用也随之增加。本研究仍以 PF 化疗方案为基础,分别同步时辰放疗及常规放疗,旨在不断增加治疗费用的基础上,观察时辰放疗对局部晚期鼻咽癌的治疗效果,提高放射治疗效率,观察各种不良反应,探索肿瘤放疗的新方式。

1 材料及方法

1.1 病例选择与一般资料

通过伦理审批后收集德阳市人民医院在 2017 年 5 月至 2018 年 5 月符合入组条件的局部晚期鼻咽癌初治病例 46 例,其中可评估病例 45 例,用随机表法(随机序列由肿瘤科档案管理员保管,电话联系获取)分为时辰放疗组 22 例,常规放疗组 23 例。两组病例在年龄、性别、病理类型及临床分期等方面差异无统计学意义($P>0.05$)。

1.2 方法

1.2.1 入组及排除标准 入组标准:1)经病检确诊的初治局部晚期鼻咽癌患者(2010UICC 分期标准);2)年龄 18-70 岁,性别不限;3)KPS 评分 ≥ 80 分;4)无严重心、肺、肝、肾等重要器官功能障碍,白细胞 $\geq 4.0 \times 10^9$ mmol/L,血小板 $\geq 100 \times 10^9$ mmol/L,血红蛋白 ≥ 120 g/L。排除标准:1)肿瘤原发灶或淋巴结入组前已行局部治疗(如放化疗、颈清扫术等,活检除外);2)严重肺部或心脏疾病史;3)5 年内曾患其他恶性肿瘤者;4)孕妇或哺乳期妇女;5)有严重的过敏史或特异体质者。在入组前所有患者需完善三大常规、生化、常规心电图、纤维鼻咽镜、鼻咽及颈部增强 MRI、全身骨显像(ECT)及胸、腹部重要器官的影像检查等。

1.2.2 同期化疗 顺铂 25 mg/($m^2 \cdot d$),d1-3,普通化疗输液器上午 9:00-11:00 时完成输注;微量泵泵入 5-Fu,持续 96 小时,总量 2.5 g/ m^2 ,以上为一周期用药。21-28 天重复,共完成 4 周期。

1.2.3 放疗 所有病例均接受全靶区三维适形调强放疗(IM-RT),根据国际辐射单位和计量委员会(international commission on radiation units and measurements)相关原则,GTVnx 为临床、影像学检查获得的鼻咽肿瘤及其侵犯范围;GTVnd 为临床和(或)影像学观察符合诊断标准的肿大淋巴结(包括咽后淋巴结);CTVnx 为 GTVnx+ 外放 5 mm+ 鼻咽各壁;PTVnx 为 CTVnx+ 外放 3 mm;临床靶区 CTV1 包括 PTVnx 及周围高危区域和上颈淋巴结引流区;CTV2 范围包括颈部照射范围同时超出淋巴结转移部位 1~2 个颈区;CTV 外扩 3 mm 是为

PTV。靶区勾画均参照患者 MRI 影像。并分别勾画临近的各危及器官。处方剂量 PTVnx 68-72 Gy,PTVnd 66-68 Gy,PTV1 60-66 Gy,PTV2 50-56 Gy,分割 31-33 次,每天一次,每周 5 次。根据设定的靶区剂量和危及器官耐受剂量以及可接受的范围,系统将自动进行逆向设计运算,从中选择最优的计划。计划完成后,时辰放疗组 20:00-22:00 放疗,常规放疗组 8:00-10:00 放疗。

1.2.4 T 淋巴细胞亚群测定 采用碱性磷酸酶-抗碱性磷酸(AAP)法,应用白细胞分化抗原 CD3/CD8/CD45/CD4 检测试剂盒(流式细胞仪法-FITC/PE/PerCP/APC)英文名为 BD Multitest CD3/CD8/CD45/CD4,配合流式细胞仪使用,分别在治疗前、治疗结束时采集两组病例静脉血,测定 T 淋巴细胞亚群。

