

# Merkel-cell carcinoma: Preoperative clinical diagnosis and therapeutic implications



Ann. Ital. Chir., 2014 85: 352-357  
pii: S0003469X1402226X

Vittorio Pasta, Massimo Vergine, Valerio D'Orazi, Paolo Scipioni, Massimo Monti, Adriano Redler

Department of Surgical Sciences, "Sapienza" University of Rome, Policlinico, "Umberto I", Rome, Italy

## Merkel-cell carcinoma: preoperative clinical diagnosis and therapeutic implications

*The authors report the personal experience of some patients undergoing surgery for carcinoma of Merkel and discuss the diagnosis and therapeutic approach guided by literature and international guidelines. Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumour, which prefers the Caucasian race in adulthood. Approximately 78% of patients are over than 59 years, the most common location is at the level of the head and neck (50.8%) and less frequently in the limbs (33.7%). The literature is discordant about the causes and risk factors for this cancer. In fact, some authors describe major risk factor the immunosuppression, still others see prolonged exposition to UV radiation increases the risk for the onset of this tumor. Metastasizes early to the skin (28%), the lymph nodes (27%), liver (13%), lung (10%), bone (10%) and encephalon (6%), and may recur both locally (30-60%) and both locoregional (40-73%). Our experience confirms the difficulty of preoperative clinical diagnosis and a correct therapeutic approach to Merkel cell carcinoma for the lack of specific characteristics as first clinical assessment, which may keep the suspect nature. International guidelines provide a wide excision (3 cm in largeness and 2 cm in depth) to reduce the risk of disease recurrence, preferring adjuvant chemotherapy not radiotherapy. For lesions of stage I-II over the wide excision also regional lymphadenectomy is performed or, more rarely, the technique of sentinel lymph node.*

KEY WORDS: Adjuvant chemotherapy, Lymph nodes metastases, Merkel-cell carcinoma, Radiotherapy, Surgery

## Background

Merkel-cell carcinoma (MCC) is a rare and aggressive skin cancer, sometimes referred to as a neuroendocrine carcinoma of the skin, described for the first time by Toker in 1972 who reported five cases of so-called "trabecular carcinoma of the skin"<sup>1</sup>. The same author in

1978 described three new cases of malignancy with the same characteristics and with cytological presence of granules of neurosecretory type, similar to those described for the first time by Merkel in 1875<sup>2</sup>, and for this reason why the term "Merkel-cell carcinoma" is still used to indicate such a tumor. The diagnosis can be difficult, because the tumor may resemble metastatic neuroendocrine tumours, lymphoma, leukemia, adnexal tumors, and melanoma, and it may occur in association with other skin tumours<sup>3,4</sup>. Immunohistochemical studies are helpful in establishing the diagnosis<sup>1</sup>. In a recent study carried out in 3870 cases it was shown that this tumor arises preferentially in adulthood Caucasian man<sup>5</sup>. In approximately 78% of patients older than 59 years, the most common location is at the level of the head and neck (50.8%) and less frequently at the limbs (33.7%), although in this latter one a new case was recently report-

Pervenuto in Redazione Settembre 2013. Accettato per la pubblicazione Dicembre 2013

Correspondence to: Valerio D'Orazi (e-mail: info@valeriodorazi.com)

ed 6. The average diameter of the tumor is 29 mm and the histological diagnosis makes use of immunohistochemistry to detect neuroendocrine cytoplasmic markers specific for Neuron Specific Enolase (NSE), Cytokeratins (Cytokeratins 20), and chromogranins A<sup>7</sup>. For the etiopathogenesis, the literature is discordant about the causes and risk factors for this malignancy. In fact, some authors describe immunosuppression as the major risk factor<sup>8-10</sup>, although potential viral factors as well as prolonged ultraviolet (UV) light exposure<sup>11,27</sup> are considered the greatest risks for MCC occurrence. As well as for melanoma, MCC is more frequent and aggressive after immunosuppression for organ transplantation and following lymphoproliferative disorders such as B-cell lymphoma<sup>12,16</sup>.

