

Resection and reconstruction of giant cervical metastatic cancer using a pectoralis major muscular flap transfer: A prospective study of 16 patients

XIANGMIN ZHANG^{1*}, FOLIN LIU^{2*}, XIAOLIN LAN^{1*}, JING HUANG³, KEQING LUO¹ and SHAOJIN LI³

¹Department of Head and Neck, Tumor Hospital of Ganzhou; ²Institute of Cancer Research, First Affiliated Hospital of Gannan Medical University; ³Ganzhou Institute of Cancer Research, Ganzhou, Jiangxi, P.R. China

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Abstract. If not promptly or properly treated, certain cervical metastatic cancers that develop from unknown primary tumors may rapidly grow into giant tumors that can invade the blood vessels, muscle and skin. The present study examined the feasibility and efficacy of radical neck dissection combined with reconstruction using the pectoralis major myocutaneous flap for the treatment of giant cervical metastatic cancers that have developed from unknown primary tumors and have invaded the skin. A total of 16 patients who met the inclusion criteria were subjected to radical neck dissection to adequately resect invaded skin, and the pectoralis major myocutaneous flap was used to repair the large skin defect created in the cervical region. Following the surgery, the patients received concurrent chemoradiotherapy. The pectoralis major myocutaneous flap survived in all 16 patients, with no cases of flap necrosis. In addition, no post-operative lymphedema, paresthesia or dysfunction of an upper extremity occurred due to the cutting of a pectoralis major muscle. In 9 cases, patients were satisfied with their post-operative shoulder movement at the donor site; in the remaining 7 cases, patients felt greater weakness in this region following surgery relative to prior to surgery. The 14 male patients were generally satisfied with the post-operative appearance of the donor region, whereas the 2 female patients were dissatisfied with the appearance of this region. Follow-up for 6-53 months after the patients were discharged following surgery and chemotherapy revealed that the recurrence of cervical tumors in 6 cases. Overall, radical neck dissection combined with the use of the pectoralis major

myocutaneous flap for reconstruction is a feasible approach for the treatment of giant cervical metastatic cancers that have developed from unknown primary tumors and have invaded the skin. Post-operative concurrent chemoradiotherapy should be administered to improve the local control rate and patient quality of life, allowing a satisfactory therapeutic efficacy to be achieved.

Introduction

In recent years, the application of positron emission tomography-computed tomography (PET-CT), comprehensive endoscopy involving random biopsies, laser-induced fluorescence endoscopy, genetic testing and other techniques have significantly increased the rate at which primary tumors are detected in cases of cervical metastatic cancer (1-5). However, the primary tumor cannot be found in 3-5% of these cases (6,7). In certain cases during which patients with cervical metastatic cancer involving an unknown primary tumor either do not receive prompt treatment or receive inappropriate treatment during the course of an individualized, multidisciplinary treatment process, metastatic cancer may grow rapidly to form giant tumors that invade the blood vessels, muscle and skin. Radiotherapy cannot be performed in these cases due to the involvement of the skin, and chemotherapy is frequently ineffective. As a consequence, salvage surgery followed by post-operative chemoradiotherapy is the preferred therapeutic approach for these cases.

Focal considerations of salvage radical neck dissection include not only appropriately addressing issues associated with the exposure of internal tissues, hemostasis, and the treatment of the internal jugular vein and carotid artery, but also protecting the vagus nerve, the cervical sympathetic trunk, the phrenic nerve and the brachial plexus. After completing a radical neck dissection, a suitable flap must be obtained for the reconstruction of the affected region. The pectoralis major myocutaneous flap includes a large quantity of tissue; thus, this flap can adequately repair defects in cervical tissue caused by radical neck dissection, and this flap may therefore be utilized for a complete reconstruction that addresses these defects (8-10). In addition, this flap has a rich blood supply, exhibits strong resistance to infection and necrosis, and heals

Correspondence to: Professor Shaojin Li, Ganzhou Institute of Cancer Research, 19 Huayuan Qian Road, Ganzhou, Jiangxi 341000, P.R. China
E-mail: lsj1362@126.com

*Contributed equally

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rapidly. Thus, the use of this flap does not delay post-operative chemoradiotherapy or raise concerns regarding the exposure of the carotid artery due to post-operative flap necrosis. Therefore, the flap meets the clinical requirements for the treatment of patients with cervical metastatic cancer involving an unknown primary tumor (8-10). The present study examined the feasibility and efficacy of radical neck dissection combined with reconstruction using the pectoralis major myocutaneous flap for the treatment of giant cervical metastatic cancers that have developed from unknown primary tumors and have invaded the skin.