1.3 不良反应及疗效评价

以 RTOG 急性放射损伤分级标准来评价各种不良反应,同时分级量化。临床疗效评价则采用 2000 版实体瘤治疗疗效评价标准(RECIST1.1),分为完全缓解(CR)、部分缓解(PR)、疾病稳定(SD)、疾病进展(PD)。完成所有治疗后,按期复查鼻咽及颈部增强 MRI、纤维鼻咽镜以及相关影像,评价该治疗模式的近期疗效。

1.4 统计学方法

应用 SPSS 19.0 软件进行统计分析,在资料满足正态分布、方差齐性的前提下,统计分析前先使用两独立样本 t 检验和 χ^2 检验比较两组患者的一般资料,其年龄、性别、病理类型、分期等一般资料比较中,差异无统计学意义($P>0.05$)。计数资料率的比较用 χ^2 检验;等级资料比较采用秩和检验;在两组治疗对免疫功能的影响进行统计学比较则采用的是独立样本 t 检验及配对 t 检验, $P<0.05$ 为差异有统计学意义。

2 结果

本研究纳入的病例随机分组后,两组在年龄、性别、病理类型及临床分期等方面差异无统计学意义($P>0.05$)。

2.1 近期临床疗效

治疗结束后 3 个月,时辰放疗组有效率(CR+PR 病例数/总病例数)为 90.91%,高于常规放疗组 82.61%,但差异无统计学意义;在完全缓解率(CR 病例数/总病例数)方面,时辰放疗组 50.00%,而常规放疗组为 21.74%,存在统计学差异(见表 1)。治疗后 6 个月,完全缓解率时辰放疗组 95.45%明显高于常规放疗组 73.91%,且差异有统计学意义(见表 2)。

2.2 近期急性放射不良反应

近期急性放射不良反应的观察包括放射性黏膜炎、放射性皮肤炎、味觉减退、喉放射反应、鼻腔口腔部黏膜溃疡、咽食管反应和口干,对比发现,两组比较虽然并无统计学差异(见表 3),但在放射性皮肤炎和黏膜炎对患者生活质量影响较大的不良反应观察中,时辰放疗放射性皮炎的发生率 59.10%较常规放疗组 65.22%低,且时辰放疗组 3-4 级发生率 22.73%也较常规放疗组 30.43%低。在放射性黏膜炎方面,时辰放疗组 3-4 级发生率 22.73%低于常规放疗组 30.43%,显示出了一定优势。

2.3 两组免疫功能变化比较

时辰放疗组 CD4/CD8 在治疗后升高,虽治疗前后的对比差异无统计学意义($P>0.05$),但提示了时辰放疗可能对研究对

象的免疫功能有改善作用。而常规放疗组中 CD4/CD8 值在治疗后较治疗前比值明显降低,且治疗前后的差异有统计学意义 ($P<0.05$),可能提示常规放疗有损伤研究对象的免疫功能的作用。

表 1 治疗后 3 月两组完全缓解率(CR)比较

Table 1 Comparison of complete remission rate (CR) between the two groups 3 months after treatment

Recent efficacy evaluation	Time radiotherapy group (22)	Routine radiotherapy group (23)	Total number of cases (45)	χ^2	P
CR	11	5	16	3.919	0.048
PR	9	14	23		
SD	2	4	6		
PD	0	0	0		

表 2 治疗后 6 月完全缓解率(CR)比较

Table 2 Comparison of complete remission rate (CR) at 6 months after treatment

Recent efficacy evaluation	Time radiotherapy group (22)	Routine radiotherapy group (23)	Total number of cases (45)	χ^2	P
CR	21	17	38	3.972	0.046
PR	1	6	7		
SD	0	0	0		
PD	0	0	0		