The approach to the study of MCC has been deepened with the classification made in 1991 at the Memorial Sloan-Kettering Cancer Center based on the experience of 70 cases up to the 2011 with the classification drawn up by the American Joint Committee on Cancer (AJCC) that determines tumor staging according to its localization, lymph node (LN) involvement, and metastasis<sup>3</sup>. Clinically, the MCC appears as a fast-growing tumor nodule, red-violet in color, covered with translucent skin, usually nontender to palpation and sometimes ulcerated.

Because of these characteristics, it is important to perform differential diagnosis to exclude basal cell or squamous cell carcinoma, cutaneous lymphoma, cheratocarcinoma, neuroblastoma, and skin metastases of malignant tumors.

The early diagnosis and radical surgery are the fundamental basis for a correct clinical approach to the disease, reducing the risk of recurrence of the tumor. However, adjuvant radiotherapy or chemotherapy may greatly eliminate the possibility of systemic involvement. Thus, the MCC behaviour is very aggressive as it metastasizes early to the skin (28%), LNs (27%), liver (13%), lung (10%), bone (10%), and encephalon (6%), and may recur both locally (30-60%) and at locoregional level (40-73%) and the presence of metastases suggests high index of recurrence<sup>12</sup>. Some authors have described the possibility of a metastasis to axillary lymph nodes at a distance of two years by the removal of an arm MCC with a high mitotic index and areas of intratumoral necrosis. In presence, then, of a histological highly aggressive, wide excision is needed associated with a locoregional lymphadenectomy and eventually radiotherapy<sup>13</sup>. Other authors support that, in Stage I disease, the mainstays of treatment are surgery and radiation<sup>14</sup>.

We report two cases of MCC that underwent surgery to remove the tumor mass in an unusual localization such as the gluteal region. Then, the presence of LN metastases in one of the two tumors gave indication for chemotherapy while the other one underwent radiotherapy after surgery.

## Patients and Methods

This article relates the experience of the last two patients with MCC came to our observation

### CASE N. 1

A 55 years old, Caucasian man, in apparent good condition, presented at our Institute (Department of Surgical Sciences, "Sapienza" University of Rome, Italy) with a subcutaneous, not painful lesion (approximately 8 cm diameter) at the level of the right gluteal region.

An ultrasound examination of the subcutaneous tissue showed a lesion of 6.7 cm by 4.5 cm by 4.1 cm with



Fig. 1: CT of the trunk, front section. CT scan shows the primary lesion located at the level of the left gluteal region (arrow).



Fig. 2: CT of the trunk, cross section. CT scan shows the primary lesion located at the level of the left gluteal region (arrow).

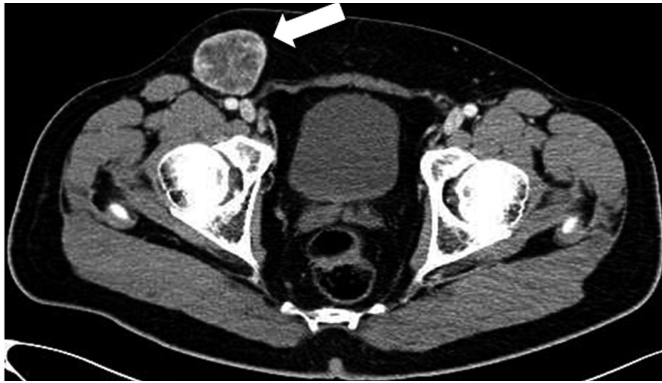


Fig 3 CT of the trunk, cross section. CT scan shows right inguinal lymph node metastases (arrow).

