

Cervical Lymph Node Metastasis of Squamous Cell Carcinoma from Unknown Primary Tumor

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ABSTRACT

The first aim of the study was to determine the survival rate of the patients with Carcinoma of the Unknown Primary (CUP) in relation to lymph node status and eventual later identification of the primary tumor. To second one was to investigate the impact of PET-CT on identification of the primary tumor. We studied 97 patients sent to our University Medical Center with diagnosis of metastasis of unknown primary tumor between 1.1.1997 and 1.9.2009. All patients had panendoscopy and some had PET-CT at later period. All susceptible patients had a surgery and postoperative radiation therapy. After the completed their treatment they were followed up at ENT department. With preoperative examinations we discovered 48 primary tumors. Only in one case of 13 the PET-CT detected the primary tumor not confirmed with other examination methods. After the treatment we found primary tumors in 10 patients. In 39 patients we didn't discover any primary tumor. The 2-year overall survival for 10 patients with found tumor was 80.0%, the 2-year overall survival for the 39 patients without discovered tumor was 73.8%. The 2-year disease-specific survival for 10 patients with found tumor was 90.0%, the 2-year disease-specific survival for 39 patients without discovered tumor was 81.6%. The 2-year overall survival for high neck level lymph node metastasis group (N=36) was 80.1%, the 2-year overall survival for low neck level lymph node group (N=13) was 61.5%. PET-CT method was not particularly useful in detecting primary tumors in patients with metastasis with unknown primary. Patients with high neck level lymph node metastasis had statistically significant better survival.

Key words: unknown primary cancer, head neck cancer, PET-CT, panendoscopy, neck metastases

Introduction

Squamous cell carcinoma has, besides its aggressive local growth, a specific quite predictable metastasis pattern to the regional lymph nodes. Especially interesting cases are those with patients with metastasis in the neck lymph nodes, in which we cannot find the primary tumor, even with the most accurate clinical examination and the usage of flexible and rigid endoscopes. According to the data from the literature the incidence of patients with unknown primary tumor varies tremendously and accounts to as low as 2% to as high as 15%¹⁻⁵. The reason for such a big difference in undiscovered primary tumors is in the different protocols and follow up of the patients used in different institutions. Another important factor is whether we limit ourselves to only the squamous cell carcinoma or also on the other types of cancer (undifferentiated, adenocarcinoma). The definition of the carcinoma of the unknown primary tumor (CUP) has changed

throughout the time; in the early 70s the diagnosis of the CUP had been made in cases where the primary tumor hadn't been found at the autopsy as well. Nowadays the diagnosis of the CUP can only be made after the primary tumor is not found after the accurate patient's history, clinical exam, ultrasound, X-ray, endoscopic examination and biochemical blood workup. In some rare cases a primary tumor is found after the treatment of the metastasis.

As there are different protocols of the examinations in the cytologically confirmed metastasis in the neck lymph nodes, there are also different approaches to the treatment.

In this article the diagnostic protocol and the treatment of these patients is shown as done in the Department of Otorhynolaryngology and Maxillofacial Surgery in the UMC Maribor.

Patients and Methods

We have performed a retrospective analysis of the patients diagnosed with the CUP (confirmed with fine needle biopsy), who were admitted to the department between January 1st 1997 and June 1st 2011. The survival analysis was performed for patients admitted until Sept. 1st 2009 for having minimal 2 year follow up.

All patients had endoscopic examination of the upper aerodigestive system (panendoscopy) either in local or in general anesthesia. The endoscopic exam included: examination of the larynx and pharynx with rigid or flexible telescopes, flexible bronchoscopy and rigid esophagoscopy. All suspicious lesions were biopsied and ipsilateral tonsillectomy was performed together with curettage of the nasopharynx. After 2008 most of the patients had had a PET/CT prior to panendoscopy. PET/CT was performed in other institution. All sites showing increased uptake of the ¹⁸F deoxyglucose were also biopsied.

