Guideline Resource Unit
guru@ahs.ca

Nasopharyngeal Cancer Treatment

Effective Date: March, 2021

Cancer Care Alberta

Clinical Practice Guideline HN-003 – Version 2
www.ahs.ca/guru

Background

The most recent Canadian cancer statistics suggest approximately 250 new cases of nasopharyngeal cancer (NPC) are identified in Canada each year, resulting in 90 deaths.[1] NPC arises from the lining of the nasopharynx, the narrow tubular passage behind the nasal cavity and although rare in North America, is common in Southern China, Southeast Asia, North Africa and the Arctic. Risk factors for NPC include, race (Asian, African or Inuit ancestry), sex (male), diet (salt-cured foods) and exposure to the Epstein-Barr virus. Some studies have reported that tobacco use may contribute to the development of NPC, however, this link is much weaker than the link between tobacco use and most other types of head and neck cancers.

Three types of NPC have been classified by the World Health Organization including, keratinizing squamous cell carcinoma, non-keratinizing differentiated carcinoma and undifferentiated carcinoma. In North America, as in endemic region, the undifferentiated subtype type is the most common [2]. Although the different types of NPC exist, the treatment is usually the same and the stage of cancer is more important in predicting a person's prognosis than the type. NPC is staged according to the tumour node metastasis (TNM) system. For more information on the TNM classifications, along with anatomic stage/prognostic groups, please refer to Appendix A.

NPC is commonly treated with radiotherapy (RT) and chemotherapy. Surgery at the primary site is not often used as first-line treatment because of the anatomical location of the nasopharynx and its proximity to critical neurovascular structures.

This guideline was developed to outline treatment recommendations for patients with NPC. These guidelines should be applied in the context of the recommendations outlined in Alberta Health Services, CancerControl Alberta guideline, The Organization and Delivery of Healthcare Services for Head and Neck Cancer Patients.

The 8th edition of the AJCC staging system has been used for this guideline.

Guideline Questions

1. What diagnostic and baseline investigations are recommended for patients with suspected or confirmed NPC?
2. What are the recommended treatment options for NPC?
3. What is the recommended follow-up after treatment for NPC?

Search Strategy

PubMED, MEDLINE and Cochrane Database of Systematic Reviews were searched from 2000 to May, 2020 for literature on the treatment of NPC. The search term *nasopharyngeal neoplasm* (MeSH) was used. Results were limited to phase III clinical trials, comparative studies, controlled clinical trials, guidelines, meta-analyses, multicenter studies, practice guidelines, randomized controlled trials and

systematic reviews involving human subjects (19+ years) and published in English. Although phase II studies may be referenced in the discussion section, only phase III randomized studies and meta-analyses were considered for the literature search and review.

The ECRI Guidelines Trust® and SAGE Directory of Cancer Guidelines were also searched from 2008 to May 2020 for guidelines on nasopharyngeal cancer.

Target Population

The recommendations outlined in this guideline are intended for adults over the age of 18 years with NPC. Different principles may apply to pediatric patients.

Recommendations

The Alberta Provincial Head and Neck Tumour Team reviewed the recommendations of several different guidelines, including those from the European Society for Medical Oncology,[3] the Spanish Society of Medical Oncology[4] and the National Comprehensive Cancer Network.[5] The Alberta Provincial Head and Neck Tumour Team have adopted the recommendations of the ESMO and NCCN, with modifications to fit the Alberta context.

1. **Diagnosis and baseline investigations.** The following investigations are recommended at diagnosis for all patients with suspected or confirmed early stage NPC: (adapted from ESMO 2012)[3] *(ESMO rating, Level of Evidence: III Strength of Recommendation: B)*

    - Complete head and neck examination
    - Nasopharyngeal exam and biopsy
    - Chest imaging
    - Magnetic resonance imaging (MRI) with gadolinium of nasopharynx and base of skull to clavicles and/or computed tomography (CT) with contrast
    - CT, Positron emission tomography-computed tomography (PET-CT), and/or bone scan to rule out distant disease as indicated (i.e. for advanced stage or for clinical/biochemical concerns).
    - Examination under anesthesia with endoscopy, as indicated
    - Dental evaluation
    - Nutrition, speech and swallowing assessment/therapy and audiogram

2. **Treatment options.** Patient participation in clinical trials is recommended. For standard treatment, all cases should be presented and discussed at a multidisciplinary Tumour Board to decide the best treatment option for each patient.

Early-stage (T1, N0, M0): Definitive RT to the nasopharynx and elective RT to the neck is recommended. (*Level of Evidence: II, Strength of Recommendation: B)*[3-5,14,15]

- Primary**:**
  - Total dose: 66–70 Gy
  - Conventional fraction dose: 2.0–2.2 Gy
  - Daily Monday-Friday in 6–7 weeks
- Neck**:**
  - Uninvolved nodal stations: 54–60 Gy
  - Conventional fraction dose: 1.6–2.0 Gy

Intensity-modulated radiation therapy (IMRT) should be used to reduce critical structure doses to acceptable levels.