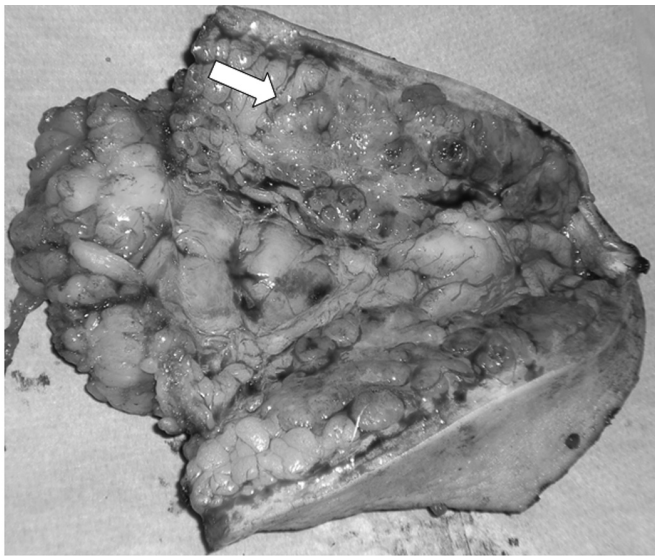


Fig. 4 .Image of the surgical specimen. The imagine of the surgical specimen shows a mass with grey irregular margins. The arrow indicates the edge of the tumour with part of normal tissue.

irregular profiles and defined margins showing intense and anarchic vascularisation. A computed tomography (CT) of the upper abdomen, chest, and brain, without and with contrast agent, confirmed the presence of a parenchymatous neoformation (6.4 cm maximum diameter) with irregular profiles and defined margins (Fig. 1 and Fig. 2), without distant metastases. Moreover, a voluminous neo-formation (5 cm) in the right inguinal lymphonodal region was also evidenced (Fig. 3). A magnetic resonance imaging (MRI) of the corresponding soft tissue, without and with contrast medium, showed a neoformation (6x4 cm) with irregular margins and increased intralesional vascularisation, in correspondence of subcutaneous adipose tissue of the right gluteal region, 1 cm away from the gluteus maximus muscle. Although the neoformation remained confined to the subcutaneous suprafascial plane, it infiltrated the surrounding tissues

in continuity with the overlying skin. The patient was then subjected to wide margin excisional removal of the tumor of the right buttock. The aponeurosis of the gluteus maximus muscle, adherent to the tumor, were also removed along with inguinal ipsilateral LNs for the histological analyses (Fig. 4) The surgical wound was reconstructed with a Limberg flap (even though microsurgical flap could be performed, as previously reported<sup>16</sup>). Surgical specimen showed that the tumor was completely removed along with part of normal tissue.

#### Histopathologic findings

Histological examination revealed, at the level of hypodermis, a coarsely nodular neoformation consisting of small and medium size cells, with round nucleus, finely granular salt-and-pepper chromatin and rare nucleoli with thin acidophilus cytoplasmic border and tumor infiltrating lymphocytes (Fig. 5). These cells were arranged in nests and cords separated by fibrovascular septa, sometimes thick. On immunohistochemical staining, the tumor cells were positive for cytokeratin 20 in a dotlike perinuclear pattern (Fig. 6), vimentin and CD99 (not shown). Both the morphologic and immunophenotypic features are characteristic of Merkel-cell carcinoma. Tumor cells were also found in one of the removed lymph nodes, the largest one detected with the CT. Immunohistochemistry analysis showed high mitotic index (> 20x10 high-power fields -HPF), and positive staining for CK20 and in a lesser extent for S100. Because of the high biological aggressiveness and the presence of lymph nodes metastases, after surgery the

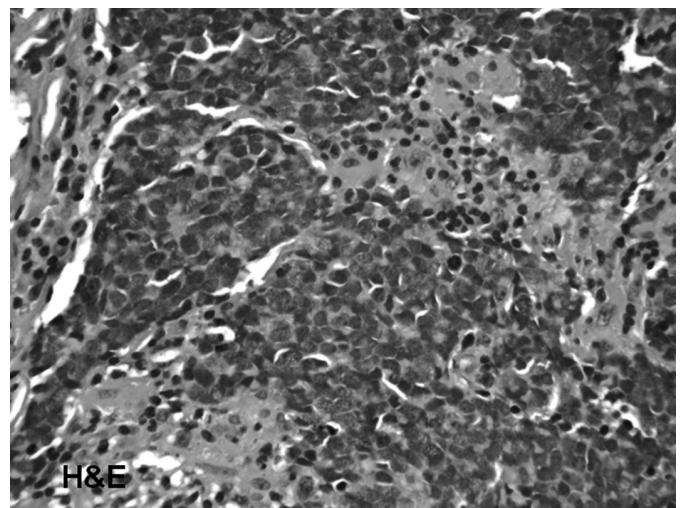


Fig. 5. Biopsy specimen of the tumor neoformation. The tumor is seen to be composed of small and medium size cells, with round nucleus, finely granular chromatin salt-and-pepper and rare nucleoli with thin acidophilus cytoplasmic border; the presence of tumor infiltrating lymphocytes is also evident (H&E, 40x).

