**II-IVA期鼻咽癌的根治性放化综合治疗：中国临床肿瘤学会（CSCO）和美国临床肿瘤学会（ASCO）联合临床实践指南**

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| **化疗联合放疗根治性治疗II-IVA期鼻咽癌的根治性放化综合治疗：中国临床肿瘤学会（CSCO）和美国临床肿瘤学会（ASCO）联合临床实践指南****指南问题:**1. 对于II-IVA期鼻咽癌患者，推荐的放疗技术和分割模式是？
2. 对于II-IVA期鼻咽癌患者，在放疗中加入化疗的推荐时机是？
3. 对于接受同期化疗的鼻咽癌患者，推荐的化疗方案是？
4. 对于接受诱导化疗的鼻咽癌患者，推荐的化疗方案是？
5. 对于接受辅助化疗的鼻咽癌患者，推荐的化疗方案是？

**指南推荐:*****放疗****推荐1.1* 对于所有鼻咽癌患者，推荐使用每日图像引导的调强放疗。如果无法提供调强放疗，推荐将患者转至可以实施调强放疗的机构。（类型：循证；利大于弊；证据质量：高；推荐强度：强）*推荐1.2* 对于所有鼻咽癌患者，序贯加量放疗或同步推量放疗均可使用。（类型：循证；利大于弊；证据质量：中等；推荐强度：中等）*推荐1.3* 对于所有鼻咽癌患者，放疗推荐的处方剂量为70Gy（分割次数33-35，单次剂量2.0-2.12 Gy）， 7周内（每天一次，每周5次）完成。可以根据肿瘤体积及其对放（化）疗的反应来调整剂量。（类型：循证；利大于弊；证据质量：高；推荐强度：强）*推荐1.4* 对于所有鼻咽癌患者，应仔细勾画大体肿瘤靶区（GTV）。靶区勾画应遵循共识指南，并充分利用包括图像融合在内的技术手段。推荐将MRI与CT图像融合进行靶区勾画，尤其是在观察潜在的肿瘤颅底侵犯以及排除或确认颅神经受累和/或颅内侵犯时。 （类型：共识；证据质量：中等；利大于弊；推荐强度：强）*推荐1.5* 对于已接受诱导化疗的鼻咽癌患者，推荐将诱导化疗前后的CT模拟图像融合，以明确治疗前的病变范围。GTV推荐遵循诱导化疗前的肿瘤范围，尤其是在骨质解剖结构内的病变。 （类型：共识；证据质量：中等；利大于弊；推荐强度：中等）*推荐1.6*淋巴结靶区（从双侧咽后淋巴结水平至IV、V区淋巴结水平）的勾画应遵循国际共识指南。Ib区淋巴结不推荐预防性照射，除非有鼻腔前半部受累，或者II区淋巴结大于2 cm、包膜外侵或双侧受累。如果颈部没有可疑淋巴结转移，则可考虑不予未受累侧下颈部进行预防照射。（类型：共识；证据质量：中等；利大于弊；推荐强度：中等）***化疗时机****推荐2.1* 对于T2N0（AJCC第八版）鼻咽癌患者，不推荐常规化疗，但如果存在不良预后指标，如肿瘤体积大或EBV DNA拷贝数高，则可考虑进行化疗。（类型：循证；弊大于利；证据质量：中等；推荐强度：中等）*推荐2.2* 对于T1-2N1（AJCC第八版）鼻咽癌患者，特别是T2N1患者，可使用同期化疗。（类型：循证；弊大于利；证据质量：中等；推荐强度：中等）*推荐2.3* 对于III-IVA期（除外T3N0）（AJCC第八版）鼻咽癌患者，推荐在同期放化疗的基础上加用诱导化疗。（类型：循证；利大于弊；证据质量：高；推荐强度：强）*推荐2.4* 对于III-IVA期（除外T3N0）（AJCC第八版）未接受诱导化疗的鼻咽癌患者，推荐在同期放化疗后加用辅助化疗。 （类型：循证；利大于弊；证据质量：中等；推荐强度：中等）注解：目前尚无比较诱导化疗联合同期放化疗和同期放化疗联合辅助化疗的头对头试验，因此当下哪种化疗时机更优尚未明确。*推荐2.5* 对于T3N0（AJCC第八版）鼻咽癌患者，推荐使用同期放化疗。辅助化疗或诱导化疗也可使用。 （类型：循证；利大于弊；证据质量：中等；推荐强度：中等）***同期化疗****推荐3.1*对于没有相关禁忌症的鼻咽癌患者，推荐在放疗的同时使用每周（40 mg/m²）或每三周（100 mg/m² 或至少 80 mg/m²）方案的顺铂化疗。