Advanced-stage (T1, N1–3; T2–4, Any N, M0): Concurrent chemoradiotherapy (chemoRT) with cisplatin is recommended. Adjuvant chemotherapy using platinum (cisplatin or carboplatin)/5-fluoruracil (5-FU) remains the current standard of care [6]. Data regarding substitution of induction chemotherapy for adjuvant therapy is evolving with promising reports [7-10] although there remains insufficient evidence to adopt as standard of care but could be considered in select situations (i.e. for very advanced cancers for which radical RT not feasible due to dosing constraints). The choice of chemotherapy should be individualized based on patient characteristics (i.e. performance status, comorbidities etc.). Where there is clinical evidence of residual disease in the neck, neck dissection is recommended, if feasible. *(Level of Evidence: I, Strength of Recommendation: A)*[6-10]

Distant metastatic disease (Any T, Any N, M1): All treatment of patients with distant metastatic disease is palliative in nature. If available, patients should consider participating in a clinical trial. Palliative RT can be considered in select cases. In patients with good performance status, palliative chemotherapy may be considered. Referral to palliative care services can be offered to patients. *(Level of Evidence: III, Strength of Recommendation: B)* [3,11,]

Recurrent or persistent disease: Restaging should be done to assess local, regional and distant disease. Biopsy of recurrent lesion(s) is recommended, as clinically indicated. Treatment should be individualized based on patient performance status and extent of disease.

Treatment options include:

- Salvage nasopharyngectomy, or
- Re-irradiation with brachytherapy, and/or
- Stereotactic guided treatments

3. **Follow-up and surveillance:** The following schedule should be taken into account to manage complications related to treatment, to detect disease recurrence and/or the development of

new disease: (adapted from NCCN and ESMO 2012) *(Level of Evidence: II, Strength of Recommendation: B)* [3-5]

- Head and neck examination (note that the ranges are based on risk of relapse, second primaries, treatment sequelae, and toxicities):
    - Year 1, every 1 to 3 months
    - Year 2, every 2 to 6 months
    - Year 3–5, every 4 to 8 months
    - After 5 years, annually, as clinically indicated
- Post-treatment baseline imaging of primary and neck, if treated, within 6 months of treatment for T3–4 or N2–3 disease only; further reimaging, as indicated
- Annual thyroid-stimulating hormone (TSH) screening up to 5 years
- Speech/swallowing assessment and rehabilitation, as clinically indicated
- Hearing evaluation and rehabilitation, as clinically indicated
- Follow-up with a registered dietitian to evaluate nutritional status and until the patient achieves a nutritionally stable baseline
- Routine hospital-based dental follow-up and evaluation up to 3 years

Discussion

Initial Work-Up and Supportive Care Evaluation

NPC is most often diagnosed when an individual goes to their physician with a lump in the neck. A complete head and neck examination is required to begin to diagnose NPC. Attention should be paid to the most common presenting symptoms including a neck mass, cervical lymphadenopathy and bilateral involvement. Epistaxis (nasal bleeding), nasal congestion, hearing loss, otitis media (middle ear infection) and headaches are also common symptoms. For individuals with suspected NPC, a more thorough examination of the nasopharynx by a specialist is needed. The diagnosis of NPC can only be confirmed with a tissue biopsy. Imaging studies using MRI with gadolinium and/or CT with contrast of the head and neck areas should be considered to evaluate the local and regional extent of disease. Consideration should be given to assess for metastatic disease (i.e. CT, bone scan, PET/CT etc.) based on extent of presenting disease and clinical/biochemical concerns. Dental evaluation is required in all patients who require radiation treatment, prior to the commencement of treatment to assess, restore or extract decayed teeth. Finally, nutritional counselling, speech and swallowing assessment/therapy and audiogram are critical to optimize quality of life during and after treatment. Patients should have access to Speech-Language Pathology during and after treatment, as clinically indicated.

Treatment for Patients with Early-Stage NPC (T1, N0, M0)

For patients with early stage NPC, optimal outcomes can be expected employing RT alone. Guidelines published by the European Society for Clinical Oncology (ESMO),[3] National

Comprehensive Cancer Network (NCCN)[5] and the Spanish Society of Medical Oncology (SEOM)[4] support this recommendation. Evidence suggests that the overall survival (OS) rate for patients with early stage NPC is approximately 80 percent to 90 percent with RT alone.[12] Although a survival benefit for chemoRT over RT alone was suggested in a subgroup analysis of two phase III trials,[13] patients with early stage NPC have largely been excluded from clinical trials using combined modality treatment, likely given the good treatment outcome after RT alone.

The consensus from the Alberta Provincial Head and Neck Tumour Team is that radiation doses of 66–70 Gy with 2.0–2.2 Gy/fraction over 6 to 7 weeks (daily, Monday to Friday) is needed for primary tumour treatment. For uninvolved nodal stations, a total dose of 54–60 Gy with 1.6–2.0 Gy/fraction is needed. Two randomized studies have shown that IMRT is superior to conventional RT techniques in preserving parotid function and resulted in less severe late xerostomia (dry mouth) without affecting local control in patients with early stage NPC.[14-15]

Treatment for Patients with Advanced-Stage NPC (T1, N1–3; T2–4 , Any N)

Although patients with Stage I (so called early-stage NPC) have good outcomes with RT alone, more intensive treatment strategies are recommended to manage advanced-stage disease; RT alone for advanced-stage disease should be limited to individuals who would not be candidates for systemic therapy.