In patients where the primary tumor was not found we performed ipsilateral comprehensive neck dissection. Postoperatively patients were irradiated under an unknown primary protocol, encompassing upper aerodigestive tract (from nasopharynx to hypopharynx) if primary tumor was not found with boost to the region with metastasis. Patients were irradiated 5 days a week in 2 Gy fractions with tumor dose 60 Gy. Radiotherapy was performed at the Institute of Oncology in Ljubljana. After the treatment we followed the patients on a regular basis. For the first year the follow up visits were scheduled every 2 months and from the second year on, the time in months between visits corresponded the years passed since the start of the treatment (e.g. if 4 years have passed since the start of the treatment, the examination was done every 4th month). Follow up included an accurate physical exam with the help of flexible endoscopes, Chest X ray (once a year). Ancillary tests were performed depending on clinical presentation (e.g. CT scan, MR...)

Patients were divided into two groups: in the first are patients in whom the primary tumor was never identified, and in the second are patients in which the primary tumor was identified after the treatment of the lymph node metastases during a follow up.

Statistical Methods

All information was collected retrospectively and processed with the statistical package MedCalc (Version 11.6., MedCalc Software, Mariakerke, Belgium) at the Faculty of Medicine, University of Maribor, Slovenia. The overall survival and disease-specific survival were calculated using the Kaplan-Meier method⁶.

The time interval for calculating overall survival was determined as the time between the date of diagnosis and the day of death, regardless of the cause of death. For calculating disease-specific survival, the time interval between the date of diagnosis and the date of death was calculated only if death was considered as being causally related to the progression of the regional disease.

Results

In the period between 1.1.1997 and 1.9.2009 we managed 96 patients with a cervical lymph node metastasis of the unknown primary. Twelve of these patients were excluded from the review. After additional immunocytochemical staining or repeated fine needle biopsy in 6/12 patients squamous cell carcinoma was not confirmed. Two patients had metastasis of adenocarcinoma, two metastasis of clear cell carcinoma, one had an extraosseous plasmocytoma and one patient had a B cell lymphoma. One female patient had been previously treated for breast cancer; another patient was in such poor condition that no diagnostic workup or specific treatment was possible. In 3 patients we found suspicious changes in the lungs on a Chest X ray, which were later confirmed as primary bronchial carcinoma. In 1 patient we found a cancer of the nasopharynx with a flexible endoscopy.

In 22/84 patients we identified primary tumor before or at the beginning of the therapy, in 10 patients the primary tumor was identified on further examinations after the treatment for metastases on the neck. Panendoscopy with one-sided tonsillectomy, curettage of the nasopharynx and biopsy from the suspicious places were done in all 84 patients. A PET-CT scan was done in 28/84 patients. According to the protocol the PET-CT should be done before the panendoscopy, but that was not always possible, because of the logistic problems. Only 10/28 had PET/CT scan done before the panendoscopy. PET/CT scan identified primary tumor in 8 out of 28 patients.

With the panendoscopy, ipsilateral tonsillectomy and curettage of the nasopharynx and random biopsy from the base of the tongue we found a primary tumor in 22/84 patients. In 1 patient with a nasopharyngeal carcinoma a surgeon could not find suspicious place, but the nasopharyngeal cancer was later confirmed with the help of the PET-CT. The biopsy guided with the result of the PET-CT, was also done in a patient with carcinoma on the base of the tongue, because the primary tumor was not identified during the panendoscopy. Out of 22 patients in which the primary tumor was found during the panendoscopy, 8 of these had a PET-CT scan. In 7 patients the primary tumor was found during the panendoscopy. In 1 patient in whom the cancer of the tonsils was found on serial sections, there was no pathological uptake on PET-CT scan in the tonsillar region.

In 10/22 we found a primary tumor in the tonsils, in 3/22 in the hypopharynx and in 3/22 in the supraglottic region. In 1/22 the tumor was identified in the base of the tongue, in 1/22 in the glossotonsillar sulcus, 1/22 in the nasopharynx and in 1 patient on the lungs.