（类型：循证；证据质量：高；利大于弊；推荐强度：强）*推荐3.2*对于没有相关禁忌症的鼻咽癌患者，推荐使用3程每三周方案或7程每周方案的同期顺铂化疗，顺铂的累积剂量至少要达到200 mg/m²。（类型：非正式的专家共识；利大于弊；证据质量：中等；推荐强度：中等）*推荐3.3*对于有禁忌症而无法使用顺铂化疗的鼻咽癌患者，同期化疗可使用奈达铂（100 mg/m2，每三周一次）代替。可选的其他药物包括卡铂（曲线下面积 [AUC] 5-6，每三周一次）或奥沙利铂（70 mg/m2，每周一次）。（类型：循证 ；利大于弊；证据质量：中等；推荐强度：强）*推荐3.4*对于有禁忌症而无法使用铂类药物化疗的鼻咽癌患者，可使用氟嘧啶类药物（如卡培他滨、5-氟尿嘧啶、替加氟）进行同期化疗。（类型：循证；证据质量：低；利大于弊；推荐强度：弱）***诱导化疗****推荐4.1*对于所有接受诱导化疗的鼻咽癌患者，推荐使用基于铂类药物的诱导化疗方案。如无禁忌证，可选的方案有：GP方案（吉西他滨 1000 mg/m2 d1，d8；顺铂 80 mg/m2 d1）或TPF方案（多西他赛 60-75 mg/m² d1；顺铂 60-75 mg/m² d1；5-氟尿嘧啶 每天600-750 mg/m²，持续静脉滴注 d1–5）；其他可选的方案包括PF方案（顺铂 80-100 mg/m² d1；5-氟尿嘧啶 每天800-1000 mg/m²，持续静脉滴注 d1–5），PX方案（顺铂 100 mg/m² d1；卡培他滨 每天2000 mg/m² d1-14）和TP方案（多西他赛 75 mg/m² d1；顺铂 75 mg/m² d1）。（类型：循证；证据质量：中等；利大于弊；推荐强度：强*推荐4.2*对于接受诱导化疗的鼻咽癌患者，诱导化疗推荐每3周一次，共3程或至少2程。（类型：循证；利大于弊；证据质量：中等；推荐强度：强）*推荐4.3*对于接受诱导化疗的鼻咽癌患者，推荐在最后一程诱导化疗第一天起的21-28天内开始进行同期放化疗。（类型：非正式的专家共识；证据质量：中等；利大于弊；推荐强度：中等）***辅助化疗****推荐5.1*对于所有接受辅助化疗的鼻咽癌患者，推荐使用PF方案（顺铂80mg/m2 d1 或20 mg/m2 d1-5；5-氟尿嘧啶 每天1000mg/m2持续静脉滴注d1-4 或每天800 mg/m2持续静脉滴注d1-5），每4周一次，共3程。（类型：循证；证据质量：高；利大于弊；推荐强度：强）*推荐5.2*对于所有接受辅助化疗且有禁忌症而无法使用顺铂的鼻咽癌患者，可联合使用卡铂（AUC 5）与5-氟尿嘧啶。（类型：循证；证据质量：中等；利大于弊；推荐强度：中等）*推荐 5.3* 对于所有接受辅助化疗且有禁忌症无法而使用铂类药物的鼻咽癌患者，非铂类药物在辅助化疗中的应用目前仍处于试验阶段，不推荐在临床试验之外的常规临床实践中使用。（类型：循证；证据质量：中等；弊大于利；推荐强度：强） |

**推荐**

**临床问题1**

对于II-IVA期鼻咽癌患者，推荐的放疗技术和分割模式是？

***推荐1.1***

对于所有鼻咽癌患者，推荐使用每日图像引导的调强放疗。如果无法提供调强放疗，推荐将患者转至可以实施调强放疗的机构。（类型：循证；利大于弊；证据质量：高；推荐强度：强）

***推荐1.2：***

对于所有鼻咽癌患者，序贯加量放疗或同步推量放疗均可使用。（类型：循证；利大于弊；证据质量：中等；推荐强度：中等）

***文献回顾与临床解读***

与传统的二维或三维放疗相比，调强放疗能使肿瘤细胞致死量的分布适应不规则形状，从而能够在保护邻近重要结构的同时对鼻咽癌进行高剂量照射。调强放疗在降低毒性方面的获益，如神经毒性、口干、张口困难和吞咽困难，已在三项随机对照试验80,92,95和多项meta分析中得以证明。13,29 一项随机对照试验80和数项meta分析还表明，调强放疗提高了鼻咽癌的疾病控制率和生存率。11,13,29

