Case report

Rhabdomyosarcoma: a rare laryngeal neoplastic entity

Il rabdomiosarcoma: una rara entità neoplastica laringea

B. PITTORE, G. FANCELLO[1], P. COSSU ROCCA[2], G.P. LEDDA, G. TORE

Ear, Nose and Throat Department, "Santissima Trinità" Hospital, ASL 8 Cagliari; [1] Ear, Nose and Throat Department, "Paolo Dettori" Hospital, ASL 2 Tempio Pausania, Sassari; [2] Institute of Pathology, University of Sassari, Sassari, Italy

SUMMARY

A case of pleomorphic rhabdomyosarcoma of the larynx is presented, which is extremely rare in a laryngeal site. The symptomatology and macroscopic aspect of the neoplasm can simulate the presence of other neoplastic variants of the larynx, and, for this reason, histological examination must be associated with immunohistochemistry for correct diagnosis and treatment.

KEY WORDS: Larynx • Malignant tumours • Pleomorphic rhabdomyosarcoma • Prognostic factors

RIASSUNTO

Nel presente lavoro, esponiamo un caso di rabdomiosarcoma pleomorfo della laringe. È una entità neoplastica molto rara in sede laringea. La sintomatologia e l'aspetto macroscopico di questa neoplasia simulano la presenza di altre varianti neoplastiche laringee. Per tale motivo, riteniamo fondamentale ai fini diagnostici e conseguentemente terapeutici, le procedure istologiche associate alla metodologia immunoistochimica.

PAROLE CHIAVE*: Laringe • Tumori maligni • Rabdomiosarcoma pleomorfo • Fattori prognostici*

Acta Otorhinolaryngol Ital 2010;30:52-57

Introduction

Rhabdomyosarcoma (RMS) is the most frequent soft tissue tumour in paediatric patients, accounting for up to 50% of all soft tissue sarcomas [1], while in adults, RMS may represent about 15-20% of all soft tissue sarcomas [2]. The neoplasm has a mesenchymal origin and involves skeletal muscle, and can, therefore, be localized in almost any site. In paediatric patients, it is most frequently localized to the cervical-cephalic and genito-urinary regions; in adults, RMSs involving the thorax and extremities account for 2-5% of all soft tissue sarcomas [3]. Three histological subtypes have been identified: embryonal with the botryoid and alveolar histiotypes that generally affect young children and adolescents [4], and the pleomorphic histiotype that is usually encountered in adult patients [2]. RMS is a malignant neoplasm characterized by extensive loco-regional spread and a tendency for secondary seeding through lymphatic and haematological routes.

Since 1972, the Intergroup Rhabdomyosarcoma Study Group (IRSG) has conducted a series of prospective randomized trials aimed at improving cure rates, while minimizing treatment-related morbidity, using combined modality treatment (surgery, radiotherapy and chemotherapy). Four successive protocols (IRS-I; IRS-II; IRS-III; and IRS-IV) were illustrated [5-8]. Currently, IRSG is enrolling patients in IRS-V [8].

Case report

A 75-year-old male was referred to our attention in April 2006 with dysphonia that had been worsening for approximately one year. Objective examination revealed a bilateral leukoplakia localized in the true vocal cords. The patient was submitted to microlaryngoscopy, and a biopsy was taken, the histological examination of which showed hyperkeratosis of the vocal cords with slight basal dysplasia. The patient then underwent a full excisional biopsy. Follow-up was carried out monthly with laryngoscopic examination. In November 2007, the patient presented with a neoplasm on the left vocal cord with irregular margins and consequent reduction of the airway diameter; there was no clinically appreciable cervical lymphadenopathy. During the same month, direct microlaryngoscopy was performed, and a biopsy was taken from the neoplasm on the left vocal cord. Histological examination (Fig. 1A-D) showed the presence of fused cells of variable dimension, with eosinophilic cytoplasm, that were frequently irregular and hyperchromic