Remaining 62 patients had true unknown primary. Out of these 62 patients we excluded 9 of them from the research because of their general poor condition, which did not allow for treatment with curative intent and so their treatment was only symptomatic. In 4 patients we have a follow up shorter than 2 years, and therefore they were excluded from survival analysis.

For survival analysis we included 49 patients. Mean age at time of diagnosis was 61 years. Median follow-up was 36 months. Minimum follow-up of the patients alive at the end of the study was 24 months.

In 10/49 patients we identified a primary tumor during the follow up. In 4/10 the primary tumor was discovered outside the area of the head and neck. In 3 patients the primary tumor was identified in the abdomen (gastric cancer in 2/10 and urinary bladder tumor in 1/10) and at 1 in the chest (lung cancer). In 6 patients the primary tumor was found in the head and neck region, in four in the oropharynx and in two in the oral cavity. All of the patients who had been diagnosed with a primary tumor outside the head and neck region died soon after the discovery of the tumor. Two of them died because of the disease progress, one from septic shock and one because of the complications after the surgery. Currently 3/10 patients with tumor in the head and neck are still alive. Two have a tumor in oropharynx and one with a cancer of the floor of the mouth.

In 39/96 patients we could not identify primary tumor during the preoperative workup or during follow up and were treated with a neck dissection and postoperative irradiation.

Table 1 represents both groups of patients and their current status (age, gender, smoking, alcohol). The two groups are: »CPT«- with confirmed primary tumor and »WPT« - without primary tumor

The 2-year overall survival for CPT group was 80.0% ($\pm 12.6\%$ standard error), the 2-year overall survival for WPT group was 73.8% ($\pm 7.1\%$ standard error) (Figure 1). The difference between groups is not statistically significant (log-rank test, $p=0.75$).

The 2-year disease-specific survival for CPT group was 90.0% ($\pm 9.5\%$ standard error), the 2-year disease-specific survival for WPT group was 81.6% ($\pm 6.3\%$ standard error) (Figure 2). The difference between groups is not statistically significant (log-rank test, $p=0.28$).

We analyzed the difference between the patients with metastasis in the upper and lower regions of the neck:

The 2-year overall survival for high neck level lymph node metastasis group (N=36) was 80.1% ($\pm 6.7\%$ standard error), the 2-year overall survival for low neck level lymph node group (N=13) was 61.5% ($\pm 13.5\%$ standard error) (Figure 3). The difference between groups is statistically significant (log-rank test, $p=0.009$).

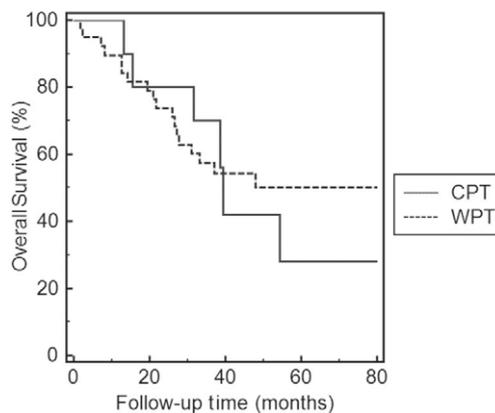


Fig. 1. Overall survival: CPT- with confirmed primary tumor; WPT - without primary tumor.

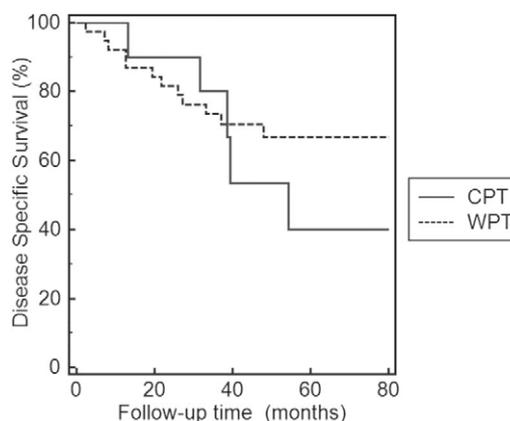


Fig. 2. Disease-specific survival: CPT- with confirmed primary tumor; WPT - without primary tumor.