在高精度放疗期间应实施每日图像引导，以最大限度地减少分次放疗间的摆位误差。每日图像引导还可以在放疗期间对计划靶区（PTV）的边缘进行调整，并对几何变化和剂量变化进行监测。114-118

可以用序贯加量或同步推量技术实施调强放疗。一项纳入了209名患者的III期随机对照试验57发现这两种方法的疗效及毒性相近。前者的靶区能够适应患者的解剖变化。后者维持单一的治疗计划，更方便且节省资源。

**推荐1.3：**

对于所有鼻咽癌患者，放疗推荐的处方剂量为70Gy（分割次数33-35，单次剂量2.0-2.12 Gy）， 7周内（每天一次，每周5次）完成。可以根据肿瘤体积及其对放（化）疗的反应来调整剂量。（类型：循证；利大于弊；证据质量：高；推荐强度：强）

**文献综述与临床解释**

鼻咽癌患者的结局已明显改善。但是，鼻咽癌放疗后长期存活者常伴随较大的毒性反应。119 放疗分割次数是影响晚期毒性的主要因素之一。Intergroup 0099110和RTOG 0225试验120采用了处方剂量为70Gy、分割33-35次、每周5次、单次剂量2.0至2.12 Gy的放疗方案，展示出良好的疗效和可接受的毒性反应。由于有残留病灶的患者的预后较差，121,122 对于在调强放疗结束时MRI可检出残留病灶的患者，可以考虑加用1-2次2-4 Gy的放疗。对于反应良好的小原发灶，可以考虑稍微降低总剂量（例如66-68 Gy）。应避免使用更大的分割次数，特别是在与化疗联合使用时，因其疗效尚未得到证实，且晚期毒性可能较大。香港NPC-990296,123和NPC-050171,124试验未能证明每周放疗6次的加速分割模式的临床获益优于每周放疗5次的传统分割模式。

**推荐1.4：**

对于所有鼻咽癌患者，应仔细勾画大体肿瘤靶区（GTV）。靶区勾画应遵循共识指南，并充分利用包括图像融合在内的技术手段。推荐将MRI与CT图像融合进行靶区勾画，尤其是在观察潜在的肿瘤颅底侵犯以及排除或确认颅神经受累和/或颅内侵犯时。 （类型：共识；证据质量：中等；利大于弊；推荐强度：强）

**文献综述与临床解释**

在鼻咽癌的靶区勾画中，专家小组推荐遵循相关国际共识指南， 包括靶区和危及器官的勾画127-129以及调强放疗的计划设定。130该指南鼓励放疗科医生与放射科医生一起分析CT / MRI图像，以了解病变累及的范围以及对诱导化疗的反应（如果有使用）。

**推荐1.5：**

对于已接受诱导化疗的鼻咽癌患者，推荐将诱导化疗前后的CT模拟图像融合，以明确治疗前的病变范围。GTV推荐遵循诱导化疗前的肿瘤范围，尤其是在骨质解剖结构内的病变。 （类型：共识；证据质量：中等；利大于弊；推荐强度：中等）

**文献综述与临床解释**

根据国际共识指南128的推荐，无论诱导化疗疗效如何，应在不超过重要结构的最大耐受量的前提下对诱导化疗前的GTV给予全治疗剂量照射。这对于颅底侵犯尤为重要，因为难以充分了解骨质解剖结构内的病变范围，且该部位缺乏有效的挽救方案。 Yang等55的III期随机对照试验纳入了212例局部晚期鼻咽癌患者，比较了根据诱导化疗后的MRI勾画GTV与维持诱导化疗前GTV进行治疗的患者的疗效和毒性。诱导化疗后GTV的计划靶区（PTV）在两组中均达到70 Gy，而诱导化疗前GTV的PTV则随机分到70 Gy的A组和64 Gy的B组。两组之间的疾病控制率和生存率没有差异。 4级晚期毒性也相似，但诱导化疗前GTV接受64 Gy的患者的口干评分更高，认知功能也更好。

**推荐1.6：**

淋巴结靶区（从双侧咽后淋巴结水平至IV、V区淋巴结水平）的勾画应遵循国际共识指南。Ib区淋巴结不推荐预防性照射，除非有鼻腔前半部受累，或者II区淋巴结大于2 cm、包膜外侵或双侧受累。如果颈部没有可疑淋巴结转移，则可考虑不予未受累侧下颈部进行预防照射。（类型：共识；证据质量：中等；利大于弊；推荐强度：中等）