表 3 急性放射不良反应

Table 3 Acute adverse radiation reactions

Adverse reactions	Time radiotherapy group (22 cases)					Routine radiotherapy group (23 cases)					Z	P
	Level 1	Level 2	Level 3	Level 4	Total number of cases	Level 1	Level 2	Level 3	Level 4	Total number of cases		
Radiation mucositis	2	9	4	1	16	1	9	6	1	17	-0.681	0.496
Radiation dermatitis	3	5	4	1	13	2	6	4	3	15	-0.689	0.491
Decreased taste	0	2	0	0	2	2	1	0	0	3	1.333	0.182
Laryngeal radiation response	12	6	1	0	19	10	5	0	0	18	-0.423	0.673
Mucosal ulcer of nasal cavity and oral cavity	2	3	1	0	6	3	2	1	0	6	-0.433	0.665
Pharyngeal and esophageal reactions	1	2	0	0	3	3	1	0	0	4	-1.021	0.307
Dry mouth	1	1	0	0	2	1	2	0	0	3	0.333	0.739

表 4 治疗后两组免疫功能比较

Table 4 Comparison of immune function between the two groups after treatment

Item	Time radiotherapy group		P	Routine radiotherapy group		P
CD3	Before treatment	40		46		
	After treatment	58		56		
CD4	Before treatment	24		30		
	After treatment	35		33		
CD8	Before treatment	26		21		
	After treatment	16		16		
CD4/CD8	Before treatment	1.85	>0.05	2.16	<0.05	
	After treatment	2.15		1.74		

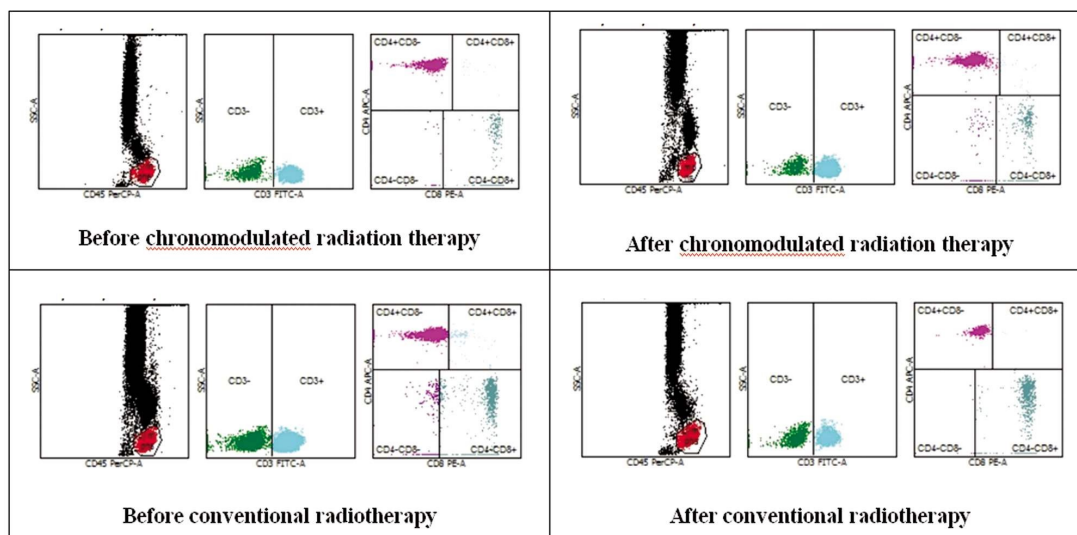


图1 流式细胞图集

Fig.1 Atlsa of flow cytometry

3 讨论

现阶段晚期恶性肿瘤主要的治疗手段仍然为全身化疗配合局部放疗。时辰治疗在化疗方面的研究已取得不错的进展^[30],而针对肿瘤放疗的时辰治疗研究开展尚少。大量的基础研究结果证实,不同的细胞对射线的敏感性因其自身周期不同而有明显的差异^[31-33]。干细胞集团同步的情况下,动物细胞致死量在昼夜节律的不同时相中也存在差异^[34]。体外实验中,国内外学者得出了一致结果,如能选择适当的时间给予肿瘤组织照射,针对肿瘤细胞敏感期,预期可以提高放射治疗有效率^[14,34,35],这一结果预示时辰放疗的优越性。SChan^[36-38]等人的荟萃分析提示:头颈部患者时辰放疗可能有更好的获益。有了以上研究结果,本课题组在通过伦理审查的情况下实施了时辰放疗,选择 20:00-22:00 作为时辰放疗时间段,8:00-10:00 作为常规放疗时间段。本研究结果中可以看到,时辰放疗组有效率(CR+PR 病例数/总病例数)高于常规放疗组,但差异无统计学意义。然而在分析完全缓解率(CR 病例数/总病例数)中,我们发现无论是治疗后 3 个月还是治疗后 6 个月,时辰放疗组都明显高于常规放疗组,且差异有统计学意义($P<0.05$)。在进行急性放射不良反应的观察对比中我们发现,两组比较虽然并无统计学差异,但时辰放疗却降低了放射性皮炎的发生率,在减少严重放射性口腔黏膜炎方面中,也显示出了一定优势。