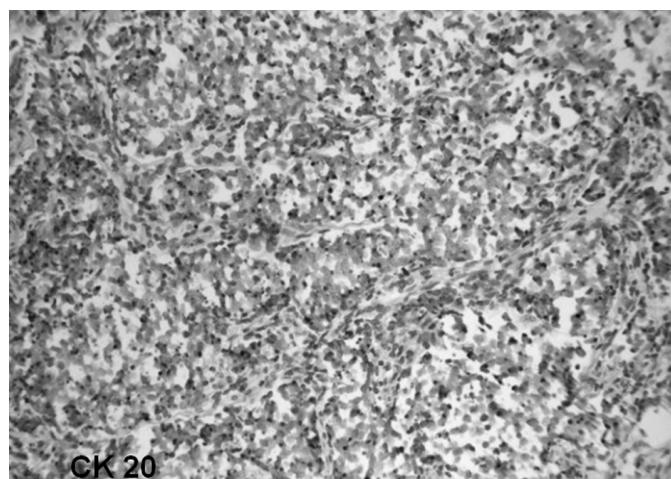


Fig. 6. Biopsy specimen of the tumor neoformation. Immunohistochemical staining for cytokeratin 20 shows a perinuclear dotlike pattern, confirming cells to be Merkel cells (20× magnification).

patient underwent chemotherapy with cisplatin and doxorubicine (CHT). After two years the patient is alive and disease's free.

#### CASE N. 2

A 75 year old, Caucasian man presented at our Institute (Department of Surgical Sciences, "Sapienza" University of Rome, Italy) with an asymptomatic, two months old skin lesion, in the right gluteal region. The nodule appeared rounded (2 cm), erythematous, neither tender nor painful, characterized by a progressive increase in volume. The region where the nodule appeared was never exposed to the sun light, on the other hand the patient referred of a previous little trauma in the same region. An ultrasound examination showed a hypoechoic, lobulated, inhomogeneous lesion (2.4 cm) of the subcutaneous tissue in continuity with the near dermis. Fine needle aspiration biopsy, under ultrasound guidance, revealed a lymphoproliferative lesion, suggesting the presence of potential small cell lung carcinoma or lymphoma. Further analyses were then planned to make tumor staging and histological examination. A total body CT, with contrast agent, keep out the presence of both pulmonary and secondary tumor location while showed a solid subcutaneous neo-formation (3,5 cm maximum diameter) with polycyclic margins, without internal microcalcifications, in the right gluteal region adhering to the gluteus maximus muscle. The CT analysis did not show lymphadenopathy in both pelvic and inguinal region. A MRI of corresponding soft tissue, or with without contrast medium showed a neo-formation 6 cm by 4 cm with irregular margins and increased intralesional vascularisation, in correspondence of subcutaneous adipose tissue of the right gluteal region, 1 cm away from the glu-

teus maximus muscle. This neo-formation also showed characteristics of invasiveness in the surrounding tissues, although it remaining confined to the subcutaneous plane nearby the corresponding skin. These findings first suggested the hypothesis of sarcoma because of the absence of clear involvement of loco-regional lymph nodes. Therefore, we decided to perform an excisional biopsy of the neo-formation, by means of cylindrical scalpel (tru-cut), obtaining a tissue section suitable for a thorough histological evaluation. The patient was therefore subjected to an ample surgical removal of the tumor, in the right gluteal region, that included also the fascia and a portion of the gluteus maximus muscle near the tumor.