**文献综述与临床解释**

鼻咽癌在鼻咽粘膜内具有高度浸润性。 CTV的勾画应遵循国际共识指南，128并注意任何可能的扩散途径。为了降低治疗毒性，已有相关临床试验和回顾性队列研究对靶区的选择性照射进行了探索，例如不对IB区淋巴结或未受侵累侧下颈部进行照射。两项回顾性研究131,132表明，保留Ib区淋巴结的调强放疗是安全可行的，但以下患者除外：IIA区淋巴结≥2 cm和/或包膜外侵犯、N2期患者、或肿瘤原发灶侵犯由Ib区淋巴结作为第一站淋巴结引流的区域。不对未受侵侧下颈部进行预防性照射的安全性已在一项meta分析21、一项纳入N0患者的小型随机对照试验 76以及多项回顾性研究中得到证实。133-135

**临床问题2**

对于II-IVA期鼻咽癌患者，在放疗中加入化疗的推荐时机是？

**推荐2.1**

对于T2N0（AJCC第八版）鼻咽癌患者，不推荐常规化疗，但如果存在不良预后指标，如肿瘤体积大或EBV DNA拷贝数高，则可考虑进行化疗。（类型：循证；弊大于利；证据质量：中等；推荐强度：中等）

**推荐2.2：**

对于T1-2N1（AJCC第八版）鼻咽癌患者，特别是T2N1患者，可使用同期化疗。（类型：循证；弊大于利；证据质量：中等；推荐强度：中等）

**文献综述与临床解释**

在传统二维放疗时代，Chen等86报道的一项随机对照试验结果表明，对于II期鼻咽癌患者，与单纯放疗相比，同期放化疗能显著提高5年OS和PFS。与单纯放疗相比，加入同期化疗降低了远处转移率，但没有显著提高局部控制率。然而，值得注意的是，该研究使用的是中国1992年分期系统，根据第7版UICC / AJCC TNM分类标准，其中13％的患者将被重新分类为N2 / III期。该试验的10年长期结果与初始报告的结论一致，但提示同期放化疗所带来的生存获益主要体现在T2N1患者中。51 在调强时代，同期化疗在II期鼻咽癌中的作用尚未明确。几项主要纳入了回顾性研究的meta分析15,19,24结果表明，对II期鼻咽癌，单纯调强放疗可以达到与同期放化疗相同的治疗效果。最近，Huang等48报告了一项纳入84名II期鼻咽癌患者的II期随机试验的结果。该试验中位随访时间为75个月，他们观察到同期放化疗组的5年OS（94％vs. 100％；P = .25）和PFS（87％vs. 90％；P =.72）并没有优于单纯调强放疗。II期鼻咽癌包括三个亚组（T2N0和T1-2N1），其中N1患者发生远处转移的风险较高，136 一项正在进行的评估调强放疗联合同期化疗疗效的大型随机对照试验（CinicalTrials.gov识别号：NCT02633202）有望为该亚组的患者提供合适的治疗方法。结合其他预后因素，例如血浆EBV DNA，137,138 或可对异质性较大的II期鼻咽癌患者进行风险分层，并针对高危亚组采取最合适的化疗方案。

**推荐2.3：**

对于III-IVA期（除外T3N0）（AJCC第八版）鼻咽癌患者，推荐在同期放化疗的基础上加用诱导化疗。（类型：循证；利大于弊；证据质量：高；推荐强度：强）

**推荐2.4：**

对于III-IVA期（除外T3N0）（AJCC第八版）未接受诱导化疗的鼻咽癌患者，推荐在同期放化疗后加用辅助化疗。 （类型：循证；利大于弊；证据质量：中等；推荐强度：中等）

注解：目前尚无比较诱导化疗联合同期放化疗和同期放化疗联合辅助化疗的头对头试验，因此当下哪种化疗时机更优尚未明确。

**推荐2.5：**

对于T3N0（AJCC第八版）鼻咽癌患者，推荐使用同期放化疗。辅助化疗或诱导化疗也可使用。（类型：循证；利大于弊；证据质量：中等；推荐强度：中等）

**文献综述与临床解释**

具有里程碑意义的Intergroup 0099随机试验发现同期放化疗和辅助化疗的生存终点优于单纯放疗，从而确立了同期放化疗作为局部晚期（III-IVA期）鼻咽癌的标准疗法的地位。110随后来自流行地区的随机试验证实了在局部晚期鼻咽癌中同期放化疗加或不加辅助化疗生存获益都大于单纯放疗。62,75,78,85,98,100-102一项纳入了19项随机对照试验的个体数据（IPD）meta分析显示，同期放化疗加或不加辅助化疗可最为显著提高OS。37相比之下，辅助化疗或诱导化疗加单纯放疗并不能显着提高生存率。因此，同期放化疗被认为是局部晚期鼻咽癌治疗的核心。

