

## Unknown Primary Cancer in Head and Neck : Role of Radiation Therapy

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Up until the 1940s several authors reported cervical lymph node metastasis of unknown primary being caused by bronchogenic carcinomas of cysts of the neck since Volkmann in 1882. In 1944 Martin et al. were the first to clearly differentiate between bronchogenic carcinoma and the incidence of cervical CUP (carcinoma of unknown primary)<sup>1)</sup> Commes et al. described a cervical lymph node metastasis without diagnosis the malignant disease as "carcinoma of unknown primary"<sup>2)</sup>. Later on, prerequisites for the diagnosis of a CUP were defined as follows: biopsy and consecutive histological examination on a lymph node confirms malignant cell growth and makes a primary tumor at the location of the biopsy unlikely, while physical examinations and those carried out with technical equipment do not detect any primary tumor<sup>3)</sup>.

In a small percentages between 0.5 and 7.0% of patients with enlarged cervical lymph node, the primary lesion cannot be found, even after extensive evaluation<sup>3)</sup>. In cervical CUP the most frequent histopathological diagnoses were squamous cell carcinoma (65–76%) followed by undifferentiated carcinoma (13–14%), adenocarcinoma (13%) an lymphoepithelial (8%) carcinoma<sup>4)</sup>. In approximately 10–40% of patients with cervical CUP there is emergence of the occult primary tumor<sup>5)</sup>. Patients with enlarged lymph nodes in the upper neck have a good prognosis when treated aggressively, compared with those with enlarged lymph nodes in the low internal jugular chain or supraclavicular fossa<sup>3)6)</sup>. The latter patients are more likely to have primary lesions located below the clavicles, which carry a much worse prognosis. The majority of patients have either squamous cell or poorly differentiated carcinoma. Those with adenocarcinoma almost always have a primary lesion below the clavicles, although if the nodes are located in the upper neck, we must exclude salivary gland, thyroid or parathyroid primary tumor.

Patients should be evaluated with through physical examination including careful evaluation of the head and neck. A needle biopsy or lymph node should be performed. After chest radiograph, a CT or MRI of the head and neck is obtained to detect an unknown primary lesion arising from the mucosa of head and neck. Direct laryngoscopy and examination under anesthesia are performed with direct biopsies of nasopharynx, tonsils, base of tongue, and pyriform sinuses as well as any abnormalities noted on CT or MRI or suspicious mucosal lesions noted at laryngoscopy<sup>7)</sup>. Patients with adequate lymphoid tissue in tonsillar fossa should undergo an ipsilateral tonsillectomy<sup>8)</sup>. More recently newer imaging techniques such as positron emission tomography scans may identify primary lesions<sup>9)</sup>. The results of a diagnostic evaluation for an unknown primary site in 130 patients at University of Florida shows that the primary site was discovered in more than 40% of patients and most often site were the tonsillar fossa or base of tongue<sup>8)</sup>.

The management of patients with unknown primary cancer of the head and neck has become controversial. Management options for patients with metastatic to cervical lymph nodes from an unknown primary carcinoma of head and neck include treatment of ipsilateral lymph nodes and treatment of head and neck mucosal sites and bilateral lymph nodes. Traditionally, it was believed that treatment of all potential primary sites with radiotherapy improves outcome but the argument against radiation therapy to potential mucosal primary sites is that the effectiveness in reducing the rate of developing carcinomas in head and neck mucosal primary is not established based on randomized data<sup>10-13)</sup>.

Many investigators have reported that despite improving locoregional control in patients treated with postoperative extended field radiotherapy no survival benefit has been

noted<sup>5)13)14)</sup>. Recently some authors have challenged the use of extended field radiotherapy in patients with more favorable disease<sup>5)15-17)</sup>. The authors state that with approximately 90% control of disease with single modality, combined therapy is not necessary.