The 2-year disease-specific survival for high neck level lymph node metastasis group (N=36) was 85.6% ($\pm 6.0\%$ standard error), the 2-year overall survival for low neck level lymph node group (N=13) was 74.1% ($\pm 12.9\%$ standard error) (Figure 4). The difference between groups is statistically significant (log-rank test, $p=0.02$).

The survival rate for patients with extracapsular spread compared to the patients without is not statistically significantly different (Figure 5). Figure 6 represents survival curves for different stages of the nodal disease. It is evident that patients with more advanced

TABLE 1
TWO GROUPS OF PATIENTS AND THEIR STATUS

	CPT group confirmed primary tumor	WPT group without primary tumor
No of patients	10	39
Gender (F/M)	1F / 9M	10F / 29M
Age at diagnosis (mean \pm SD)	53.8 (± 15.1)	63.1 (± 10.8)
Smoking (Yes/No)	9Y / 1N	28Y / 11N
Alcohol (Yes/No)	8Y / 2N	25Y / 14N

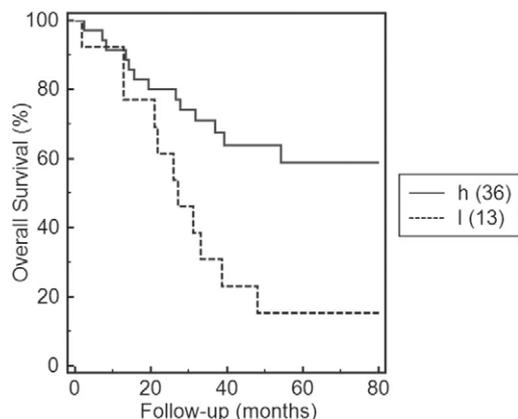


Fig. 3. Overall survival of all patients regarding to neck level lymph node: h-high/l-low (No of cases).

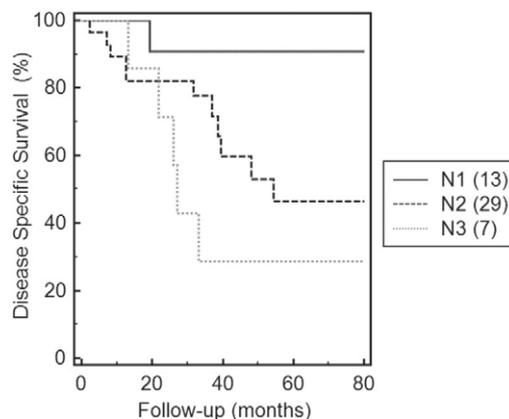


Fig. 6. Disease-specific survival of all patients – N subgroups (No of cases).

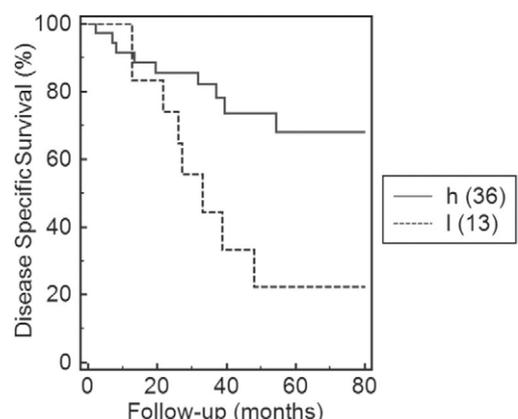


Fig. 4. Disease-specific survival of all patients regarding to neck level lymph node: h-high/l-low (No of cases).