值得注意的是，Intergroup 0099试验是在传统放疗时代进行的。在调强放疗时代，鼻咽癌中同期放化疗加用辅助化疗是否可给患者带来额外获益存在争议。一项III期随机试验的初步结果84显示，在局部晚期鼻咽癌中单纯同期放化疗组与同期放化疗加辅助化疗组的所有结局终点均无显着差异，长期结果63也证实了这些发现（5年OS：80％ vs. 83％，P = .35； 5年PFS：71％ vs. 75％，P = .72）。在另一项III期试验中61，104名放疗后血浆EBV DNA阳性的高危鼻咽癌患者被随机分配至观察组或吉西他滨+顺铂辅助化疗组。该研究是鼻咽癌中第一个基于生物标记物驱动的随机对照试验。其结果显示，辅助化疗无法显著提高OS与PFS（5年OS：64％ vs. 68％；P = .79；PFS：49％ vs. 55％；P = .75）。几项meta分析23,30,139,140的结果显示，尽管同期放化疗加辅助化疗组可观察到有潜在的获益趋势，但同期放化疗加用辅助化疗后患者的生存结局并没有得到显著改善。患者对根治性放疗后辅助化疗的耐受性相对较差，通常只有50–76％的患者完成了规定的辅助化疗疗程，61,84,91,96,98,99,110这可能解释了为什么辅助化疗较难带来额外的生存获益。

与辅助化疗相比，诱导化疗具有许多潜在的优势，例如，及早缓解患者症状，消除微小转移灶，以及更好的顺应性等2,44。然而，早期比较同期放化疗加或不加诱导化疗的随机试验69,83,89的结果并不一致，这可能是因为使用了不同的诱导方案或样本量不足所导致的。近年来，来自广州的三项大型多中心随机对照试验 49,50,52,64,66陆续在国际上发表。这些研究分别使用了多西他赛、顺铂和5-氟尿嘧啶（TPF）52,66、顺铂加5-氟尿嘧啶（PF）50,64、以及吉西他滨加顺铂（GP）49的诱导化疗方案。这些研究证实了诱导化疗联合同期放化疗在OS、PFS和无远处转移生存方面的优势。52,66对来自流行地区的四项试验的IPD合并分析50,52,64,66,69,89证实诱导化疗加同期放化疗可以显着改善OS（危险比[HR]为0.75； 95％置信区间[CI]为0.57至0.99； 5年绝对获益为6％）和PFS（HR为0.70； 95％CI为0.56至0.86； 5年绝对获益为9％），而生存获益主要来自远处转移的降低。一项来自突尼斯和法国的小型随机试验纳入了83名局部晚期鼻咽癌，结果表明TPF诱导化疗能显著提高PFS和OS。60因此，除了同期放化疗，诱导化疗在调强放疗时代局部晚期鼻咽癌的治疗中也起着重要的作用，主要是通过提高远处转移控制率来提高生存获益。

不过，应该指出的是，大多数评估同期放化疗加诱导化疗的试验都是在流行地区进行的；诱导化疗在非流行地区鼻咽癌患者中的适用性需要进一步研究。此外，由于缺乏直接比较这两种方法的前瞻性随机试验的数据，目前尚不确定哪种化疗顺序，即诱导-同期或同期-辅助，在当下效果更好。仅对以同期放化疗为对照的临床试验进行推断性比较，诱导化疗在减少远处转移方面似乎优于辅助化疗。未来还需要进行比较诱导化疗加同期放化疗和同期放化疗加辅助化疗的头对头随机试验。

与其他局部晚期的患者相比，T3N0 鼻咽癌患者治疗失败的风险相对较低。138因此，一些研究在同期放化疗基础上增加辅助化疗63,84或诱导化疗的随机对照试验中，这一亚组被排除了。49,50,52,64,66 考虑到缺乏随机试验的数据，专家组推荐对T3N0患者要慎重权衡在同期放化疗的基础上加用辅助化疗或诱导化疗的利弊 。