The volume of radiotherapy is also subject of controversy. A randomized trial comparing the therapeutic value of comprehensive vs. volume-limited radiotherapy is being considered. Several authors have recommended irradiation of bilateral neck plus mucosal irradiation whereas others have advocated bilateral or ipsilateral neck treatment alone<sup>13)16)18)</sup>. Coster et al<sup>15)</sup> reported 24 patients with unilateral metastatic lymph nodes treated with neck dissection alone and 13% of patients developed carcinoma in head and neck mucosal sites. Weir et al<sup>14)</sup> reported 85 patients treated with radiation alone to ipsilateral lymph nodes and 59 patients treated with radiation alone to mucosal sites and bilateral lymph nodes. They concluded radiation and no radiation to mucosal sites resulted in comparable rates of survival (48% vs. 37%) and the rate of developing primary carcinoma was lower for patients treated with radiation to mucosal sites than no radiation (2% vs. 7%). But the irradiation technique used to treat the neck alone actually resulted in significant exit dose to the oropharynx, the most likely site of and occult primary site. The authors concluded that radiation did not reduce the rate of developing primary carcinoma. In contrast, many other retrospective data suggest that radiation therapy reduces the rate of developing primary carcinoma in head and neck<sup>10)13)16)18)19)20)</sup>. Also Jesse et al observed a significant worsening of the prognosis for patients when a primary tumor was found<sup>21)</sup>. Bataini et al<sup>10)</sup> reported 4% of developing primary carcinoma after treating with neck dissection followed by radiation to mucosal sites and bilateral lymph nodes in 48 patients or radiation therapy alone to mucosal sites and bilateral lymph nodes in 90 patients. Colletier et al<sup>19)</sup> reported 6% of patients developed carcinomas in primary sites within radiation port and 4% outside radiation port after neck dissection followed by radiation to mucosal sites and bilateral lymph nodes. Reddy and Marks<sup>13)</sup> concluded that radiation reduced the rate of developing carcinomas in head and neck mucosal sites. Erkal HS et al<sup>20)</sup> reported that the rate of developing carcinomas in mucosal sites for patients treated for unknown primary carcinomas of head and neck was similar to the rate of developing

metachronous carcinomas in known primary head and neck carcinoma, demonstrating the effectiveness of radiation in reducing the rate of developing carcinomas in mucosal sites. Harper et al<sup>16)</sup> and Iganej et al<sup>18)</sup> also showed an apparent benefit from elective mucosal irradiation.

The mucosal site to be treated with radiation in unknown primary carcinoma of head and neck are dependent on the level of nodal involvement<sup>22)</sup>. For patients with level I nodal involvement, treatment of oral cavity, Waldeyer's ring and oropharynx is recommended. Treatment of mucosal sites is often withheld for patients with level I nodal involvement because of the potential morbidity associated with radiation to oral cavity and the relative ease in detection and treatment of carcinomas developing in the oral cavity<sup>22)</sup>. For patients with level II, III, upper level V involvement, radiation to nasopharynx, oropharynx, larynx, and hypopharynx is recommended. Radiation therapy is often delivered to the nasopharynx and oropharynx for patients with level II and level V<sup>11)</sup>. For patients with level III nodal involvement, treatment of the nasopharynx, oropharynx, hypopharynx, and larynx is often recommended<sup>22)</sup>. But radiation may be confined to the nasopharynx and oropharynx because of the low rates of detecting occult carcinomas in the hypopharynx and larynx, and potential complications after radiation therapy to hypopharynx and larynx<sup>8)</sup>. Also for patients with level III nodal involvement, treatment of nasopharynx may be not necessary, the relatively high incidence of retropharyngeal nodal involvement requires the base of skull to be included in radiation portals. For patients with level IV nodal involvement, treatment to Waldeyer's ring, larynx, hypopharynx is recommended. If patients have lower level V lymphadenopathy, treatment to larynx and hypopharynx is recommended.

The management options for unknown primary carcinoma of head and neck include neck dissection alone, radiation alone and radiation with neck dissection. Treatment decisions are based on the extent of nodal involvement<sup>10)</sup>. For N1 nodal disease, neck dissection and radiation alone are associated with equivalent rates of nodal disease control<sup>23)</sup>. Radiation therapy with neck dissection is recommended for patients with N1 nodal metastasis who have a history of incisional or excisional biopsy and who have extracapsular extension<sup>5)24)</sup>. Reddy et al<sup>13)</sup> reported an 80% rate of nodal control for patients treated with radiation to ipsilateral lymph nodes and

100% for patients treated with radiation to bilateral cervical lymph nodes for patients with N1 disease. Coster et al<sup>15)</sup> reported that 15% of patients had recurrent disease in ipsilateral lymph nodes after neck dissection alone.