Stage II (intermediate risk): While SEOM[3] recommends RT alone for stage II (so called intermediate-stage NPC), both ESMO[3] and NCCN[5] recommend concurrent chemotherapy. In a randomized phase III trial, 230 patients with stage II NPC were randomly assigned to RT or concurrent chemoRT without adjuvant chemotherapy. Results showed that the addition of weekly cisplatin to RT significantly improved the 5-year OS rate (from 85.8 percent to 94.5 percent), progression-free survival (PFS) (from 77.8 percent to 87.9 percent) and distant metastasis-free survival (from 83.9 percent to 94.8 percent)[12]. However the concurrent chemoRT arm experienced significantly more acute toxic effects, including leukopenia/neutropenia, nausea/vomiting and mucositis. Late toxic effects were similar between the two groups. Although this trial suggests a benefit from a concurrent chemoRT approach for stage II NPC patient, further randomized trials are warranted.

Stage III/IV (high risk). ESMO, NCCN and SEOM all recommend concurrent chemoRT in patients with stage III and IV A-B NPC. The updated MAC-NPC meta-analysis by *Blanchard et al.* of chemotherapy as an adjunct to RT in locally advanced NPC (n=4806) found that the addition of chemotherapy to standard RT provides a small but significant survival benefit in patients with NPC [6]. The pooled hazard ratio (HR) of death was 0.79 (95 percent confidence interval [CI] 0.73-0.86, p=0.006) corresponding to an absolute benefit of 6.3 percent at five years from chemotherapy compared to radiotherapy alone. A significant interaction was observed between chemotherapy timing and OS, with the highest benefit derived from concomitant chemotherapy with adjuvant chemotherapy (12.4% absolute difference (CI 6.8-18%).

Adjuvant chemotherapy following concurrent chemoRT. Several randomized phase III trials have investigated the efficacy of concurrent chemoRT with[16-19] or without [20] adjuvant chemotherapy. ChemoRT followed by adjuvant chemotherapy has been shown to increase overall survival and decrease local, regional and distant recurrence rates without a substantial increase in local toxicity.

In the landmark phase III randomized Intergroup study 099, 147 patients with stage III and IV NPC were treated with either chemoRT followed by adjuvant chemotherapy or RT alone. The study was closed and reported on early because the hazard ratio (HR) between the RT and combined arm was 3.28. The 3-year OS estimate for the combination arm was 76 percent versus 46 percent for the RT arm ($p<0.001$). The 3-year PFS estimate for the combination arm was 66 percent versus 26 percent for the RT arm ($p<0.001$). The chemotherapy regimen used in the Intergroup study is generally considered the standard. In the study, the investigational arm received chemotherapy with cisplatin (100 mg/m^2) on days 1, 22 and 43 during RT. Following RT, chemotherapy with cisplatin (80 mg/m^2 on day 1) and fluorouracil (5-FU) (1,000 mg/m^2/d on days 1 to 4) was administered every 4 weeks for three cycles.[16] Alternative regimens that are easier to administer than cisplatin have also been investigated. In a prospective, randomized, non-inferiority, open trial comparing concurrent chemoRT with carboplatin to concurrent chemoRT with cisplatin in patients with locally advanced NPC (n=206), the toxicity and tolerability of the cisplatin containing regimen limited the number of patients who managed to complete the full course of treatment. In addition, there was no difference in terms of disease-free survival (DFS) and OS between the two regimens.[21]

In a more recent phase III trial, patients with non-metastatic stage III or IV NPC were randomly assigned to concurrent chemoRT plus adjuvant chemotherapy or concurrent chemoRT alone (n=508).[22] Patients in both arms received cisplatin weekly (40 mg/m^2) up to 7 weeks with radiotherapy. The concurrent chemoRT plus adjuvant chemotherapy arm subsequently received adjuvant cisplatin (80 mg/m²) and 5-FU (800 mg/m² per day) every 4 weeks for 3 cycles. After a median follow-up of 37.8 months, the estimated 2-year failure-free survival rate was 86 percent in the concurrent chemoRT plus adjuvant chemotherapy arm versus 84 percent in the concurrent chemoRT only group (HR=0.74, 95% CI 0.49–1.10, p=0.13). However, several limitations are noteworthy including a short follow-up period, the exclusion of T3–4N0 patients and the variability of RT techniques used.

Two meta-analyses involving over ten randomized trials of more than 2,500 patients with advanced NPC reported an absolute benefit on OS of 4–6 percent at 5 years with the use of chemotherapy. However, the survival benefit of the addition of chemotherapy was noted when chemotherapy was given concomitantly with radiotherapy.[6]

In summary, the evidence suggests that concurrent chemoRT should be considered for all advanced-stage patients; the addition of adjuvant chemotherapy should be based on the clinician's judgment, the patient's performance status and goals of therapy.

