Provincial Unknown Primary of Head and Neck Cancer Treatment Guidelines

Approved at the Provincial Head and Neck Cancer Guideline Meeting
May 8, 2015

Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Recommendations for drug treatment presented in the Cancer Agency guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca for information on cancer drug listing and funding.

Benefits and risk of the proposed should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

Content:

BACKGROUND

The unknown primary represents 3-5% of head and neck cancer diagnoses. An unknown or 'occult' primary is one where a primary tumour cannot be identified after appropriate investigation, in a patient with no prior history of head and neck cancer. The vast majority present with metastatic lymphadenopathy in the neck.[1] 90% will prove to be squamous cell carcinoma, with the remainder including adenocarcinoma, lymphoma, melanoma, and thyroid cancers as well as other more rare histologies.[2] After complete workup, a primary site of origin will ultimately be discovered in approximately half of cases. [3] Tonsils and base of tongue are the 2 most common originating sites, comprising 80-85% of detected primary sites.[3]

For patients with a prior history of head and neck cancer presenting with neck lymphadenopathy alone, recurrent disease should be considered before de novo occult primary of the head and neck.

WORKUP

All patients with a neck mass should be seen in consultation and undergo a complete history and physical examination with focus on the H&N area. An upfront multidisciplinary discussion including surgical, oncologic and diagnostic input is associated with better outcomes.[4] If available, office endoscopy performed on initial visit is useful to evaluate the entire upper aero-digestive tract.

FNA of a neck mass is preferred over open biopsy. If inconclusive, core biopsy can be considered. Open biopsy as a standalone diagnostic procedure should be avoided as this can complicate and compromise subsequent treatment.[5] If open biopsy is performed, efforts should be made to have this done in a setting where the patient can proceed to definitive surgical management at the same time, as indicated.

Workup should always include CT of the head and neck and chest x-ray. CT chest can be considered in patients with a large nodal burden or involving lower neck or supraclavicular nodes. p16 testing is recommended if adequate tissue is available. A positive result points more strongly towards a tonsil or base of tongue primary site (70% of oropharyngeal squamous cell carcinomas are HPV positive).[6] EBV testing is optional. Although data is mixed, PET/CT scan may reveal a primary site not otherwise detected.[7] MRI may add value to define soft tissue extension for suspected primary tumours not well visualized on CT or with trans-oral or endoscopic exam, such as those of sinonasal origin.

When imaging and office endoscopy do not reveal a primary, the patient will proceed to examination under anesthesia with panendoscopy and biopsy. If a clear primary location is identified or suspected, biopsy is obtained. If no primary is seen, directed biopsies from at-risk sites are typically recommended; although this is controversial.[8] Tonsillectomy will diagnose more primaries than tonsillar biopsy.[9] Bilateral vs unilateral tonsillectomy is controversial. The rate of synchronous bilateral tonsillar cancer is quite low, however contralateral spread may be up to 10%.[10] A positive diagnosis after tonsillectomy can reduce the toxicity of treatment owing to smaller, more directed radiation fields; however a non-diagnostic result confers only the greater morbidity of tonsillectomy vs tonsillar biopsy alone. Decision is ultimately at the clinician's discretion. In general, tonsillectomy is favored.

The value of PET/CT scan is greatly reduced if done after biopsy of mucosal sites, due to the high likelihood of false positive results. Whenever possible, it should be completed prior to panendoscopy and biopsy. Wait time delays for PET should be weighed by the treating physician against the clinical urgency of biopsy and subsequent treatment.

STAGING

AJCC 7th edition (2009):

- N1 - Unilateral metastases in cervical lymph nodes, 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral retropharyngeal lymph nodes, 6 cm or less in greatest dimension
- N2 - Bilateral metastases in cervical lymph nodes, 6 cm or less in greatest dimension, above the supraclav fossa
- N3a – Metastases in a lymph node(s) greater than 6 cm
- N3b – Extension to the supraclavicular fossa

MANAGEMENT

If primary tumour is found, treated should be directed according to the primary.