Patients with N2a disease may be treated with radiation alone. Neck dissection is not performed for patients with no persistent nodal disease after radiation. Radiation therapy followed by planned neck dissection is recommended for patients with N2a nodal disease that persist after radiation, and for patients with N2b, N2c, and N3 nodal disease in attempt to reduce the incidence of recurrent nodal disease<sup>8)</sup>. Radiation therapy is delivered to bilateral lymph nodes because of the relatively higher risk for developing recurrent disease in contralateral lymph nodes for patients treated with radiation to ipsilateral lymph node alone<sup>25)</sup>. In postoperative radiation, they recommend beginning radiotherapy within 3 to 6 weeks after surgery and delivering 60–63Gy over 6 weeks to the region of the neck deemed to be at greatest risk<sup>19)</sup>. To treat the potential mucosal sites, they recommend radiation dose to mucosa 50–55Gy at 1.8–2Gy per fraction and to give a boost dose of 6–10cGy in 3–5 fraction to any suspected primary site<sup>16)</sup>. In radiation therapy +/- neck dissection setting, radiation doses of >60Gy at 2–2.2Gy per fraction are required for nodes 3–6cm in size. Nodes 7–8cm in size required higher doses in excess of 64Gy at 2–2.2Gy per fraction<sup>23)</sup>. Patients with  $\geq 3$ cm in size would undergo a neck dissection 4–6 weeks following irradiation. After 45–50Gy, they reevaluate the patient with the surgeon to assess the probability of resecting the node. The dose to the node is then boosted if it is thought to be unresectable at that time or borderline resectable owing to fixation. Nodes  $\geq 7$ cm frequently require doses in excess of 60–70Gy, particularly if they are initially thought to be fixed. Rapid and complete regression of neck nodes during radiation may predict a better chance for control by radiation therapy alone, so that patients in this category may be treated without a neck dissection depending on the initial size of the node and the dose delivered<sup>23)</sup>.

Patients who have unresectable neck disease have a very poor prognosis. Radiotherapy alone can only cure a small portion of these patients. Concurrent chemoradiation therapy (CCRT) improves loco-regional disease control and overall survival in patients with advanced head and neck cancers.

Argiris A et al<sup>26)</sup> reported 25 patients treated with CCRT including potential mucosal sites and bilateral neck nodes (median total dose 60Gy) of N2N3 head and neck unknown primary carcinoma. The 5 year progression free and overall survival was 87% and 75% respectively. The authors conclude that CCRT results in high rates of loco-regional and distant control and long term survival for good performance status patients. Therefore, efforts to incorporate chemotherapy into radiotherapy to enhance anti-tumor activity should be continue.

Some patients presenting with metastatic carcinoma to the neck nodes from unknown head and neck primary site is treated with palliative intent because of poor medical condition, extensive nodal involvement, and/or distant metastasis at presentation. Treatment of the neck depends on the extent and location of the lymphadenopathy. Erkal et al<sup>20)</sup> reported 40 patients were treated palliatively at University of Florida. Treatment was delivered to the neck alone to a dose of 30 Gy in 10 fractions over 2 weeks or 20Gy in two fractions with 1 week inter-fraction interval. The nodal response rate was 65% and the symptomatic response rate was 57% at 1 year. The 1 year absolute and cause specific survival rates were 25%.

The main complications associated comprehensive radiation therapy are xerostomia and difficulty in swallowing. The rates of osteonecrosis, myelitis, and radiation induced malignant tumors are very low<sup>20)</sup>. The rates of complication after radiation are dependent on the mucosal sites treated and total radiation doses<sup>11)22)</sup>. The main complications associated with radiation to metastatic lymph nodes and neck dissection include laryngeal edema, subcutaneous fibrosis, wound breakdown, and wound infection. The rates of cranial nerve damage, carotid artery exposure, and rupture are low. Complication rates after radiation to metastatic lymph nodes and neck dissection are dependent on lymph nodes treated, radiation dose per fraction, total radiation dose<sup>27)</sup>.

## References

- 1) Martin HE, Morfit HM: *Cervical lymph node metastasis as the first symptom of cancer. Surg Gynecol Obstet. 1944;78:133-159*
- 2) Comess MS, Beahrs OH, Dockerty MB. *Cervical metastasis from occult carcinoma. Surg Gynecol Obstet. 1957;104:607-613*
- 3) Ulmann JE, Philips TL: *Management of the patient with cancer of unknown primary site. In: DeVita VT et al. eds. Cancer: Principles and Practice of Oncology. Philadelphia: J.B. Lippincott*