Neoadjuvant (induction) chemotherapy. Neoadjuvant chemotherapy alone prior to RT (i.e., without concurrent chemotherapy) is not routinely indicated for definitive treatment of locally advanced NPC

when followed by RT. While the NCCN shows induction chemotherapy followed by chemoRT as a treatment option, there is major disagreement.[5] Trials of neoadjuvant chemotherapy in patients with locoregionally advanced NPC followed by RT alone have failed to show significant survival benefits compared to RT alone.[23-25] To evaluate the long-term outcome in patients with NPC treated with induction chemotherapy and RT versus RT alone, Chua et al. conducted a pooled data analysis of two phase III trials (n=784).[26] Although the addition of cisplatin-based induction chemotherapy to RT was associated with a decrease in relapse by 14.3 percent and cancer-related deaths by 12.9 percent at 5 years, there was no improvement in OS (61.9 percent vs. 58.1 percent, p=0.092) because of more frequent late intercurrent deaths in the induction chemotherapy and radiotherapy arm.

Another treatment option under study is sequential therapy with the administration of induction chemotherapy followed by concurrent chemoRT. Preliminary results from several recent phase III studies [7-10] have revealed promising improvements over chemoRT alone although no study to date has compared this strategy to chemoRT followed by adjuvant chemotherapy. There remains concern regarding toxicity from induction chemotherapy precluding pursuit of chemoRT (which remains the main contribution of benefit) in a significant proportion of individuals. Although there remains insufficient evidence to adopt as standard of care, this sequencing could be considered in select situations (i.e. for very advanced cancers for which radical RT not feasible due to dosing constraints).

Alternative RT schedules. Recent advances in radiobiology have allowed changes to conventional treatment modalities with the intention of achieving better locoregional control without increasing long-term toxicity. Increasing evidence exists that outcomes in head and neck squamous cell cancer may benefit from alternative fractionation schedules, including hyperfractionation and accelerated fractionation regimens. [27,28] A phase III trial randomized 189 patients with T3–4, N0–1, M0 NPC to one of four arms, accelerated versus conventional RT, with or without adjuvant chemotherapy.[29] All groups were given 2 Gy per fraction; the number of fractions per week was 5 in the conventional arms versus 6 in the accelerated arms. Patients assigned to chemoRT arms received concurrent cisplatin (100 mg/m^2) every 3 weeks for 3 cycles followed by adjuvant cisplatin (80 mg/m^2) plus 5-FU (1000 mg/m^2/day) every 4 weeks for 3 cycles. The accelerated-fractionation RT plus concurrent-adjuvant chemotherapy arm achieved a significantly higher failure-free rate (88 percent at 5 years) than accelerated fractionation without chemotherapy (56 percent, p=0.001), or conventional fractionation with (65 percent, p=0.027) or without chemotherapy (63 percent, p=0.013). As compared with the conventional-fractionation RT alone arm, the increase in late toxicity was statistically insignificant (36 percent vs. 20 percent, p=0.25). Despite the favourable results, the authors note patients should be duly informed that the use of accelerated fractionation with chemotherapy currently remains experimental and vigilant follow-up is required if this therapy is selected.

Treatment for Patients with Distant Metastatic Disease (Any T, Any N, M1)

Treatment failures in patients with locally advanced NPC are mainly distant metastasis, which develop in approximately 20 percent of patients.[30] For patients with distant metastasis, treatment is palliative in nature. RT can be administered to palliate symptoms. Participation in a clinical trial, if

available, is the preferred treatment option. In metastatic NPC patients with good performance status, cisplatin-containing regimens are accepted as the standard with cis/gem preferred given advantages seen when compared to Cis/FU.[11],[31-33] Other active agents include taxanes, gemcitabine, oxaliplatin, vinorelbine, irinotecan, capecitabine, methotrexate and anthracyclines. Targeted therapies (cetuximab, sorafenib, erotinib, gefitinib) and immunotherapies have been studied, but their role is currently investigational.[34] Referral to palliative care programs should be considered early on in the patient's care to help relieve suffering and improve quality of life. Speech-Language Pathologists should participate in the palliation of dysphagia. Clinical and instrumental assessment can be provided as necessary. Management of aspiration should take into account patient's wishes and informed choice, as well as their tolerance of aspiration.

Treatment for Patients with Recurrent or Persistent Disease

Patients with recurrent or persistent NPC should be restaged after primary treatment to assess local, regional and distant disease. PET can detect head and neck tumour recurrence when it may be undetectable by other clinical methods.[35] As clinically indicated a confirmatory needle biopsy of the area in question is recommended. Treatment should be individualized based on patient performance status and extent of disease. According to *Lee et al*.[36], treatment options include salvage nasopharyngectomy, or re-irradiation with brachytherapy, and/or stereotactic guided treatments.