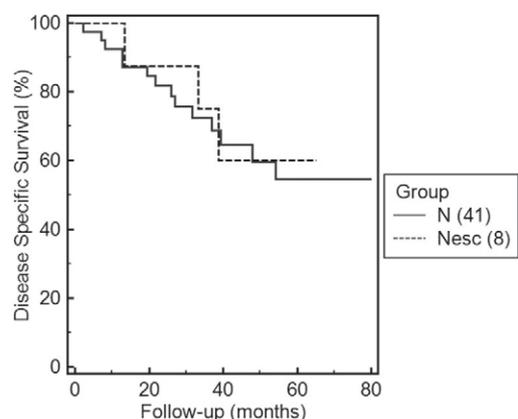


Fig. 5. Disease-specific survival of all patients – N subgroups (No of cases).

nodal disease have lower survival than those with a single node.

The 2-year disease-specific survival for N group (N=41) was 81.7% ($\pm 6.2\%$ standard error), the 2-year disease-specific survival for Nesc group (N=8) was 87.5%

($\pm 11.7\%$ standard error) (Figure 5). The difference between groups is not statistically significant (log-rank test, $p=0.83$).

The 2-year disease-specific survival for N1 group (N=13) was 90.9% ($\pm 8.7\%$ standard error), for N2 group (N=29) was 82.1% ($\pm 7.2\%$ standard error), and for N3 group (N=7) was 71.4% ($\pm 17.1\%$ standard error) (Figure 6). The difference between groups is not statistically significant (log-rank test, $p=0.10$).

Discussion

Patients with CUP usually have advanced cancer, but we cannot identify primary tumors. There are different protocols for preoperative management of the carcinoma of the primary tumor. Nowadays the most popular is PET-CT. There are different opinions about accuracy of these methods. Deron with co workers⁷ could not find any primaries on his 18 patients; however Wong and Saunders found 8 primaries in their 17 patients. In this current research we identified 8 primaries in 28 patients. Only in two patients out of 8 we couldn't identify primary tumor during the panendoscopy: in a patient with nasopharyngeal cancer and a patients with base of the tongue carcinoma. Therefore only in these two patients PET-CT had advantage over the panendoscopy. On the other way PET-CT is successful method if it is combined with panendoscopy. With PET-CT the detection rate of the suspicious places that were sampled is higher compared to the panendoscopy alone. Panendoscopy, combined with ipsilateral tonsillectomy, nasopharynx curettage and tongue base biopsy has helped to identify 22 primaries in 84 patients. Ten patients had tonsillar cancers. Most of them were found after serial sections of the tonsil at histology. Some authors^{9,10} advocate both-sided tonsillectomy. On the other hand there are authors¹¹ who avoid routine tonsillectomy, and they advocate only physical exam with meticulous palpation. They perform tonsillectomy only in patients with clinically abnormal tonsil. It is not plausible for a small, early tonsillar cancer to metastasize into contralateral lymph nodes. We believe

that bilateral tonsillectomy is not indicated in CUP patients. With bilateral tonsillectomy the chances for post-operative bleeding are increased, but it makes oropharynx symmetrical, which could be an important factor for follow up. The symmetry is greatest argument in favor for bilateral tonsillectomy. In this series we didn't identify cancer in contralateral tonsil before or during the treatment as well as in the follow up period.

During the follow up we identified ten primaries. Four patients had primaries outside of head and neck region. All four patients didn't have PET-CT scan. For this reason we do not know if this patients had small primaries before neck dissections, however on abdominal ultrasound examinations and chest X ray we could not find any suspicious places. In other 6/10 patients during the follow up we identified primaries in head and neck region, despite the postoperative radiotherapy. Three of these six patients had had PET-CT scan. In all six patients there was no increased uptake 18F-odeoxyglucose during the diagnostic workup. All patients with confirmed primaries outside of head and neck died very quickly after diagnosis. Patients with identified primary in the head and neck have better survival rate compared to patients where primary could not be identified.

Boscolo-Rizzo with co-workers¹³ treated 88 patients with CUP. Survival rate of this patients was 50,9 % at two years but only 25,3 % at five years. Our patients have 72% two years survival and 35% five years survival. Disease specific survival is much better and for two years is 80 and 40% for five years. This survival is within the range reported in the literature 35-66%^{14–16}.