Materials and methods

Ethics statement. The Ethical Committee of the Tumor Hospital of Ganzhou Review Board (Ganzhou, Jiangxi, China) approved the study protocol (20060502), and the study was conducted in accordance with the principles of the Declaration of Helsinki regarding research involving human subjects. Each of the patients provided written informed consent to participate after the nature of the study had been explained to them.

Case inclusion criteria. The included subjects were required to meet the following criteria: i) Diagnosis of lymph node metastatic cancer based on pathological examination; ii) no history of malignancy or surgery for a tumor of unknown nature; iii) no clear symptoms associated with particular organ systems and an absence of multiple metastases outside of the cervical region; iv) no evidence of primary tumors from clinical and laboratory tests; v) lymph node metastatic cancer that affects the skin, but does not infringe on the hypopharynx, larynx or esophagus, with a maximum tumor diameter of ≥ 10 cm; vi) a Karnofsky performance score of ≥ 80 ; vii) an expected survival time of >6 months; viii) no lesions in vital organs and the ability to tolerate the surgery; and ix) the patient volunteered for the study and signed an informed consent form.

Case exclusion criteria. Patients were excluded from the study if they meet any of the following criteria: i) A clear primary tumor; ii) bilateral cervical lymph node metastasis; iii) lymph node metastatic cancer that did not affect the skin, involved a maximum tumor diameter of <10 cm, or affected the hypopharynx, larynx or esophagus; and iv) lesions in vital organs or an inability to tolerate the surgery.

Clinical data. A total of 16 patients were enrolled, including 14 males and 2 females. The enrolled patients were between 38 and 68 years of age, with a mean age of 54.7 years. Each individual was subjected to a physical examination of the head and neck, enhanced CT scanning of the nasopharynx, neck and chest, color Doppler ultrasonography of the abdomen, laryngoscopy, esophageal endoscopy and electronic bronchoscopy. Tumor markers and other indicators revealed no primary tumors, and emission CT examinations revealed no bone metastases. A total of 7 patients underwent routine PET-CT examinations that did not identify any primary tumors or any metastases other than the known cervical metastasis. The clinical data are presented in Table I.

Table I. General clinical data for the examined patients.

Parameter	No. of cases (%)
Age, years	
30-45	5 (31.3)
46-60	9 (56.2)
≥ 61	2 (12.5)
Gender	
Male	14 (87.5)
Female	2 (12.5)
KPS score	
≥ 90	12 (75.0)
80-89	4 (25.0)
Starting position of the tumor	
Upper neck region (regions I-III)	6 (37.5)
Lower neck region (regions IV-V)	2 (12.5)
Upper and lower neck regions (regions I-III and regions IV-V)	8 (50.0)
Pathological type	
Stage I squamous	3 (18.8)
Stage II squamous	6 (37.5)
Stage III squamous	5 (31.2)
Unclassified	2 (12.5)
N stage	
N3 ($10 \text{ cm} \leq N \leq 15 \text{ cm}$)	11 (68.8)
N3 ($N > 15 \text{ cm}$)	5 (31.2)
Skin invasion	
$<10 \text{ cm}$	10 (62.5)
$\geq 10 \text{ cm}$	6 (37.5)
Prior treatment history	
No chemoradiotherapy	3 (18.8)
Induction chemotherapy, ≤ 2 treatments	6 (37.5)
Induction chemotherapy, >2 treatments	7 (43.7)
Radiotherapy	0 (0.0)

KPS, Karnofsky performance score; N, node.

Surgery and reconstruction. Patients were subjected to radical neck dissection. If necessary, a portion of the carotid artery was removed, and vascular anastomosis or vascular grafting was performed. Subsequently, a reconstruction was conducted using the pectoralis major myocutaneous flap. The shape and size of the flap obtained for this purpose varied based on the size and shape of each skin defect. The largest skin paddle used in this study had dimensions of $23 \times 15 \text{ cm}$.