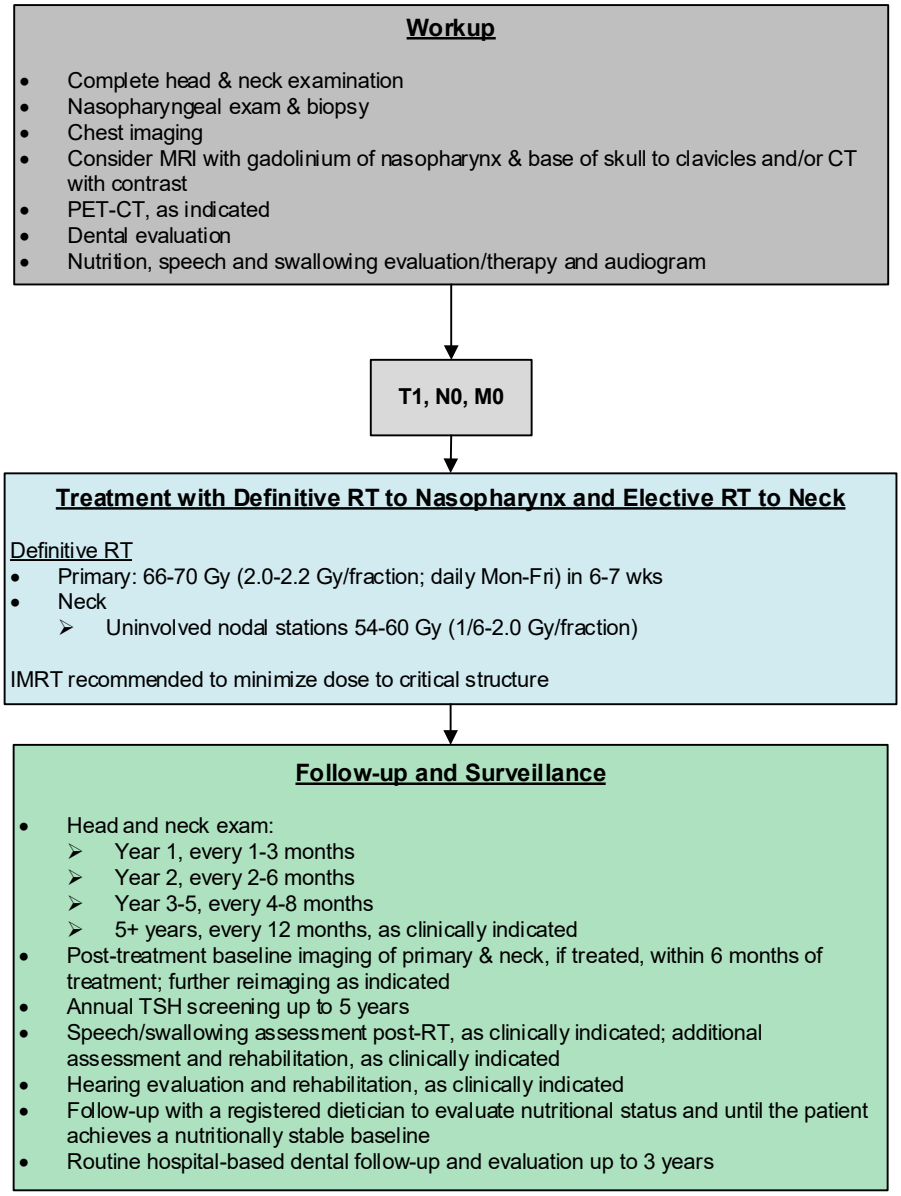
Follow-up and Surveillance

Similar to NCCN recommendations [5], in Alberta the follow-up of patients with NPC is recommended every 1 to 3 months in the first year after treatment, every 2 to 6 months in the second year, every 4 to 8 months in years 3 to 5 and then only yearly, as clinically indicated, in the period five years after treatment. Surveillance of TSH is recommended annually for up to 5 years. Additionally, speech/hearing and swallowing evaluation and rehabilitation are suggested, as clinically indicated. Follow-up with a registered dietitian to evaluate nutritional status and until the patient achieves a nutritionally stable baseline is recommended due to common weight loss in NPC patients. Finally, routine hospital-based dental follow-up and evaluation is recommended annually up to 3 years.