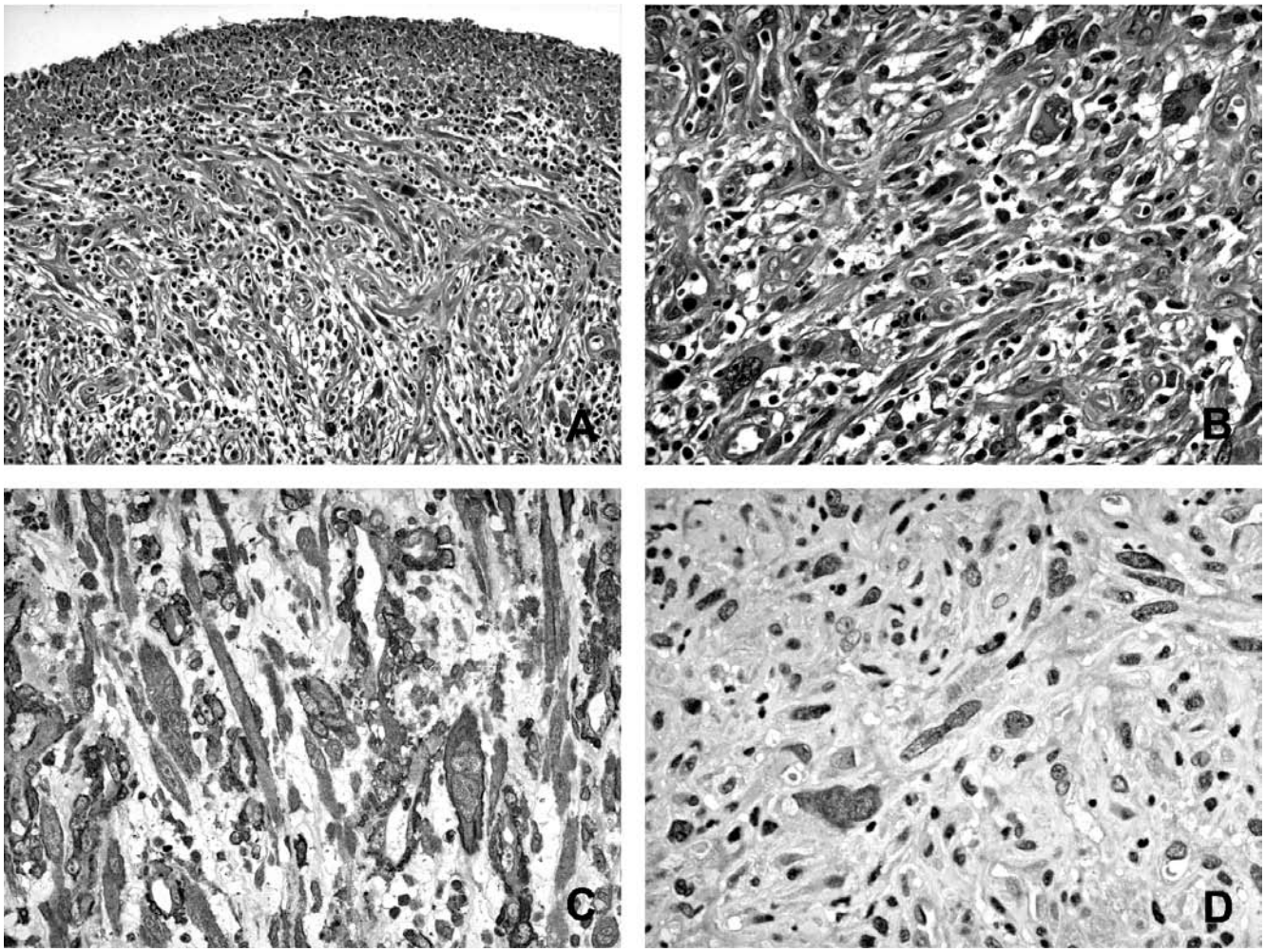

Fig. 1. Pleomorphic rhabdomyosarcoma of larynx. Histology shows an exophytic, extensively ulcerated nodular lesion, characterized by proliferation of atypical spindle cells (A. H&E, magn. 200X) admixed with large, multinucleated round cells with abundant eosinophilic cytoplasm (B. H&E, magn. 400X); immunohistochemistry displays strong and diffuse positive cytoplasmic stain for smooth muscle actin (C. magn. 400X) and focally positive nuclear stain for myogenin (D. magn. 400X) in neoplastic cells.

with large or multiple nuclei. Immunohistochemical testing revealed staining of vimentin, actin and myogenin, which confirmed the diagnosis of pleomorphic RMS.