Post-operative care. After surgery, various aspects of the flap, including color, texture, temperature, degree of capillary filling and swelling, were closely observed. A good airway and suction drainage were ensured by careful observation and the provision of relevant care. Care was also provided to strengthen patients' postures, oral cavity health, nutritional status and psychological conditions, as well as to alleviate pain.

Post-operative chemoradiotherapy. Chemoradiotherapy was started at 4-6 weeks post-surgery. In cases of complete surgical resection with pathologically negative margins, patients were subjected to 60-66 Gy in 30-33 fractions of radiotherapy for 6-7 weeks; in cases with visible residual tumor tissue, patients received 66-70 Gy in 33-35 fractions of radiotherapy for 6-7 weeks. During radiotherapy, concurrent chemotherapy involving 6 treatments of 30 mg/m²/week cisplatin (DDP) was administered.

Results

Surgical and post-operative conditions. Among the 16 cases, there were no cases of major hemorrhages due to carotid artery rupture. In 2 cases, direct suture repair of blood vessels was performed, as the carotid artery adventitia ruptured when a tightly adhering tumor was separated from this artery. In 1 case, a segment ~1.5 cm in length was resected from the carotid artery, and a tension-free end-to-end anastomosis was performed once the artery was freed. There was 1 case in which the internal carotid artery was removed as intraoperative findings revealed an occlusion in this artery. The vagus nerve was partially removed in 2 cases, followed by a local end-to-end anastomosis in 1 case and a long thoracic nerve graft anastomosis in the other case. There were 2 cases of phrenic nerve resection. The brachial plexus and cervical sympathetic trunk were retained in all 16 cases. During the surgeries, frozen skin exhibited negative margins, and the pectoralis major myocutaneous flap was used for reconstruction in each case.

Post-operative pathology. Post-operative pathological analysis revealed that there were 3 cases of well-differentiated squamous carcinoma, 8 cases of moderately-differentiated squamous carcinoma and 5 cases of poorly-differentiated squamous carcinoma. The tumors had invaded the muscle and skin in each examined case.

Appearance and chemoradiotherapy tolerance. All pectoralis major myocutaneous flaps survived, with no cases of necrosis. In 14 cases, primary healing of the surgical wound occurred without incident; in the remaining 2 cases, a small quantity of exudate from the surgical wound was observed after the removal of cervical sutures, although the wounds healed after their dressings were changed. Following cervical reconstruction, the patients' necks were essentially symmetrical and exhibited a satisfactory appearance. Chemoradiotherapy began 4-6 weeks after the surgery. In all cases, the flap exhibited good tolerance during and after radiotherapy, and no interruptions in radiotherapy occurred due to flap necrosis.

Donor region condition. In the 16 examined cases, no patients experienced lymphedema, paresthesia or dysfunction of an upper extremity due to the cutting of the pectoralis major muscle. In 9 cases, patients were satisfied with their post-operative shoulder movement at the donor site; in the remaining 7 cases, patients felt greater weakness in this region following surgery relative to prior to surgery. The 14 male patients were generally satisfied with the post-operative appearance of the donor region, whereas the 2 female

patients were dissatisfied with the appearance of this region due to the manifestations of differences in breast size and nipple asymmetry.

Conditions during follow-up. Follow-up periods began on the date that chemoradiotherapy was completed and ended on December 31, 2013. All 16 cases were followed, with follow-up periods ranging from 6 to 53 months. During follow-up, the recurrence of cervical tumors occurred in 6 cases and mortality occurred in 9 cases. Detailed follow-up information is presented in Table II.