If no primary is found, initial management options include surgery, radiotherapy or combined chemoradiation. Prior to treatment, consultation with dietician and placement of a PEG tube is not mandatory but is often helpful. In most cases treatment of the primary mucosal sites will not include the oral cavity and so dental consult and creation of dental guards is not usually required.

cN1: Options include radical neck dissection alone, neck dissection followed by adjuvant radiotherapy, or radiotherapy alone. Modified radical dissection likely confers similar survival as radical with appropriate adjuvant therapy, when final pathology reveals >N1 disease.[11]

Approximately 25% of patients will eventually present at the primary site after neck dissection alone, and 15% will recur in the neck (60% if ECE if present). There is no randomized data comparing neck dissection alone vs radiotherapy alone.[12]

Clear indications for adjuvant radiotherapy (+/- chemotherapy) after neck dissection include:

- ≥N2 disease
- ECE
- positive margin
- previous neck violation

ECE and positive margins will warrant the addition of chemotherapy to PORT unless otherwise contraindicated

≥cN2: Combined chemo + radiation therapy is recommended. Surgical management is an option though not preferred upfront. Adjuvant radiotherapy improves locoregional control. For very large nodes, consideration can be made for neck dissection first to remove bulk of disease, followed by adjuvant radiotherapy or chemoradiation.

IMRT technique using integrated boost can reduce toxicity, and is standard for head and neck cancers.[13] Whether definitive or adjuvant, treatment fields should cover suspected primary sites and the ipsilateral or bilateral neck. There is no data comparing ipsilateral vs bilateral neck radiotherapy for the H&N cancer of unknown primary. Due to the lack of knowledge of the lateralized drainage of the primary (the reasonable possibility of the primary being from the base of tongue), bilateral is generally preferred. [14] Traditionally, primary sites would include nasopharynx, oropharynx, hypopharynx and larynx. In the modern era, high quality endoscopic optics can allow safe omission of the nasopharynx and larynx. Occult disease is less easily ruled out elsewhere, and so treatment fields for primary site will generally include the oropharynx and hypopharynx. p16 positivity may also help reduce field sizes.[15] In general the neck volumes will include levels Ib-V and RP nodes. Modifications can be based on number, size and location of nodes as well as suspected primary site.

Example RT prescription dosing is as follows:

- 66-70Gy to gross nodal disease,
- 60-63Gy to high risk nodal levels and likely mucosal primary sites
- 54-56Gy to elective nodal levels

What is defined as high risk nodal levels is ultimately up to the individual treating physician.

Persistent or progressive nodal disease after radiotherapy should warrant surgical consultation for salvage neck dissection.

M1: Patients will metastatic disease should be referred to medical oncology for discussion of systemic therapy. Palliative radiotherapy for symptom control may be indicated or best supportive care.

RECURRENT DISEASE

Recurrence is a poor prognostic factor.[17] In cases of suspected recurrent disease, biopsy should be obtained when possible along with re-staging investigations including at minimum CT of the head and neck and chest x-ray or CT chest. The patient should be considered in a multidisciplinary setting.

Management decisions depend on the location (primary site, new primary site, neck or distant), the histology, time since initial diagnosis and prior therapies. The overall condition and functional status of the patient should also be carefully considered.

In general, surgical management is favored for patients previously treated with radiotherapy, and likewise those previously having undergone surgery alone should be considered for radiotherapy (+/- chemotherapy). Neck recurrence alone may be adequately treated with neck dissection if no previous surgical dissection. Cases involving previous treatment with surgery and radiotherapy present a more difficult clinical situation which can benefit from multidisciplinary consultation. Some patients may be eligible for repeat radiotherapy even to high doses. Small localized recurrences may be managed surgically in some cases. Recurrence at the base of skull or other difficult-to-access locations can benefit from external consultation at centers equipped with gamma knife or SBRT technologies. Other options include palliative radiotherapy or best supportive care.

References:

1. Abbruzzese JL, Abbruzzese MC, Hess KR, Raber MN, Lenzi R, Frost P. *Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients.* J Clin Oncol 1994;6:1272-80.
2. Vaamonde P, Martin Martin C, del Rio Valeiris M, Labella Caballero T. *A study of cervical lymph node metastases of unknown primary tumour.* Eur Arch Otorhinolaryngol 2002;53:601-6.
3. Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site, Laryngoscope 119;2348-2354,2009.
4. Friedland PL, Bozic B, Dewar J, Kuan R, Meyer C, Phillips M. Impact of multidisciplinary team management in head and neck cancer patients. *British Journal of Cancer.* 2011;104(8):1246-1248.
5. Robbins KT, Cole R, Marvel J, Fields R, Wolf P, Goepert H. *The violated neck: cervical node biopsy prior to definitive treatment.* Otolaryngol Head Neck Surg 1986;94:605-10.
6. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MR, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Ander WF, Rosenvberg PS, Gillison ML. *Human papillomavirus and rising oropharyngeal cancer incidence in the United States.* J Clin Oncol 2011;29(32):4294

7. Johansen J, Buus S, Loft A, et al: Prospective study of 18FDG-PET in the detection and management of patients with lymph node metastases to the neck from and unknown primary tumour: results from the DAHANCA-13 study, *Head Neck* 30:471-478, 2008.