**临床问题3**

对于接受同期化疗的鼻咽癌患者，推荐的化疗方案是？

**推荐3.1：**

对于没有相关禁忌症的鼻咽癌患者，推荐在放疗的同时使用每周（40 mg/m²）或每三周（100 mg/m² 或至少 80 mg/m²）方案的顺铂化疗。（类型：循证；证据质量：高；利大于弊；推荐强度：强）

**推荐3.2：**

对于没有相关禁忌症的鼻咽癌患者，推荐使用3程每三周方案或7程每周方案的同期顺铂化疗，顺铂的累积剂量至少要达到200 mg/m²。（类型：非正式的专家共识；利大于弊；证据质量：中等；推荐强度：中等）

**推荐3.3：**

对于有禁忌症而无法使用顺铂化疗的鼻咽癌患者，同期化疗可使用奈达铂（100 mg/m2，每三周一次）代替。可选的其他药物包括卡铂（曲线下面积 [AUC] 5-6，每三周一次）或奥沙利铂（70 mg/m2，每周一次）。（类型：循证 ；利大于弊；证据质量：中等；推荐强度：强）

**推荐3.4：**

对于有禁忌症而无法使用铂类药物化疗的鼻咽癌患者，可使用氟嘧啶类药物（如卡培他滨、5-氟尿嘧啶、替加氟）进行同期化疗。（类型：循证；证据质量：低；利大于弊；推荐强度：弱）

**文献回顾和临床意义**

根据之前比较同期放化疗加或不加辅助化疗与单纯放疗62,78,86,98,100,110的疗效的Ⅲ期临床试验，我们推荐在放疗的同时使用顺铂100 mg/m2每三周一次或40 mg/m2每周一次的化疗。这些试验证实了在局部晚期鼻咽癌中同期放化疗优于单纯放疗。值得注意的是，三项试验62,98,110使用了每三周一次的化疗方案；两项试验78,100使用了每周一次的化疗方案；还有一项由Chen等人开展的试验86使用了7程30 mg/m2每周一次的方案。已有头对头的临床试验对三周和每周方案进行了比较。由Lee等人报道的一项Ⅱ期小型随机对照试验67发现，两种方案的疗效和毒性无显著差别，每周方案似乎更有利于提高患者的生活质量。一项纳入526例局部晚期鼻咽癌患者的大型Ⅲ期随机对照试验正在进行中（ChiCTR-TRC-12001979）。初步结果显示，两种方案的生存结局未见差异，但是与每三周一次（100 mg/m2 x 2）的方案相比，每周一次（40 mg/m2 x 6）的方案中白细胞减少（27.3% vs 16.2%）和血小板减少（4.8% vs 1.2%）的发生率更高。142该研究的最终结果将有助于全面评估不同的给药方案。值得注意的是，每三周一次的方案中顺铂的累积剂量（200 mg/m2）低于每周一次的方案（240 mg/m2）。

现有证据提示，对于疗效而言，顺铂的累积剂量的作用比给药方案更为重要。在这一方面，目前尚无1级证据来指导同期顺铂化疗的最佳剂量强度，尽管一些Ⅲ期临床试验的探索性分析提示，顺铂的累积剂量不应低于200 mg/m2以保证疗效。17,123,143如果在诱导化疗后再进行同期化疗，回顾性分析显示所需要的顺铂累积剂量可能为160 mg/m2即可。144-146对于有禁忌症而无法使用顺铂化疗的患者，可选的其他同期化疗药物包括卡铂（曲线下面积 [AUC] 5-6）87,94,147、奥沙利铂（70 mg/m2，每周一次）97和奈达铂（100 mg/m2，每三周一次）56。有禁忌症无法使用铂类药物化疗的患者可选择氟嘧啶类药物如优福定101等进行同期化疗。

**临床问题4**

对于接受诱导化疗的鼻咽癌患者，推荐的化疗方案是？

**推荐4.1：**

对于所有接受诱导化疗的鼻咽癌患者，推荐使用基于铂类药物的诱导化疗方案。如无禁忌证，可选的方案有：GP方案（吉西他滨 1000 mg/m2 d1，d8；顺铂 80 mg/m2 d1）或TPF方案（多西他赛 60-75 mg/m² d1；顺铂 60-75 mg/m² d1；5-氟尿嘧啶 每天600-750 mg/m²，持续静脉滴注 d1–5）；其他可选的方案包括PF方案（顺铂 80-100 mg/m² d1；5-氟尿嘧啶 每天800-1000 mg/m²，持续静脉滴注 d1–5），PX方案（顺铂 100 mg/m² d1；卡培他滨 每天2000 mg/m² d1-14）和TP方案（多西他赛 75 mg/m² d1；顺铂 75 mg/m² d1）。（类型：循证；证据质量：中等；利大于弊；推荐强度：强）