#### Histopathologic findings

The macroscopic findings of the surgical specimen showed a nodular yellowish gray tumor (3.3 cm) and the histopathologic diagnosis were consistent with Merkel-cell carcinoma infiltrating the subcutaneous tissue. Immunohistochemistry analyses showed intense, punctuate positivity for paranucleare Cytokeratins, mild paranuclear positivity for Chromogranin in few tumor cells. The segments of excised skeletal muscle and of the removed cutaneous and subcutaneous tissue did not show tumor infiltration. The post surgery period was regular and without complication, then, the patient was treated with ten cycles of regional radiotherapy and after four years is alive and disease free.

#### Discussion

In this paper we showed two new cases of cutaneous Merkel-cell carcinoma. This tumor is rare and often appears without specific characteristics as first clinical assessment, which may keep the suspect nature. Our experience confirms the difficulty of preoperative clinical diagnosis and of a correct therapeutic approach for this very uncommon tumor. Thus, the patients did not show any type of symptomatology at the level of the lesion, moreover, the nodule was in uncommon localization and in an area not usually exposed to sunlight (gluteal region), despite UV rays are risk factor of major importance for this kind of tumor<sup>22-10</sup>. Furthermore, the presence in one of the two patients of lymph node metastasis, suggested different therapeutical treatment after surgery.

In this tumor, surgical therapy has to be prompt and radical, with the surgical excision of the primary lesion wide and deep (with healthy margins section of at least 3 cm lateral and 2 cm in depth) according to the international guidelines suggesting that a wide excision reduces the risk of recurrence<sup>26</sup>. In both of our cases, both the morphologic and immunophenotypic features

after surgery were consistent with Merkel-cell carcinoma. In the first case, however, CT and MRI showed a voluminous neof ormation (5 cm) in the right inguinal lymphonodal region. For this reason, the therapeutic approach was tumor removal and lymphadenectomy, and reoperation with enlargement of the cranial and caudal sides of the tumor, and removal of the belt of the gluteus maximus and the portion of the tumor.

Although in most patients Merkel-cell carcinoma appears as a local-regional disease, it is in fact a systemic disease, with recurrences at nodal and systemic sites in most of patients. In our first case, the choice to administer systemic chemotherapy after surgery was appropriate for this patient and undoubtedly dictated by the outcome of the histological diagnosis, which confirmed the presence of loco-regional lymph node metastasis which, in this aggressive tumor, means high index of recurrence<sup>19</sup>. The neoplasm, in fact, is characterized not only by high aggressiveness but also by rapid diffusion mainly via the lymph nodes<sup>3,20,21</sup> and chemotherapy is deemed to be more indicated for the possible diffusion of the cancer. For stage I and II disease, regional lymphadenectomy over the wide excision, as well as analysis of the sentinel lymph node (SLN) is required. The SLN is a useful technique to select cases needing a more extensive lymphadenectomy and adjuvant therapy<sup>22,23</sup>. For stage III disease, chemotherapy is administered, either such as monotherapy or in combination, though the results are not always satisfactory<sup>24</sup>. Chemotherapy is used primarily as palliation in advanced stages of this cancer, schemes involving the use of cyclophosphamide, doxorubicin, vincristine and etoposide and cisplatin with a response rate of 69% in patients with locally advanced disease and 57% in patients with distant metastases<sup>25</sup>. In the second case, instead, the lack of tumor infiltration and LN metastasis, suggested to perform ten cycles of regional radiotherapy after surgery and in four years the patient was disease free. Definitely best therapeutic results in MCC are achieved with adjuvant radiotherapy after radical surgical treatment, as demonstrated by a study showing the median survival of 63 months after radiotherapy compared to an average of 45 months survival without adjuvant radiation therapy<sup>25,26</sup>. However, radiotherapy would not be useful to control distant micrometastasis in the event of lymph node involvement. Therefore in this second case without lymph node metastases we used adjuvant radiotherapy.