A report of a typical case. In early November 2011, a mass was inadvertently discovered in the right side of the neck of a 39-year-old male. This mass produced no pain or fever. The patient took self-selected herbal medications, but this treatment produced no improvement. Instead, the mass exhibited progressive enlargement and caused intermittent needle-like pain; therefore, the patient was examined in another hospital in January 2012. On January 31, CT examination revealed nodules and patchy shadows in the upper lobe of the right lung, which suggested the possibility of an old case of tuberculosis. A re-examination of the right neck mass was therefore recommended, and the idea that this mass was a neoplastic lesion was considered. The results of a needle biopsy (C4942) on February 2 suggested that the mass could be a metastatic squamous cell carcinoma with extensive hemorrhage and necrosis. PET-CT examination (P0992) on February 10 revealed that the right-sided neck mass exhibited central necrosis, which raised the possibility of a malignant tumor (perhaps primary or neurogenic). Pressure on the mass caused the trachea to shift to the left. Multiple small nodules and cord-like shadows were observed in the apex of the right lung, a finding consistent with the manifestations of tuberculosis. Two three-week cycles of a chemotherapy regimen that included docetaxel (75 mg/m², day 1), DDP (75 mg/m², day 1) and 5-fluorouracil (0.5 g/m², days 2-5) were administered; this treatment did not significantly affect the tumor, but ameliorated the patient's symptom of prickling sensations. The patient was hospitalized in the Tumor Hospital of Ganzhou on April 2. A physical examination at this time revealed no varicose veins, a soft neck, leftward deviation of the trachea and a right-sided cervical tumor of ~13x10 cm in size. The surface of the tumor was covered with ~10x8 cm of red skin, which felt soft to the touch, indicating possible tissue necrosis, and had relatively unclear boundaries; the mass was painful but relatively rigid (Figs. 1 and 2). No palpable masses were found in the left carotid region. Indirect endoscopic examination of the nasopharynx revealed no tumors. Bilateral vocal cord activity was normal, with no apparent space-occupying lesions in this region. No primary tumor or other metastases beyond the cervical tumor were identified in a comprehensive examination. CT examination revealed a tumor without clear boundaries located in the right side of the neck (Fig. 1). On April 14, under general anesthesia, the patient was subjected to a radical right neck dissection combined with pectoralis major myocutaneous flap reconstruction (Figs. 3 and 4). The dissected pale yellow necrotic tissue was 16x15x10 cm in diameter (Fig. 5) which revealed a tumor mass, 12x10x10 cm in diameter. Post-operative pathological examination revealed

Table II. Patients' surgical and follow-up results.

Case no.	Carotid condition	Visible residual tumor	Start time for post-operative chemoradiotherapy, weeks	Follow-up duration, months	Neck recurrence	Survival condition	Cause of mortality	Primary tumor
1	Normal	No	4	22	Yes	Succumbed	Lung metastasis	Unknown
2	Normal	No	4	48		Succumbed	Nasopharyngeal hemorrhage	Nasopharyngeal cancer
3	Normal	No	4	36	Yes	Alive		Unknown
4	Normal	No	5	32	Yes	Succumbed	Bone metastasis	Tonsil
5	Normal	Brachial plexus	4	11	Yes	Succumbed	Lung metastasis	Unknown
6	Adventitia repair	No	4	18		Succumbed	Lung metastasis	Unknown
7	Normal	No	4	25	Yes	Succumbed	Neck recurrence	Unknown
8	Normal	No	4	16		Succumbed	Bone metastasis	Unknown
9	Normal	No	6	22		Alive		Unknown
10	Adventitia repair	Brachial plexus	5	10	Yes	Succumbed	Neck recurrence	Unknown
11	Normal	No	4	18		Alive		Unknown
12	Normal	No	5	13		Succumbed	Lung metastasis	Unknown
13	Normal	No	4	14		Alive		Unknown
14	Normal	No	4	11		Alive		Esophageal cancer
15	Artery resection	No	4	10		Alive		Unknown
16	End-to-end anastomosis	No	5	6	-	Alive	-	Unknown

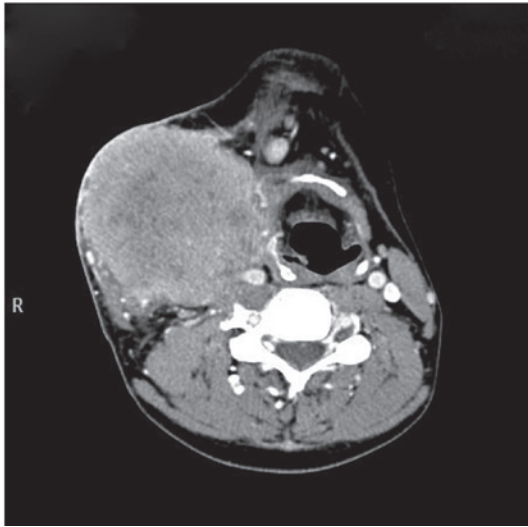


Figure 1. Computed tomography results indicating the presence of a giant mass without a clear boundary separating the mass from the carotid artery.



Figure 2. Tumor affected the patient's skin.