**文献回顾和临床意义**

2009年发表的一项Ⅱ期随机试验89首次报道在同期放化疗之前加用两个疗程多西他赛（75 mg/m2）加顺铂（75 mg/m2）诱导化疗可将鼻咽癌患者的3年OS从68%提高到94%（HR：0.24；95% CI：0.08–0.73）。随后，两个大型Ⅲ期随机对照试验49,52,66 分别评估了TPF方案（多西他赛60 mg/m2、顺铂60 mg/m2和 5-氟尿嘧啶每天600 mg/m2 ，持续静脉滴注120小时；每3周一次，共3程）和GP方案（吉西他滨 1000mg/m2 d1, d8，顺铂80 mg/m2 ；每3周一次，共3程）在局部晚期鼻咽癌患者（T3-4N0除外）中的疗效。在TPF试验52,66中，与单纯同期放化疗组相比，诱导化疗加同期放化疗组的5年OS（HR：0.65；95% CI：0.43-0.98）、PFS（HR：0.65；95% CI：0.43-0.98）、无远处复发生存率（HR：0.60；95% CI：0.38-0.95）和无局部复发生存率（HR：0.58；95% CI：0.34-0.99）均得到显著提高。尽管各种药物的剂量与另一项试验（多西他赛75 mg/m2，顺铂75 mg/m2，和 5-氟尿嘧啶 每天750 mg/m2 ，持续静脉滴注120小时）60相比已降低20%，3-4度毒性反应如中性粒细胞减少（35%），白细胞减少（27%）和腹泻（8%）的发生率较高。在另一项使用GP诱导化疗方案的试验中，49 患者的3年OS（HR：0.43；95% CI，0.24-0.77）、PFS（HR：0.51； 95% CI：0.34-0.77）和无远处转移生存（HR：0.43；95% CI：0.25-0.73）均得到提高。患者对GP方案的耐受性相对较好，3-4度的中性粒细胞减少、白细胞减少和腹泻的发病率分别为21%、11%和0.4%。其他推荐的诱导化疗方案包括PF方案（顺铂80-100mg/m2，5-氟尿嘧啶 每天800-1000 mg/m2 ，持续静脉滴注120小时）和顺铂+卡培他滨方案（PX方案；顺铂100 mg/m2，卡培他滨每天2000 mg/m2，持续给药14天）。47,50,64,71

目前尚无直接比较不同诱导化疗方案的随机对照研究。最近一项纳入278例局部晚期鼻咽癌患者的非劣效性试验显示，TPF方案和PF方案的疗效相近。148一项IPD meta分析中的间接比较发现TPF、TP和PF等不同诱导化疗方案无显著差异。22而另一项纳入28项试验8214例患者的IPD网状meta分析显示，尽管未发现显著差异，但含紫杉类药物的诱导化疗方案的OS可能优于不含紫杉烷类药物的诱导化疗方案。149因此，诱导化疗方案可以视患者的情况来选择。目前有临床试验正在评估诱导化疗中用洛铂或奈达铂等其他铂类药物替代顺铂或者用卡培他滨替代5-氟尿嘧啶是否可以在保证非劣效性的同时改善患者的生存质量（ChiCTR-TRC-13003285，NCT03503136）。

**推荐4.2：**

对于接受诱导化疗的鼻咽癌患者，诱导化疗推荐每3周一次，共3程或至少2程。（类型：循证；利大于弊；证据质量：中等；推荐强度：强）

**推荐4.3：**

对于接受诱导化疗的鼻咽癌患者，推荐在最后一程诱导化疗第一天起的21-28天内开始进行同期放化疗。（类型：非正式的专家共识；证据质量：中等；利大于弊；推荐强度：中等）

**文献回顾和临床意义**

尽管目前还没有随机试验直接比较不同疗程数的疗效差异，我们推荐进行2-3程的诱导化疗。一项回顾性分析显示在2程诱导化疗后增加诱导化疗的疗程数并不能改善鼻咽癌患者的结局。47诱导化疗过程中监测EBV DNA的水平能实时反映肿瘤对化疗的反应性以调整治疗方案，48但仍需更多前瞻性的研究来证实。考虑到目前尚缺乏评估诱导化疗和放疗之间的治疗间隔对鼻咽癌患者生存的影响的前瞻性研究，专家组推荐患者在最后一程诱导化疗第一天起的3-4周内开始进行放化疗以降低治疗失败的风险。49