## Conclusion

The Merkel-cell carcinoma is a cancer difficult to diagnose, because it can take on characteristics similar to other cancers such as basal cell carcinomas, spinaliomi, or cutaneous metastases of small-cell lung tumor. The early diagnosis and radical surgery are the fundamental bases for a correct clinical approach to the disease, reduc-

ing the risk of recurrence of the tumor. It is therefore of primary importance to shorten the time between diagnosis and therapy to reduce the use of widely demolitive interventions and to encourage the adjuvant radiotherapy rather than chemotherapy. To date, with regard to the adjuvant therapies radiotherapy has given excellent results in terms of reduction of relapse of localized disease, however, in the presence of metastases or lymph node involvement chemotherapy appears to be the first choice approach to eliminate the possibility of systemic involvement<sup>27</sup>, in a carcinoma that has very high aggressiveness despite the most radical surgical approach.

## Riassunto

Gli Autori riportano l'esperienza personale di alcuni pazienti operati per carcinoma di Merkel, e ne discutono la diagnosi e l'approccio terapeutico alla luce della letteratura e della linee guida internazionali.

Il carcinoma a Cellule di Merkel (MCC) è un tumore raro e aggressivo del sistema neuroendocrino, che predilige la razza caucasica in età adulta. Circa il 78% dei pazienti ha un'età superiore ai 59 anni, la localizzazione più frequente è a livello del collo e del capo (50,8%) e meno frequentemente agli arti (33,7%). La letteratura è discordante sulle cause e i fattori di rischio per questa neoplasia. Alcuni Autori infatti descrivono fattore di rischio maggiore, l'immunosoppressione, altri, parlano di possibili fattori virali e altri ancora vedono nell'esposizione prolungata ai raggi U-V il rischio maggiore per l'insorgenza di questo tumore.

Metastatizza precocemente alla cute (28%), ai linfonodi (27%), al fegato (13%), al polmone (10%), alle ossa (10%) e all'encefalo (6%), e può recidivare sia localmente (30-60%) sia a livello locoregionale (40-73%). La nostra esperienza conferma la difficoltà di diagnosi clinica preoperatoria e di un corretto approccio terapeutico verso il carcinoma a cellule del Merkel per la mancanza di caratteristiche specifiche alla prima valutazione clinica, che possa farne sospettare la natura. Le linee guida internazionali prevedono una ampia escissione (cm 3 in larghezza e cm 2 in profondità) per ridurre il rischio di recidiva di malattia, preferendo piuttosto la chemioterapia adiuvante che non la radioterapia. Per le lesioni di I e II stadio si esegue oltre all'ampia escissione anche linfoadenectomia regionale o, più raramente la tecnica del linfonodo sentinella.

## References

- 1 Toker C: *Trabecular carcinoma of the skin*. Arch Dermatol, 1972; 105:107-10.
2. Tang CR, Toker C: *Trabecular carcinoma of the skin: An ultrastructural study*. Cancer, 1978; 46:2311-321.