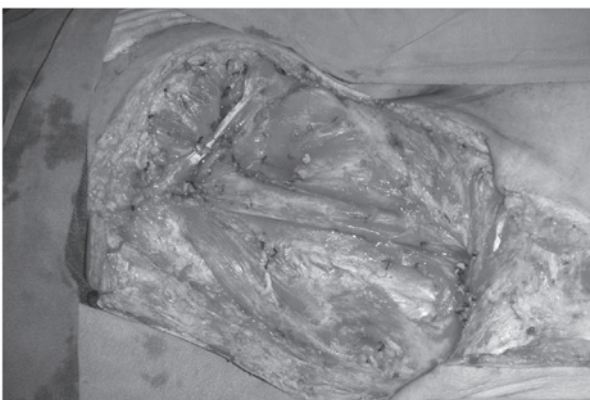


Figure 3. A giant skin defect in the cervical region was created following radical neck dissection.

tumor cells with large nuclei and abundant cytoplasm, as well as a number of prominent nucleoli and keratosis (Fig. 6). Thus, a diagnosis of moderately-differentiated squamous cell carcinoma was confirmed. Concurrent chemoradiotherapy was provided beginning at 4 weeks post-surgery, including 35 radiation treat-

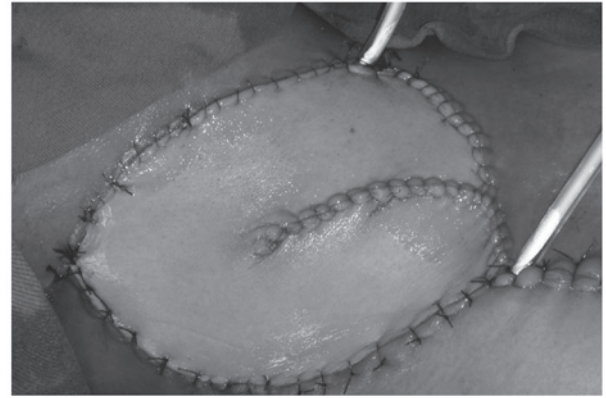


Figure 4. Appearance of the affected region following reconstructive surgery using the pectoralis major myocutaneous flap.

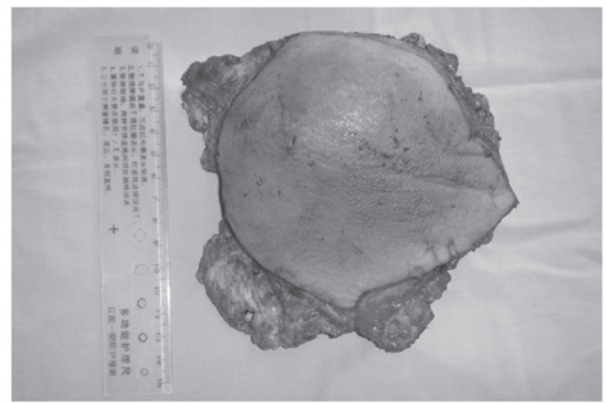


Figure 5. Neck dissection specimen.

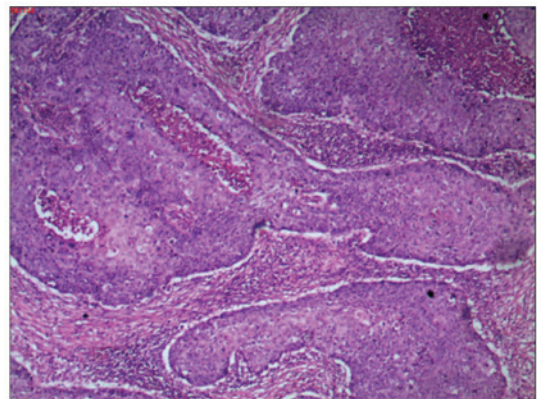


Figure 6. Pathological examination revealed disordered carcinoma nests with massive necrosis. Tumor cells with large nuclei and a number of prominent nucleoli, abundant cytoplasm and keratosis were identified (stain, hematoxylin and eosin; magnification, x40).

ments with a total absorbed dose of 70 Gy and 6 chemotherapy treatments of 30 mg/m²/week DDP. During a return visit in November, right pleural effusion was detected, resulting in a diagnosis of tuberculosis. Symptomatic and anti-tuberculosis treatments were administered, and the pleural effusion disappeared. During the course of follow-up through December 2013, no primary tumor was found and no recurrence of the cervical tumor or other metastases was detected (Fig. 7).