Considering the histological diagnosis and the highly aggressive nature of the lesion, positron electron tomography (PET) and computerized tomography (CT) of the neck and thorax were performed, although no additional anatomical sites were affected by the neoplasm. In March 2008, the patient underwent partial left laryngectomy, with an uneventful post-operative recovery. Histological examination of the whole specimen confirmed the diagnosis of pleomorphic RMS; the surgical margins were negative for tumour involvement. The consulting oncologist did not recommend chemotherapy or radiotherapy given the complete surgical removal of the lesion. So far, the patient who has undergone monthly follow-up visits that include clinical examination and videofibrolaryngoscopy, remains disease-free, 9 months after the histological diagnosis.

Discussion

Sarcomas are uncommon at laryngeal sites. In 1933, Figi [9] identified only 4 laryngeal sarcomas (0.55%) in an evaluation of 717 laryngeal neoplasms. RMSs are the most frequent sarcoma in paediatric patients, especially the embryonal and alveolar variants. They are much more infrequent in adults and represents only 3% of all sarcomas [3].

About 40% of RMSs are localized in the cervico-cephalic region [10] where, based on their location, three subtypes have been recognized: orbital, parameningeal and non-parameningeal. The orbital lesions have a better prognosis than those in other sites [11]. Non-parameningeal rhabdomyosarcomas can occur in the larynx and the larynx is affected in less than 3% of RMSs of the cervico-cephalic region [4-10]. The first case of laryngeal RMS was described by Glick in 1944 [12], and only a few cases have been well documented since then [13-17]. In a

number of case reports published on laryngeal RMS, the exact histology of the lesion has not been described and in only a few cases has their disease-free survival been charted [18 19] (Table I). In the last 10 years, only 6 cases of pleomorphic RMS of the larynx have been described. Akyol et al.[20] illustrated a case of pleomorphic RMS in a 68-year-old male; Ruske et al. [21] reported a case in a 66-year-old female; Prgomet et al. [22], in 2006, described another case of pleomorphic RMS of the vocal cord, Shayah et al. [13] reported a case of pleomorphic RMS in a 77-year-old female and, in 2007, Schrock et al. [14] described 2 cases of adult pleomorphic RMS. According to data in the literature, pleomorphic RMSs are less common than the other subtype [3], they are usually found in adults [3], while alveolar and embryonal varieties are more commonly encountered in children and adolescents [11 15 16]. Laryngeal pleomorphic RMSs are usually found more often in males than in females.

The clinical features and macroscopic laryngeal appearances do not differ substantially from the other malignant neoplasms, therefore histological and immunohistochemical studies are fundamental for correct diagnosis. Staining for vimentin indicates the mesenchymal origin, while the positivity for actin, desmin, myogenin and myoglobin indicates muscular differentiation [1]. Cytogenetic analysis can be especially helpful in the alveolar variant, which consistently shows the translocations t (2;13) (q35; q14) and t (1;13) (p36; q14), which code for the fusion oncoproteins PAX3-FKHR and PAX7-FXHR, respectively [1]. According to Grundy et al. [23] and Garay et al. [1], patients with alveolar RMS showing positivity for PAX3-FKHR have a poor prognosis.

RMSs are locally aggressive and have a tendency to metastasize by both the lymphatic and haematological routes (lung, liver, bone). Therefore, during follow-up, it is essential to plan for staging, imaging, including CT scans and standard thoracic radiographs. Nonetheless, RMS of the larynx is believed to be less aggressive than in other cervico-cephalic positions [17 24 25].

Table I. Case reports of laryngeal pleomorphic rhabdomyosarcoma.