3. Nghiem P, McKee P, Haynes H: *Merkel Cell (Cutaneous Neuroendocrine) Carcinoma*, In: *Skin Cancer. Volume of the Atlas of Clinical Oncology*, American Cancer Society. Hamilton Ontario: BC Decker Inc, 2001; 127-41.
4. Cirillo F, Vismarra M, Cafaro I, Martinotti M: *Merkel Cell Carcinoma: A retrospective study on 48 cases and review of literature*. J Oncol, 2012; Volume, Article ID 749030, 9 pages.
5. Albores-Savedra J, Batich R, Chable-Monterof: *Merkel cell carcinoma: Demographics morphology, and survival based on 3870 cases in a population based study*. J Cutan Pathol, 2010; 37:20-27.
6. Negro P, Gossetti F, Brugiotti C, Viarengo MA, Vitolo D, D'Amore L: *Merkel cell carcinoma: An un common neuroendocrine cancer*. G Chir, 2009; 30:226-229.
7. Meyer Pannwitt U, Kummerfeldt K, Bovbaris P, Caselitz J: *Merkel cell tumor or neuroendocrine skin cell carcinoma*. Langenbecks Arch Chir, 1997, 382:349-58.
8. Carlett JP, Todd WN, Carr ME Jr: *Merkel cell tumor in an HIV positive patient*. Va Med Q, 1992; 119:256-58.
9. Engels EA, Frisch M, Goedert JJ: *Merkel cell carcinoma and HIV infection*. Lancet, 2002; 359:497-98.
10. Busse PM, Clark JR, Muse VV, Liu V: *Case records of the Massachusetts General Hospital. Case 19-2008. A 63-year-old HIV-positive man with cutaneous Merkel-cell carcinoma*. N Engl J Med, 2008; 358:2717-273.
11. Miller RW, Rabkin CS: *Merkel cell carcinoma and melanoma: Etiological similarities and differences*. Cancer Epidemiol Biomarkers Prev, 1999; 8:15358.
12. Koloska ER, Koloska MS, Collins BT, Stapleton DR, Wade TP: *Early aggressive treatment for merkel cell carcinoma: Improves outcome*. Am J Surgery, 1997, 174:688-93.
13. Rossitto M, Fedele F, Pantè S, Crescenti F, Incardona S, Ciccolo A, Famulari C: *Skin neuroendocrine carcinoma metastasis. A case report*. Ann Ital Chir, 2006; 77(1):69-73
14. Sivelli R, Ghirarduzzi A, Del Rio P, Ricci R, Sianesi M: *Giant Merkel cell carcinoma of the left arm. Case report*. Ann Ital Chir, 2009; 80(6):489-92.
15. Bensaleh H, Perney P, Dereure O, Guilhou JJ, Guillot B: *Merkel cell carcinoma in a liver transplant patient*. Am J Clin Dermatol, 2007; 8:239-241.
16. Maio M, Ascierto P, Testori A, Ridolfi R, Bajetta E, Queirolo P, Guida M, Romanini A, Chiarion-Sileni V, Pigozzo J, Di Giacomo AM, Calandriello M, Didoni G, van Baardewijk M, Konto C, Lucioni C: *The cost of unresectable stage III or stage IV melanoma in Italy*. J Exp Clin Cancer Res, 2012; 31:91.
17. Tadmor T, Aviv A, Polliak A: *Merkel cell carcinoma, chronic lymphatic leukemia and other lymphoproliferative disorders: and old bond with possible new viral ties*. Ann Oncol, 2011; 22: 250-56.
18. Ortensi A, Marchese V, Lentini A, Srocco F, D'Orazi V, Gabatel R: *Reconstructive microsurgery*. G Chir, 1997; 8:688-91.
19. Yeengeprushawan A, Coit DG, Thalel: *Merkel cell carcinoma. Prognosis and management*. Arch Surg, 1991; 126:154-219.
20. Colgan MB, Tarantola TI, Weaver AL, Wiseman GA, Roenigk RK, Brewer JD, Otley CC: *The predictive value of imaging studies in evaluating regional lymph node involvement in Merkel cell carcinoma*. J Am Acad Dermatol, 2012; 67:1250-256.
21. Zaho M, Meng MB: *Merkel cell carcinoma with lymph node metastasis in the absence of a primary site: Case report and literature review*. Oncology Lett, 2012; 4:1.
22. Ames SE, Krag DN, Brady MS: *Radiolocalization of the sentinel lymph node in Merkel cell carcinoma: A clinical analysis of seven cases*. J Surg Oncol, 1998; 67:251-54.
23. Innocenzi D, Panetta C, Veneroso S, Amabile MI, Pasta V, Monti M: *The surgical treatment of thin melanoma*. G Chir, 2006; 27:133-35.
24. Garnesky KM, Nghiem: *Merkel cell carcinoma adjuvant therapy: Current data support but not chemotherapy*. J Am Acad Dermatol, 2007; 57:166-169.
25. Sundaresan P, Hruby G, Hamilton A, Hong A, Boyer M, Chatfield M, Thompson JF: *Definitive radiotherapy or chemoradiotherapy in the treatment of Merkel cell carcinoma*. Clin Oncol (R Coll Radiol), 2012; 24:131-36.
26. Majorca P, Smith D, Ellenhorn Joshua DI: *Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma skin*. J Clin Oncol, 2007; 25:1043-47.
27. Triozzi PL, Fernandez AP: *The role of the immune response in Merkel cell carcinoma*. Cancers, 2013; 5, 234-54.