Figure 7. Appearance of the patient's neck following suture removal.

Discussion

The main difficulties associated with the surgical treatment of giant cervical metastatic tumors that have invaded the skin and developed from unknown primary tumors include the techniques not only for exposing blood vessels and separating these vessels from the tumor during neck dissection, but also for excising the flap and utilizing it for reconstruction. The main post-operative issues include repairing arterial ruptures, stopping bleeding associated with these ruptures and ensuring flap survival. Thus, surgical incision choices should not only consider aesthetics, but also be based on the principle of ensuring optimal exposure of the relevant region. If part of a tumor is located under the mandible or clavicle, causing difficulties with respect to exposing blood vessels, one option to consider is truncating the bone to enhance the exposure of these vessels and reduce surgical difficulty (11). To avoid intraoperative hemorrhage, the handling of blood vessels in hazardous regions should only be performed under direct observation and when the surgeon has absolute certainty regarding the appropriate procedure. For the majority of patients with giant cervical metastatic tumors, the carotid artery can be fully separated from the tumor; if necessary, a portion of this artery can be removed, and a vascular anastomosis or vascular graft can be performed (12-14). If limited techniques are available for the reconstruction of blood vessels or if a balloon occlusion test on this carotid artery prior to surgery produces results indicating the requirement for an carotid artery resection, then this artery can be resected (12-14) during the course of the radical neck dissection. The size and shape of the skin defect produced by a radical neck dissection determines the size and shape

of the pectoralis major myocutaneous flap obtained for reconstruction. In the present study, during surgery, after an exploration of the deep surface of the pectoralis major muscle had clearly identified the position of the pectoral branch of the thoracoacromial artery, the pectoralis major muscle fiber tissue was completely cut at 1-2 cm from the vascular pedicle, under direct visual observation. In this manner, the pectoralis major myocutaneous flap was produced; this flap was then shaped to the recipient area and used to repair the large defects in the cervical tissue and skin produced by the neck dissection. Following surgery, various aspects of the flap, including color, texture, temperature, degree of capillary filling and swelling, were closely observed, and intensive care for the flap was provided as required. Successful surgical treatment was performed for all 16 patients examined in this study. Therefore, if a patient's condition is closely monitored prior to surgery, appropriate surgical plans are conscientiously developed and the patient is closely observed and well cared for after surgery, a radical neck dissection followed by reconstruction using the pectoralis major myocutaneous flap is a safe and effective approach for treating giant cervical metastatic cancers that have invaded the skin and developed from an unknown primary tumor.

In the 2013 National Comprehensive Cancer Network guidelines for clinical practice in cases of head and neck cancer (15), surgery remains the preferred option for the radical treatment of cervical metastatic cancers associated with an unknown primary tumor. Patel *et al* (16) proposed the use of a radical neck dissection combined with adjuvant post-operative chemoradiotherapy for the treatment of pN3 cervical metastatic cancers from unknown primary sites. Shoushtari *et al* (17) reported that surgery combined with chemoradiotherapy could provide survival benefits to patients with pN3 cervical metastatic cancers from unknown primary origins. If salvage surgery is not utilized for the treatment of these types of cancers, the cervical tumors often fester, producing odors and massive hemorrhages that severely compromise quality of life and survival rates. Uncontrolled cervical tumors are the main cause of chemoradiotherapy failure and patient mortality in these cases. The surgical treatment of cervical lymph nodes by neck dissection produces relatively high control rates and can improve rates of patient survival (18,19). Therefore, radical neck dissection is particularly important for patients with giant cervical metastatic cancers that have invaded the skin and developed from unknown primary tumors. Even in cases of palliative resection, reconstruction with the pectoralis major myocutaneous flap can reduce the festering of the cervical tumor and thereby improve quality of life. Among the 16 examined patients in the present study, there were 6 cases in which cervical tumors recurred after surgery and chemoradiotherapy; however, only 2 patients succumbed due to the recurrence of cervical tumors. Thus, this indicates that radical neck dissection combined with reconstruction using the pectoralis major myocutaneous flap and post-operative concurrent chemoradiotherapy can enhance local control rates and quality of life for patients who suffer from giant cervical metastatic cancers that have invaded the skin and developed from unknown primary tumors. This treatment approach can achieve satisfactory outcomes.

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