8. Tanzler ED, Amdur RJ, Morris CG, Werning JW, Mendenhall WM. *Challenging the need for random directed biopsies of the nasopharynx, pyriform sinus and contralateral tonsil in the work up of unknown primary squamous cell carcinoma of the head and neck.* Head Neck 2014 Dec 9. doi: 10.1002/hed.23931. [Epub ahead of print]

9. Waltonen JD, Ozer E, Schuller DE, Agrawal A. *Tonsillectomy vs deep tonsil biopsies in detecting occult tonsil tumours.* Laryngoscope 2009;119(1):102-6.

10. Koch WM, Bhatti N, Williams MF, Eisele DW. *Oncologic rationale for bilateral tonsillectomy in head and neck squamous cell carcinoma of unknown primary source.* Otolaryngol Head Neck Surg 2001;124:331-3

11. Anderson PE, Shah JP, Cambronero E, et al: *The role of comprehensive neck dissection with preservation of the spinal accessory nerve in the clinically positive neck.* Am J surg 1994;168:499-502

12. Hamoir M, Machiels JP, Reychler H, Schmitz S, Thariat J, Gregoire V. *Lymph node metastases from squamous cell carcinoma of unknown primary site. Is it time to change of paradigm?* Bull Cancer 2014;101(5):455-60

13. Staffurth J, Radiotherapy Development Board. *A review of the clinical evidence for intensity-modulated radiotherapy.* Clin Oncol (R Coll Radiol) 2010;22(8):643-57

14. Reddy SP, Marks JE, *Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs ipsilateral neck irradiation.* Int J Radiat Oncol Biol Phys 1997;37:787-802

15. Fotopoulos G, Pavlidis N. *The role of human papilloma virus and p16 in occult primary of the head and neck: A comprehensive review of the literature.* Oral Oncology 2014.10.018

16. Troussier I, Barry B, Baglin AC, Leysalle A, Janot F, Baujat B, Fakhry N, Sun XS, Marcy PY, Bensadoun RJ, Thariat J. *Target volumes in cervical lympadenopathies of unknown primary: toward a selective customized approach? On behalf of REFCOR.* Cancer Radiother 2013;17(7)

17. Godden DR, Ribeiro NF, Hassanein K, et al: *Recurrent neck disease in oral cancer.* J Maxillofac Surg 2002;60:748-753

Chairperson: Dr. Shazia Mahmood

Presenters: Dr. Shazia Mahmood, Dr. Evgeny Sadikov, Dr. Debra Korol, Dr. Ali El-Gayed, Dr. Derek Suderman, Dr. Rick Jaggi, Dr. Adnan Zaidi, Dr. Bryan Brunet, Dr. Wojciech Dolata, Dr. Kamal Haider

Attendees: Dr. Aisha Ahmed, Joe Andreas, Dr. Monica Behl, Dr. Janine Benoit, Dr. Bryan Brunet, Jennifer Cameron-Turley, Lorna Campbell, Dr. Peter Chang, Dr. Tineyi Chikukwa, Dena Colleaux, Dr. Wojciech Dolata, Dr. Ali El-Gayed, Lacey Fondrick, Christel Foord, Bertha Foote, Pauline Fox, Josh Giambattista, Dr. Kamal Haider, Dr. Rick Jaggi, Dr. Miroslav Jancewicz, Dr. Debra Korol, Lana Kruger, Dr. Shazia Mahmood, Courtney McKay, Dr. Mohamed Mohamed, Dr. William Moyer, Lori Muz, Dr. Mark Ogrady, Dr. Lenny Pillay, Dr. Florence Plaza Arnold, Dr. Evgeny Sadikov, Dr. Muhammad Salim, Judy Shaw, James Smetaniuk, Dr. Derek Suderman, Dr. Niranjan Venugopal, Brenda Wilde, Michelle Zahayko, Dr. Adnan Zaidi, Dr. Bill Ziegler