Treatment Algorithm

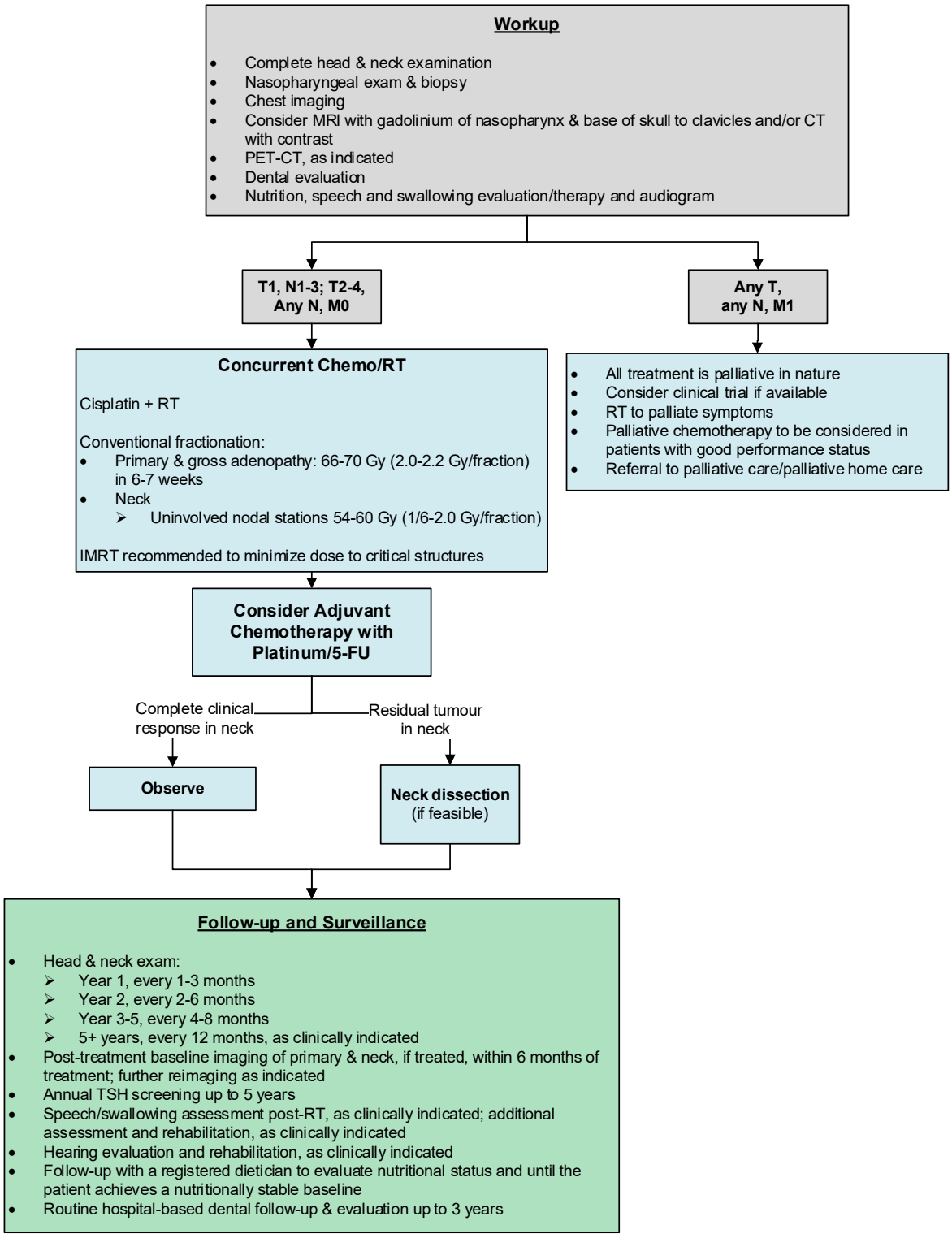
Early-Stage (T1, N0, M0)

The Head and Neck Tumour Team encourages patient participation in clinical trials.
In addition, all patient cases should be presented and discussed at a multidisciplinary Tumour Board.



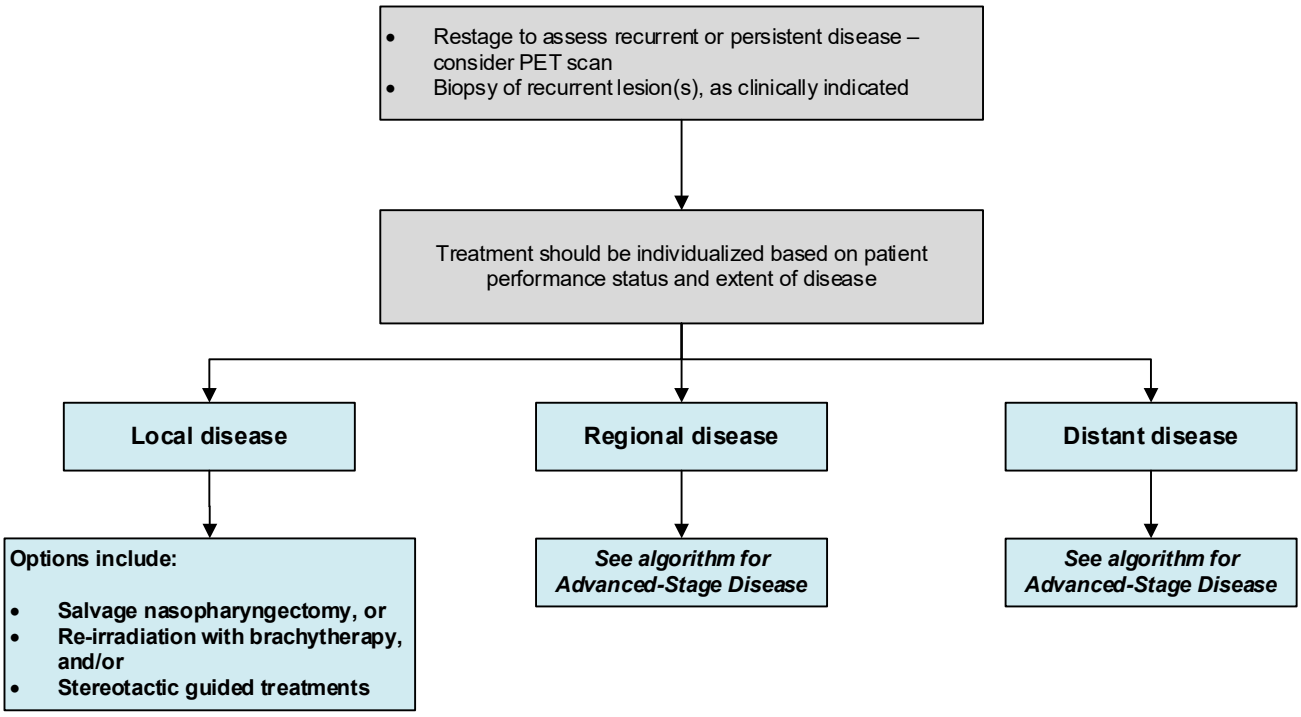
Advanced-Stage (T1, N1–3, T2–4, Any N, M0 and Any T, N, M1)

The Head and Neck Tumour Team encourages patient participation in clinical trials.
In addition, all patient cases should be presented and discussed at a multidisciplinary Tumour Board.