肿瘤的发生与机体的细胞免疫状态两者间的关系密切。恶性肿瘤患者常常合并有免疫功能低下,同时肿瘤细胞可以选择性逃脱机体的免疫监视与免疫杀伤,进一步导致肿瘤复发和转移。而 T 细胞亚群是观察机体细胞免疫状态的重要指标之一,其检测项目包括 CD3、CD4、CD8、CD4/CD8 等。在此研究中,治疗前两组 CD3、CD4、CD8、CD4/CD8 虽有一定的差异,但无统计学意义。然而经过治疗后,T 细胞亚群发生明显改变:时辰放疗组患者经过治疗后,CD4/CD8 较治疗前升高,相反常规放疗组治疗后,CD4/CD8 较治疗前明显下降。研究组分析时辰组 CD4/CD8 升高原因,有可能与治疗后肿瘤体积缩小有关。已有研究^[14,39]表明,肿瘤缩小减少了机体的肿瘤负荷,进而导致由肿瘤组织激活的体内淋巴细胞数量下降,相应的淋巴细胞释放

的免疫抑制因子等因此减少,从而机体免疫功能得到了一定程度的恢复。这一研究结果提示了,选择合适的治疗方式,不但未降低恶性肿瘤患者的免疫功能,反而可能因肿瘤负荷减少从而降低肿瘤对机体免疫系统的抑制,最终呈现机体免疫功能改善的状态。本研究中,时辰放疗组 CD4/CD8 在治疗后升高,虽治疗前后的对比差异无统计学意义,但提示了时辰放疗可能对研究对象的免疫功能有改善作用。而常规放疗组中 CD4/CD8 值在治疗后较治疗前比值明显降低,且治疗前后的差异有统计学意义,可能提示常规放疗有损伤研究对象的免疫功能的作用。

综上所述,时辰放疗在近期疗效上特别是 CR 率显示出了明显优势,一定程度上减少了急性放射损伤。通过对 T 淋巴细胞亚群测定,我们发现时辰放疗可能有改善研究对象的免疫功能的作用,尤其在 T 细胞的影响方面,较常规放疗小,这可能更利于肿瘤的控制和预防复发转移。本课题组下一步的工作就是希望通过长期随访观察证实这一设想,同时观察远期疗效和慢性放射损伤。

参考文献(References)

- [1] Harper E, Talbot CJ. Is it Time to Change Radiotherapy: The Dawning of Chronoradiotherapy? [J]. Clin Oncol (R Coll Radiol), 2019, 31(5): 326-335
- [2] Schwartzkopff O, Cornélissen G, Otsuka K, et al. India revisited: a new hospital and center culminating multidecadal cooperation. From cancer chronoradiotherapy to routine cardiovascular chronotheranostics and further joint Indian-US and international BIOCOS research [J]. Biomed Pharmacother, 2005, 59 Suppl 1(Suppl 1): S123-S131
- [3] Gupta BD, Cornélissen G, Halberg F, et al. Oral and cervical temperatures as marker variables for chronoradiotherapy of patients with cervical cancer [J]. Prog Clin Biol Res, 1987, 227B: 349-356
- [4] Wang Z, Wan C, Lay Ya, et al. Rol' biologicheskikh chasov v formirovani normy, patologii i v terapii. 2. Klinicheskaja khronoradioterapiia raka legkikh Role of biological clocks in normal conditions, pathology, and in therapy [J]. Biofizika, 1995, 40(5): 996-998
- [5] Cornélissen G, Gubin D, Halberg F, et al. Chronomedical aspects of oncology and geriatrics [J]. In Vivo, 1999, 13(1): 77-82
- [6] Halberg F, Cornélissen G, Wang Z, et al. Chronomics: circadian and circaseptan timing of radiotherapy, drugs, calories, perhaps nutraceut-