N.	Year	Author	Age (yrs)/ sex	Treatment	FU	Status
1	1964	Filipo & Crifo*	53/M	Total laryngectomy, RT	8 m	NED
2	1970	Rodriguez & Ziskind [19]	57/M	Total laryngectomy	?	?
3	1971	Laccourreye, et al.*	65/M	Total laryngectomy	41 d	DOD
4	1976	Frugoni & Ferlito [25]	33/M	Subtotal laryngectomy, RT	6 y	NED
5	1977	Marasso, et al.*	65/M	RT + CHT	?	?
6	1977	Lamendola & Buonocore**	61/M	Total laryngectomy bilat. neck dissection	1 y	NED
7	1978	Winter & Lorentzen [18]	72/F	Subtotal laryngectomy	?	?
8	1979	Seniukov, et al.*	55/M	Total laryngectomy, RT	4 m	NED
9	1979	Franz**	57/M	RT	2 y	NED
10	1987	Dodd-o, et al. [17]	5/M	Total laryngectomy	18 y	NED
11	1988	De Agostino, et al.**	70/M	Total laryngectomy	?	?
12	1994	Jahnke & Vogl**	45/M	Total pharyngolaryngectomy, cervical oesophageal and tracheal resection, CHT + RT	?	?
13	1996	Da Mosto et al. [10]	69/M	Total laryngectomy, RT	2 y	NED
14	1998	Akyol et al. [20]	68/M	Total laryngectomy, neck dissection, RT	8 m	DOD
15	1998	Ruske et al. [21]	66/F	Total laryngectomy, RT	30 m	NED
16	2006	Prgomet et al. [22]		CO2 Laser cordectomy, CHT	6 y	NED
17	2007	Shayah et al. [13]	77/F	Total laryngectomy	1 y	NED
18	2007	Schrock et al. [14]	60/M	Total laryngectomy, neck dissection, RT, CHT	20 m	NED
19	2007	Schrock et al. [14]	64/M	CO2 laser cordectomy, RT	20 m	NED
20	Our case	Pittore et al.	75/M	Partial laryngectomy	9 m	NED

** Cited by Dodd-o et al.; ** Cited by Da Mosto et al.*

Two methods for staging RMS are used. The initial staging system, adopted in the first 3 intergroup RMS studies, classifies patients on the basis of the extent of disease and the completeness of their initial surgical resection [5-7] (Table II). In the IRS-IV the TNM [8] (tumour, node and metastasis) staging system (Table III) was used in association with the previous staging system.

Based upon data in the literature, and especially in paediatric patients [11 26-33], it would appear that optimal therapy for RMS is a multimodal approach comprising surgery followed by chemo- and/or radiotherapy. This was described in the Intergroup Rhabdomyosarcoma Studies (IRS) [5-8]. The IRSG, formed in 1972, included more than 4000 patients (< 21 years) with newly diagnosed RMS allocated to 4 protocol arms. Based on the results of this study, generally accepted treatment guidelines for childhood RMS include complete resection with preservation of function, chemotherapy and radiotherapy but the choice depends on a variety of disease factors (site, extent of lesion, etc.). Different combination agents were used including actinomycin-D (A), vincristine (V) and cyclophosphamide (C). The IRS-IV introduced the use of ifosfamide (I) + etoposide (E) with or without radiotherapy. The 3-year failure-free-survival (FFS) estimates remain unchanged from that of IRS-III[8].

IRMS-V (study in progress) is using a new agent (topotecan) which has been shown to be particularly active in the treatment of alveolar RMS [8].

In a recent paper, Combs et al. [27] showed the importance of post-operative radiotherapy in 19 paediatric patients with RMS located in the cervico-cephalic region, and reported a 5-year survival of 94%, and local control of disease in 89% of the cases. Thanks to these studies, 5-year survival rates have increased from 25%, in 1970, to 70% [8].

Several prognostic indicators have been identified which

Table II. Group staging system.

Group	Definition
I	Localized disease, completely resected
	a) confined to muscle or organ of origin
	b) contiguous involvement, with infiltration outside muscle or organ of origin; regional nodes not involved
II	Compromised or regional resection
	a) grossly resected disease with "microscopic residual"
	b) regional disease, completely resected, in which nodes may be involved and/or extend into an adjacent organ
	c) regional disease with involved nodes grossly resected, but with evidence of microscopic residual
III	Incomplete resection or biopsy, with gross residual disease
IV	Distant metastasis present at onset

Table III. TNM staging classification.