Recurrent or Persistent Disease

The Head and Neck Tumour Team encourages patient participation in clinical trials.
In addition, all patient cases should be presented and discussed at a multidisciplinary Tumour Board.



References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2019. 2019;ISSN: 0835-2976.
2. Wie WI, Sham JS, et al.Nasopharyngeal carcinoma. 2005. Lancet. 2005 Jun 11-17;365(9476):2041-54 PMID: 15950718
3. Chan AT, Gregoire V, Lefebvre JL, Licitra L, et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012 Oct;23 Suppl 7:vii83-5 PMID: 20555078.
4. Pastor Borgonon M, Mesia Nin R, Pousa A L, SEOM (Spanish Society for Medical Oncology). SEOM clinical guideline in nasopharynx cancer (2017). Clin Transl Oncol 2017; 20(1): 84–8. PMID: 29098554
5. National Comprehensive Cancer Network. Head and neck cancers: version I.2020. 2020; Available at: http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed 05/29, 2020.
6. Blanchard P, Lee A , Marguet S et al. Chemotherapy and Radiotherapy in Nasopharyngeal Carcinoma: An Update of the MAC-NPC Meta-Analysis. Lancet Oncol. 2015 Jun;16(6):645-55 PMID: 25957714
7. Zhang Y, Chen L, Hu Q G et al. Gemcitabine and Cisplatin InductionChemotherapy in Nasopharyngeal Carcinoma. N Engl J Med. 2019 Sep 19;381(12):1124-1135. PMID: 31150573
8. Sun Y, Li FW, Chen YN et al. Induction Chemotherapy Plus Concurrent Chemoradiotherapy Versus Concurrent Chemoradiotherapy Alone in Locoregionally Advanced Nasopharyngeal Carcinoma: A Phase 3, Multicentre, Randomised Controlled Trial. Lancet Oncol. 2016 Nov;17(11):1509-1520 PMID: 27686945
9. Yang Q, Cao SM, Gou 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. Eur J Cancer. 2019 Sep;119:87-96 PMID: 31425966
10. Lee AW, Ngan RK, Tung SY et al. Preliminary results of trial NPC 0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced na sopharyngeal carcinoma. Cancer. 2015 Apr 15;121(8):1328-38. PMID: 25529384
11. Zhang L, Huang Y, Hong S et al. Gemcitabine Plus Cisplatin Versus Fluorouracil Plus Cisplatin in Recurrent or Metastatic Nasopharyngeal Carcinoma: A Multicentre, Randomised, Open-Label, Phase 3 Trial. Lancet 2016 Oct 15;388(10054):1883-1892.
12. Chen QY, Wen YF, Guo L, Liu H, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. J Natl Cancer Inst 2011 Dec 7;103(23):1761-1770.
13. Chua DT, Ma J, Sham JS, Mai HQ, et al. Improvement of survival after addition of induction chemotherapy to radiotherapy in patients with early-stage nasopharyngeal carcinoma: Subgroup analysis of two Phase III trials. Int J Radiat Oncol Biol Phys 2006 Aug 1;65(5):1300-1306
14. Pow EH, Kwong DL, McMillan AS, Wong MC, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006 Nov 15;66(4):981-991.
15. Kam MK, Leung SF, Zee B, Chau RM, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 2007 Nov 1;25(31):4873-4879.
16. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998 Apr;16(4):1310-1317
17. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 2005 Sep 20;23(27):6730-6738.
18. Lee AW, Tung SY, Chua DT, Ngan RK, Chappell R, Tung R, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2010 Aug 4;102(15):1188-1198.
19. Chen Y, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. Int J Radiat Oncol Biol Phys 2008 Aug 1;71(5):1356-1364.

20. Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, et al. Concurrent chemotherapy-radiotherapymcompared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 2002 Apr 15;20(8):2038-2044.
21. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, Sumitsawan Y, Tharavichitkul E, Sukthomya V, et al.Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised,non-inferiority, open trial. Eur J Cancer 2007 Jun;43(9):1399-1406
22. Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncol 2012 Feb;13(2):163-171.
23. Ma J, Mai HQ, Hong MH, Min HQ, Mao ZD, Cui NJ, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2001 Mar 1;19(5):1350-1357.
24. Hareyama M, Sakata K, Shirato H, Nishioka T, Nishio M, Suzuki K, et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. Cancer 2002 Apr 15;94(8):2217-2223.
25. Chua DT, Sham JS, Choy D, Lorvidhaya V, Sumitsawan Y, Thongprasert S, et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. Asian-Oceanian Clinical Oncology Association Nasopharynx Cancer Study Group. Cancer 1998 Dec 1;83(11):2270-2283.
26. Chua DT, Ma J, Sham JS, Mai HQ, Choy DT, Hong MH, et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. J Clin Oncol 2005 Feb 20;23(6):1118-1124.
27. Horiot JC, Bontemps P, van den Bogaert W, Le Fur R, van den Weijngaert D, Bolla M, et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol 1997 Aug;44(2):111-121
28. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003 Sep 20;362(9388):933-940.
29. Lee AW, Tung SY, Chan AT, Chappell R, Fu YT, Lu TX, et al. A randomized trial on addition of concurrentadjuvant chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. Radiother Oncol 2011 Jan;98(1):15-22.
30. Gemcitabine Plus Cisplatin Versus Fluorouracil Plus Cisplatin in Recurrent or Metastatic Nasopharyngeal Carcinoma: A Multicentre, Randomised, Open-Label, Phase 3 Trial. Lancet 2016 Oct 15;388(10054):1883-1892.
31. Xiao WW, Huang SM, Han F, Wu SX, Lu LX, Lin CG, et al. Local control, survival, and late toxicities of locally advanced nasopharyngeal carcinoma treated by simultaneous modulated accelerated radiotherapy combined with cisplatin concurrent chemotherapy: long-term results of a phase 2 study. Cancer 2011 May 1;117(9):1874-1883.
32. Wang TL, Tan YO. Cisplatin and 5-fluorouracil continuous infusion for metastatic nasopharyngeal carcinoma. Ann Acad Med Singapore 1991 Sep;20(5):601-603.
33. Au E, Ang PT. A phase II trial of 5-fluorouracil and cisplatinum in recurrent or metastatic nasopharyngeal carcinoma. Ann Oncol 1994 Jan;5(1):87-89.
34. Xue C, Huang Y, Huang PY, Yu QT, Pan JJ, Liu LZ, et al. Phase II study of sorafenib in combination with cisplatin and 5-fluorouracil to treat recurrent or metastatic nasopharyngeal carcinoma. Ann Oncol 2013 Apr;24(4):1055-1061.
35. Lowe VJ, Boyd JH, Dunphy FR, Kim H, Dunleavy T, Collins BT, et al. Surveillance for recurrent head and neck cancer using positron emission tomography. J Clin Oncol 2000 Feb;18(3):651-658.
36. Lee AW, Fee WE,Jr, Ng WT, Chan LK. Nasopharyngeal carcinoma: salvage of local recurrence. Oral Oncol 2012 Sep;48(9):768-774.
37. Amin M.B, Edge S, Greene F, AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.

Appendix A: TNM Classification and Anatomic Stage/Prognostic Groups

Table 1. TNM Classification[37]

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No tumour identified, but EBV-positive cervical node(s) involvement
Tis	Tissue in situ
T1	Tumour confided to the nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumour with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medical pterygoid, lateral pterygoid, prevertebral muscle)
T3	Tumour with infiltration of bony structure at skull base cervical vertebra, pterygoid structures and/or paranasal sinuses
T4	Tumour with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or in unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Metastasis in a lymph node >6cm and/or to the supraclavicular fossa (midline nodes are considered ipsilateral nodes)
N3a	>6cm in dimension
N3b	Extension to the supraclavicular fossa
Distant metastasis (M)	
cM0	No distant metastasis
cM1	Distant metastasis
pM1	Distant metastasis, microscopically confirmed

Table 2. Anatomic Stage/Prognostic Groups[36]

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T1,T0 T2 T2	N1 N0 N1	M0 M0 M0
III	T1,T0 T2 T3 T3 T3	N2 N2 N0 N1 N2	M0 M0 M0 M0 M0
IVA	T4 T4 T4 Any T	N0 N1 N2 N3	M0 M0 M0 M0
IVB	Any T	Any N	M1

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Head and Neck Tumour Team. Members of the Alberta Head and Neck Tumour Team Tumour Team include head/neck reconstructive surgeons, radiation oncologists, medical oncologists, nurses, pathologists, pharmacists, dentists, dieticians, and allied health professionals. Evidence was selected and reviewed by a working group comprised of members from the Alberta Head and Neck Tumour Team Tumour Team, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2013 and updated in 2021.

Maintenance

A formal review of the guideline will be conducted in 2023. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

5-FU, fluorouracil; ChemoRT, chemoradiotherapy; CT, computed tomography; DFS, disease-free survival; ESMO, European Society for Medical Oncology; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; MFS, metastasis-free survival; MRI, magnetic resonance imaging; MeSH, medical subject heading; NCCN, National Comprehensive Cancer Network; NPC, nasopharyngeal cancer; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; RFS, relapse-free survival; RT, radiotherapy; SEOM, Spanish Society of Medical Oncology; TNM, tumour node metastasis; TSH, thyroid-stimulating hormone.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Head and Neck Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Dr. Shamir Chandarana has nothing to disclose
Dr. Dan O'Connell has nothing to disclose
Dr. Brock Debenham has nothing to disclose
Dr. Harvey Quon has nothing to disclose
Dr. Marc Webster has nothing to disclose
Ritu Sharma has nothing to disclose