- cals and beyond[J]. *J Exp Ther Oncol*, 2003, 3(5): 223-260
- [7] Halberg E, Cornélissen G, Halberg F. Optimization of the chronotherapeutic index in the experimental animal laboratory [J]. *In Vivo*, 1992, 6(4): 371-385
 - [8] Zhang Y, Chen X, Ren P, et al. Synergistic effect of combination topotecan and chronomodulated radiation therapy on xenografted human nasopharyngeal carcinoma [J]. *Int J Radiat Oncol Biol Phys*, 2013, 87(2): 356-362
 - [9] Zhang B, Li MM, Chen WH, et al. Association of Chemoradiotherapy Regimens and Survival Among Patients With Nasopharyngeal Carcinoma: A Systematic Review and Meta-analysis [J]. *JAMA Netw Open*, 2019, 2(10): e1913619
 - [10] Edery I. Circadian rhythms in a nutshell [J]. *Physiol Genomics*, 2000, 3: 59-74
 - [11] Mormont MC, Levi F. Cancer chronotherapy: principles, applications, and perspectives [J]. *Cancer*, 2003, 97(1): 155-169
 - [12] Blumenthal RD, Osorio L, Ochakovskaya R. Regulation of tumor drug delivery by blood flow chronobiology [J]. *Eur J Cancer*, 2000, 36 (14): 1876-1884
 - [13] SUN Jian, XIAN Lijian, CAO Qiyuan, et al. Circadian rhythms of DNA synthesis in human nasopharyngeal carcinoma cells transplanted in nude mice [J]. *Chinese Journal of Cancer*, 2001, 20(2): 128-130
 - [14] 范治军, 刘士煜, 李科, 等. 鼻咽癌细胞生物节律及时辰照射观察 [J]. *中国辐射卫生*, 2013, 22(05): 521-523
 - [15] Frikha M, Auperin A, Tao Y, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02) [J]. *Ann Oncol*, 2018, 29(3): 731-736
 - [16] Sze H, Blanchard P, Ng WT, et al. Chemotherapy for Nasopharyngeal Carcinoma - Current Recommendation and Controversies [J]. *Hematol Oncol Clin North Am*, 2015, 29(6): 1107-1122
 - [17] Chua ML, Sun Y, Supiot S. Advances in nasopharyngeal carcinoma-"West meets East"[J]. *Br J Radiol*, 2019, 92(1102): 20199004
 - [18] Lv J, Chen Y, Zhou G, et al. Liquid biopsy tracking during sequential chemo-radiotherapy identifies distinct prognostic phenotypes in nasopharyngeal carcinoma [J]. *Nat Commun*, 2019, 10(1): 3941
 - [19] Finazzi T, Rordorf T, Ikenberg K, et al. Radiotherapy-induced anti-tumor immune response and immune-related adverse events in a case of recurrent nasopharyngeal carcinoma undergoing anti-PD-1 immunotherapy [J]. *BMC Cancer*, 2018, 18(1): 395
 - [20] Lu Y, Chen D, Liang J, et al. Administration of nimotuzumab combined with cisplatin plus 5-fluorouracil as induction therapy improves treatment response and tolerance in patients with locally advanced nasopharyngeal carcinoma receiving concurrent radiochemotherapy: a multicenter randomized controlled study [J]. *BMC Cancer*, 2019, 19 (1): 1262
 - [21] Lee VH, Lam KO, Chang AT, et al. Management of Nasopharyngeal Carcinoma: Is Adjuvant Therapy Needed? [J]. *J Oncol Pract*, 2018, 14 (10): 594-602
 - [22] Yang Q, Cao SM, Guo L, et al. Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase III multicentre randomised controlled trial [J]. *Eur J Cancer*, 2019, 119: 87-96
 - [23] Hong M, Tang K, Qian J, et al. Immunotherapy for EBV-Associated Nasopharyngeal Carcinoma [J]. *Crit Rev Oncog*, 2018, 23 (3-4): 219-234