Stage	Sites	T	Size	N	M
1	Orbit, head and neck region (excluding parameningeal sites), or the non-bladder and/or non-prostate genito-urinary region	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Bladder/Prostate, extremity, cranial parameningeal, other	T1 or T2	a	N0 or Nx	M0
3	Bladder/Prostate, extremity, cranial parameningeal, other	T1 or T2	a b	N1 N0 or N1 or Nx	M0 M0
4	All	T1 or T2	a or b	N0 or N1	M1

T1: Confined to anatomic site of origin: a) < 5 cm in diameter; b) > 5 cm in diameter; T2: extension and/or fixative to surrounding tissue: a) < 5 cm in diameter; b) > 5 cm in diameter; N0: lymph nodes not involved; N1: lymph nodes involved; Nx: unknown; M0: no distant metastasis; M1: metastasis present.

include age, tumour location, extension and histotype. Hawkins et al. [3] reported on a cohort of 84 patients with RMS and revealed better prognosis in patients aged < 20 years, tumour size < 5 cm, absence of loco-regional disease and radical surgical excision.
Wolden et al. **[34]** revealed that certain characteristics were associated with significantly poorer FFS. These included, according to Hawkins et al. [3], tumours > 5 cm or with alveolar or undifferentiated histology. The final clinical factor affecting the patient's prognosis is the extent of disease following initial surgical resection. As discussed by the Intergroup Rhabdomyosarcoma group (IRS-III and IRS-IV) [7 8], patients without residual disease (Group I) have a 90% 5-year survival rate. In patients with microscopic residual disease (Group II), survival decreases to 80%, and those with gross disease after surgery (Group III) have a 5-year survival rate of 70%.

Conclusions

Laryngeal RMS is an extremely rare tumour which responds to surgery, but may also be treated by means of chemo-radiotherapy. However, further studies are needed in order to improve our understanding of its biological behaviour and to define the most appropriate therapeutic approach.

References

1 Garay M, Chernicoff M, Moreno S, et al. *Rabdomiosarcoma alveolare congenito in un neonato*. Eur J Pediat Dermatol 2004;14:9-12.

2 Little DJ, Ballo MT, Zagars GK, et al. *Adult rhabdomyosarcoma: outcome following multimodality treatment*. Cancer 2002;95:377-88.

3 Hawkins WG, Hoos A, Antonescu CR, et al. *Clinicopathologic analysis of patients with adult rhabdomyosarcoma*. Cancer 2001;91:794-803.

4 Hicks J, Flaitz C. *Rhabdomyosarcoma of the head and neck in children*. Oral Oncol 2002;38:450-9.

5 Maurer HM, Beltangady M, Gehan EA, et al. *The Intergroup Rhabdomyosarcoma Study-I. A final report.* Cancer 1988;61:209-20.

6 Maurer HM, Gehan E, Beltangady M, et al. *The Intergroup Rhabdomyosarcoma Study-II.* Cancer 1993;71:1904-22.

7 Crist W, Gehan EA, Ragab AH, et al. *The third Intergoup Rhabdomyosarcoma Study.* J Clin Oncol 1995;13:610-30.

8 Crist WM, Anderson JR, Meza JL, et al. *Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease*. J Clin Oncol 2001;19:3091-102.

9 Figi FA. *Sarcoma of the larynx*. Arch Otolaryngol 1933;18:21-33.

10 Da Mosto MC, Marchiori C, Rinaldo A, et al. Laryngeal *pleomorphic rhabdomyosarcoma. a critical review of the literature*. Ann Otol Rhinol Laryngol 1996;105:289-94.

11 Sercarz JA, Mark RJ, Nasri S, et al. *Pediatric rhabdomyosarcoma of the head and neck.* Int J Pediat Otorhinolaryngol 1995;31:15-22.

12 Glick HN. *An unusual neoplasm in the larynx of a child (rhabdomyosarcoma)*. Ann Otol Rhinol Laryngol 1944;53:699-704.

13 Shayah A, Agada FO, Karsai L, et al. *Adult laryngeal rhabdomyosarcoma: Report of a case and literature review*. Ann Afr Med 2007;6:190-3.