The standard therapy for CUP patients is comprehensive neck dissection and postoperative radiotherapy of the neck and upper aerodigestive tract^{17,18}. Most our pa-

tients treated with curative intent had this therapeutical protocol, small number had also concomitant chemotherapy. Patients with metastases in higher neck level have significantly better survival rate than patients with lower neck metastases. This is also reported in the literature^{2,19,20}. But we have totally different results in patients with extracapsular spread. Our patients with extracapsular spread had better survival. Possible reason is a small number of the patients in this group (three patients). Patients with smaller metastasis have better two and five years survival than patients with more advanced disease, which also corresponds to the data reported in literature^{19–21}.

Conclusion

Panendoscopy with ipsilateral tonsillectomy is the optimal method for identification of the primaries in the head and neck in patients with CUP. PET-CT can be useful only in combination with panendoscopy and it might be helpful in identification of the primary outside of the head and neck. We cannot draw any conclusions since the number of the patients with PET-CT scan is too small. Patients with primaries identified outside head and neck region have worse prognosis and their survival rate is lower. Our therapy protocol with comprehensive neck dissection and post-operative radiotherapy yield comparable results to that from the literature.

Two year survival rate is encouraging. Patients in whom we discover the primary during the therapy and have their primary in the head and neck and those who have metastases in higher neck regions have a better survival rates. Because of the small number of patients a multinstitutional prospective study would be needed to evaluate the value of the PET-CT methods of treatment.

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METASTAZE NEPOZNATOG PRIMARNOG CARCINOMA NA VRATU

S A Ž E T A K

Cilj istraživanja je bio utvrditi preživljavanje bolesnika sa metastazama vrata nepoznatog planocelularnog karcinoma u ovisnosti o proširenosti metastatskog procesa i mogućeg kasnijeg otkrivanja primarnog tumora. Opredjeliti vrijednost PET-CT pretrage u traženju nepoznatog primarnog tumora. Napravljena je retrospektivna studija 97 bolesnika sa metastazama vrata nepoznatog planocelularnog karcinoma, koji su bili primljeni na liječenje na Odjel za Otorinolaringologiju i maksilofacijalnu kirurgiju Univerzitetskog kliničkog centra Maribor u razdoblju od 1.1.1997 do 1.9.2009. Kod svih bolesnika napravljena je panendoskopija, a bolesnici koji su liječeni u kasnijem periodu imaju i pretragu sa PET-CT. Svi operabilni bolesnici bili su operirani i poslije operacije zračeni. Po završetku terapije u redovnom vremenskim razmacima kontrolirani su na Otorinolaringološkom odjelu UKC Maribor. Kod 48 bolesnika primarni tumor bio je pronađen u toku pripreme za operativno liječenje. Kod 13 bolesnika primarni tumor bio je pronađen sa PET-CT pretragom, ali samo kod jednog od njih tumor nije bio pronađen drugim pretragama. Kod 39 bolesnika nismo pronašli primarni tumor, a kod deset bolesnika primarni tumor pronašli smo u kasnijem periodu. Dvogodišnje preživljavanje je kod bolesnika sa pronađenim primarnim tumorom 80,0%, a kod bolesnika bez pronađenog tumora 73,8%. Specifično dvogodišnje preživljavanje je kod bolesnika sa pronađenim tumorom 90,0%, a kod bolesnika bez pronađenog primarnog tumora 81,6%. Dvo godišnje cjelokupno preživljavanje bolesnika sa metastazama visoko na vratu (N= 36%) iznosi 80,1%, a kod bolesnika sa metastazama nisko na vratu (N=13) iznosi 61,5%. Pretraga sa PET-CT u traženju nepoznatog primarnog tumora nije se pokazala kao posebno korisna. Bolesnici sa metastazama visoko na vratu imaju statistički značajno bolje preživljavanje od bolesnika sa metastazama nisko na vratu.