 - [24] Ribassin-Majed L, Marguet S, Lee AWM, et al. What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis [J]. *J Clin Oncol*, 2017, 35(5): 498-505
 - [25] Zhu J, Duan B, Shi H, et al. Comparison of GP and TPF induction chemotherapy for locally advanced nasopharyngeal carcinoma [J]. *Oral Oncol*, 2019, 97: 37-43
 - [26] Jacinto JK, Co J, Mejia MB, et al. The evidence on effectiveness of weekly vs triweekly cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell carcinoma (HNSCC): a systematic review and meta-analysis [J]. *Br J Radiol*, 2017, 90(1079): 20170442
 - [27] Zhang HJ, Yuan GL, Liang QL, et al. Addition of bevacizumab to systemic therapy for locally advanced and metastatic nasopharyngeal carcinoma [J]. *Oncol Lett*, 2018, 15(5): 7799-7805
 - [28] Wang BC, Shi LL, Fu C, et al. A meta-analysis of cisplatin-based concurrent chemoradiotherapy with or without cetuximab for locoregionally advanced nasopharyngeal carcinoma [J]. *Medicine (Baltimore)*, 2019, 98(42): e17486
 - [29] Li MY, Liu JQ, Chen DP, et al. Glycidazole sodium combined with radiochemotherapy for locally advanced nasopharyngeal carcinoma [J]. *Asian Pac J Cancer Prev*, 2014, 15(6): 2641-2646
 - [30] Zhang P X, Jin F, Li Z L, et al. A randomized phase II trial of induction chemotherapy followed by cisplatin chronotherapy versus constant rate delivery combined with radiotherapy [J]. *Chronobiology international*, 2018, 35(2): 240-248
 - [31] Bjanason G A, Mackenzie R G, Nabid A, et al. Comparison of toxicity associated with early morning versus late afternoon radiotherapy in patients with head-and-neck cancer: a prospective randomized trial of the National Cancer Institute of Canada Clinical Trials Group (HN3) [J]. *International journal of radiation oncology, biology, physics*, 2009, 73(1): 166-172
 - [32] Griffon G, Merlin J L, Marchal C. Comparison of sulforhodamine B, tetrazolium and clonogenic assays for in vitro radiosensitivity testing in human ovarian cell lines [J]. *Anti-cancer drugs*, 1995, 6(1): 115-123
 - [33] Pawlik T M, Keyomarsi K. Role of cell cycle in mediating sensitivity to radiotherapy [J]. *International journal of radiation oncology, biology, physics*, 2004, 59(4): 928-942
 - [34] BANASIAK D, BARNETSON A R, ODELL R A, et al. Comparison between the clonogenic, MTT, and SRB assays for determining radiosensitivity in a panel of human bladder cancer cell lines and a ureteral cell line [J]. *Radiation oncology investigations*, 1999, 7(2): 77-85
 - [35] 朱彬, 王正荣. 肿瘤时间生物学研究进展 [J]. *中国处方药*, 2004, (07): 18-22
 - [36] Chan S, Rowbottom L, McDonald R, et al. Does the Time of Radiotherapy Affect Treatment Outcomes? A Review of the Literature [J]. *Clinical oncology*, 2017, 29(4): 231-238
 - [37] Goyal L M, Shukla P, Gupta D, et al. Oral mucositis in morning vs. evening irradiated patients: a randomised prospective study [J]. *International journal of radiation biology*, 2009, 85(6): 504-509
 - [38] Bjarnason G A, Jordan R C, Sothorn R B. Circadian variation in the expression of cell-cycle proteins in human oral epithelium [J]. *The American journal of pathology*, 1999, 154(2): 613-622
 - [39] 毛振华, 金凤, 吴伟莉, 等. 时辰化疗治疗初治远处转移鼻咽癌的临床研究 [J]. *中国肿瘤临床*, 2015, 42(14): 709-715