- cott. 1982:1518-1533*
- 4) Haas I, Hoffmann TK, Engers R, Ganzer U: *Diagnostic strategies in cervical carcinoma of an unknown primary. Eur Arch Otorhinolaryngol. 2002;259:325-333*
  - 5) Wang RC, Goepfert H, Barber AE, et al: *Unknown primary squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg. 1990;116:1388-1393*
  - 6) Grosbach AB: *Carcinoma of unknown primary site: A clinical enigma. Arch Intern Med. 1982;142:357-359*
  - 7) Jones AS, Cook JA, Phillips DE, Roland NR: *Squamous carcinoma presenting as an enlarged cervical lymph node. Cancer. 1993;72:1756-1761.*
  - 8) Mendenhall WM, Mancuso AA, Parson JT, et al: *Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Head Neck. 1998;20:739-744*
  - 9) Safa AA, Tran LM, Rege S, et al: *The role of positron tomography in occult primary head and neck cancers. Cancer J Sci Am. 1999;5:214-218*
  - 10) Bataini JP, Rodriguez J, Jaulerry J, et al: *Treatment of metastatic neck nodes secondary to an occult epidermoid carcinoma of head and neck. Laryngoscope. 1987;97:1080-1084*
  - 11) Carson LS, Fletcher GH, Oswald MJ, et al: *Guidelines for radiotherapeutic techniques for cervical metastases from an unknown primary. Int J Radiat Oncol Biol Phys. 1986;12:2101-2110*
  - 12) McCunniff AJ, Raben M: *Metastatic carcinoma of the neck from an unknown primary. Int J Radiat Oncol Biol Phys. 1986;12:1849-1852.*
  - 13) 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 irradiation. Int J Radiat Oncol Biol Phys. 1997;37:797-802*
  - 14) Weir L, Kean T, Cummings BJ, et al: *Radiation treatment of cervical lymph node metastases from an unknown primary: an analysis of outcome by treatment volume and other prognostic factors. Radiother Oncol. 1995;35:2006-2011*
  - 15) Coster JR, Foote RL, Olson KD, et al: *Cervical nodal metastasis of squamous cell carcinoma of unknown primary site: Indication for withholding radiation therapy. Int J Radiat Oncol Biol Phys. 1992;23:743-749*
  - 16) Harper CS, Mendenhall WM, Parsons JT, et al: *Cancer in neck nodes with unknown primary sites: the role of mucosal radiotherapy. Head Neck. 1990;12:463-469*
  - 17) Freedman D, Mendenhall WM, Parsons JT, et al: *Unknown primary squamous cell carcinoma of the head and neck: is mucosal irradiation necessary? Int J Radiat Oncol Biol Phys. 1992;23:889-890.*
  - 18) Iganej S, Kagan R, Anderson P, et al: *Metastatic squamous cell carcinoma of the neck from an unknown primary: management options and patterns of relapse. Head Neck. 2002;24:236-246*
  - 19) Colletier PJ, Garden AS, Morrison WH, et al: *Postoperative radiation for squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site: outcomes and patterns of failure. Head Neck. 1998;20:674-681.*
  - 20) Erkal HS, Mendenhall WM, Amdur RJ, et al: *Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy alone or in combination with neck dissection. Int J Radiat Oncol Biol Phys. 2001;50:55-63*
  - 21) Jesse RH, Neff LE: *Metastatic carcinoma in cervical lymph nodes with an unknown primary lesion. Am J Surg. 1966;112:547-553.*
  - 22) Million RR, Cassisi NJ, Mancuso AA: *The unknown primary. In Million RR, Cassisi NJ. 2nd ed. Management of head and neck cancer: A multidisciplinary approach. Philadelphia: JB Lippincott. 1994:311-320*
  - 23) Mendenhall WM, Million RR, Cassisi NJ: *Squamous cell carcinoma of the head and neck treated with radiation therapy: The role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys. 1986;12:733-740*
  - 24) Ellis ER, Mendenhall WM, Rao PV, et al: *Incisional or excisional neck node biopsy before definitive radiotherapy alone or followed by neck dissection Head Neck. 1991;13:177-183*
  - 25) Barkley HT Jr, Fletcher GH, Jesse RH, et al: *Management of cervical lymph node metastasis in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. Am J Surg. 1972;124:462-467*
  - 26) Argiris A, Smith SM, Stenson K, et al: *Concurrent chemoradiotherapy for N2 or N3 squamous cell carcinoma of the head and neck from an occult primary. Ann Oncol. 2003;14:1306-1311*
  - 27) Taylor JMG, Mendenhall WM, Parsons JT, et al: *The influence of dose and time on wound complications following postradiation neck dissection. Int J Radiat Oncol Biol Phys. 1992;23:41-46*