**临床问题5**

对于接受辅助化疗的鼻咽癌患者，推荐的化疗方案是？

**推荐5.1：**

对于所有接受辅助化疗的鼻咽癌患者，推荐使用PF方案（顺铂80mg/m2 d1 或20 mg/m2 d1-5；5-氟尿嘧啶 每天1000mg/m2持续静脉滴注d1-4 或每天800 mg/m2持续静脉滴注d1-5），每4周一次，共3程。（类型：循证；证据质量：高；利大于弊；推荐强度：强）

**文献回顾和临床意义**

Intergroup研究的结果确定了PF方案（顺铂80mg/m2 d1；5-氟尿嘧啶 每天1000mg/m2 d1-4，持续静脉滴注96小时，每4周一次）作为辅助化疗的标准方案。110在不改变剂量强度的前提下，PF方案中的给药方案可以有小范围调整：新加坡小组把80mg/m2的顺铂分成连续4天（d1-4）给药，每天20mg/m2；2而广州小组把5-氟尿嘧啶由每天1000mg/m2持续静脉滴注4天改为每天800mg/m2持续静脉滴注5天。78,84值得一提的是，头颈肿瘤的新辅助化疗中PF方案最初设定的是顺铂100mg/m2 d1和5-氟尿嘧啶 每天1000mg/m2 d1-d5，持续静脉滴注120小时，每3周一次。150考虑到鼻咽癌患者根治性同期放化疗后对辅助化疗的耐受性差，在上述所有试验中研究者都对PF方案进行了调整，不仅将两药剂量强度减少了20%，也将给药方案从每3周一次调整至每4周一次。尽管做出了这些改变，Intergroup研究中只有55%的患者能按计划完成3程辅助化疗，110在其他试验中辅助化疗的完成率则为46%-78%。62,71,78,84,85,98,120研究者对香港NPC-9901试验和NPC-9902试验中共441名局部晚期鼻咽癌患者进行合并分析，发现辅助化疗过程中5-氟尿嘧啶的总剂量与无远处转移生存率显著相关。151

**推荐5.2：**

对于所有接受辅助化疗且有禁忌症无法而使用顺铂的鼻咽癌患者，可联合使用卡铂（AUC 5）与5-氟尿嘧啶。（类型：循证；证据质量：中等；利大于弊；推荐强度：中等）

**文献回顾和临床意义**

如果有禁忌症无法使用顺铂，可用卡铂替代顺铂。94,152 一项单中心非劣效性随机试验在206例鼻咽癌患者中比较了Intergroup方案与同期卡铂100 mg/m2化疗后辅助卡铂（AUC 5，静脉注射）+5-氟尿嘧啶（每天1000mg/m2 持续静脉滴注96小时）的方案。使用顺铂的患者中42%完成了3程的辅助化疗，而使用卡铂的患者中73%完成了辅助化疗。两组生存结局相似；顺铂组的肾毒性、白细胞减少和贫血发生率更高，而卡铂组血小板减少的发生率更高。该小组还进行了一项多中心随机试验，在175例T2N0-T4N2M0（UICC/AJCC第七版）鼻咽癌患者中比较了卡铂同期放化疗与卡铂同期放化疗加卡铂与5-氟尿嘧啶辅助化疗。152结果表明加用卡铂和5-氟尿嘧啶辅助化疗可显著提高患者2年无瘤生存率。

**推荐 5.3:**

对于所有接受辅助化疗且有禁忌症无法而使用铂类药物的鼻咽癌患者，非铂类药物在辅助化疗中的应用目前仍处于试验阶段，不推荐在临床试验之外的常规临床实践中使用。（类型：循证；证据质量：中等；弊大于利；推荐强度：强）

**文献回顾和临床意义**

如上所述，辅助化疗的主要缺点是耐受性较差，节拍化疗是指长期以极低剂量定期进行化疗。160-163节拍化疗的高顺应性和低毒性使得该策略成为鼻咽癌患者完成根治性同期放化疗后辅助化疗的一个有吸引力的选择。164一些回顾性研究表明口服氟尿嘧啶药物节拍化疗作为辅助化疗能显著提高OS。一项研究卡培他滨节拍辅助化疗的3期试验已经完成入组（NCT02958111），可为解答这一问题提供重要证据。

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