14 Schrock A, Jakob M, Zhou H, et al. *Laryngeal pleomorphic rhabdomyosarcoma*. Auris Nasus Larynx 2007;34:553-6.

15 Dikbas O, Altundag K, Abali H, et al. *Embryonal rhabdomyosarcoma of the larynx*. Otolaryngol Head Neck Surg 2005;133:160-2.

16 Sivanandan R, Kong CS, Kaplan MJ, et al. *Laryngeal embryonal rhabdomyosarcoma*. Arch Otolaryngol Head Neck Surg 2004;130:1217-22.

17 Dodd-o JM, Wieneke KF, Rosman PM. *Laryngeal rhabdomyosarcoma. Case report and literature review*. Cancer 1987;59:1012-8.

18 Winter LK, Lorentzen M. *Rhabdomyosarcoma of the larynx. Report of two cases and review of the literature.* J Laryngol Otol 1978;92:417-24.

19 Rodriguez LA, Ziskind J. *Rhabdomyosarcoma of larynx.* Laryngoscope 1970;80:1733-9.

20 Akyol MU, Sozeri B, KucuKali T, et al. *Laryngeal pleomorphic rhabdomyosarcoma*. Eur Arch Otorhinolaryngol 1998;255:307-10.

21 Ruske DR, Glassford N, Costello S, et al. *Laryngeal rhabdomyosarcoma in adults*. J Laryngol Otol 1998;112:670-2.

22 Prgomet D, Males J, Manojlovic S, et al. *Pleomorphic rhabdomyosarcoma of the larynx - a case report and literature review*. Acta Med Croat 2006;60:255-7 (abstract).

23 Grundy R, Anderson J, Gaze M, et al. *Congenital alveolar rhabdomyosarcoma. clinical and molecular distinction from alveolar rhabdomyosarcoma in older children.* Cancer 2001;91:606-12.

24 Canalis RF, Platz CE, Cohn AM. *Laryngeal rhabdomyosarcoma*. Arch Otolaryngol 1976;102:104-7.

25 Frugoni P, Ferlito A. *Pleomorphic rhabdomyosarcoma of the larynx: A case report and review of the literature*. J Laryngol Otol 1976;90:687-98.

26 Van Rijn RR, Wilde JCH, Bras J, et al. *Imaging findings in non-cranio-facial childhood rhabdomyosarcoma*. Pediatr Radiol 2008;38:617-34.

27 Combs SE, Behnisch W, Kulozik AE, et al. *Intensity Modulated Radiotherapy (IMRT) and Fractionated Stereotactic Radiotherapy (FSRT) for children with head and neck rhabdomyosarcoma*. BMC Cancer 2007;7:177.

28 Punyco JA, Mertens AC, Baker KS, et al. *Long-term survival probabilities for childhood rhabdomyosarcoma. A population based evaluation*. Cancer 2005;103:1475-83.

29 Rodeberg DA, Paidas CN, Lobe TL, et al. *Surgical principles for children/adolescents with newly diagnosed rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group.* Sarcoma 2002;6:111-22.

[30] Daya H, Chan HSL, Sirkin W, et al. *Pediatric rhabdomyosarcoma of the head and neck. is there a place for surgical management?* Arch Otolaryngol Head Neck Surg 2000;126:468-72.

[31] Wharam MD, Beltangady MS, Heyn RM, et al. *Pediatric orofacial and laryngopharyngeal rhabdomyosarcoma. An Intergroup Rhabdomyosarcoma Study report*. Arch Otolaryngol Head Neck Surg 1987;113:1225-7.

[32] Wharam MD, Foulkes MA, Lawrence W, et al. *Soft tissue sarcoma of the head and neck in childhood: nonorbital and nonparameningeal sites. A Report of the Intergroup Rhabdomyosarcoma Study (IRS)-I.* Cancer 1984;53:1016-9.

[33] Sutow WW, Lindberg RD, Gehan EA, et al. *Three-year relapse-free survival rates in childhood rhabdomyosarcoma of the head and neck. Report from the Intergroup Rhabdomyosarcoma Study.* Cancer 1982;49:2217-21.

[34] Wolden SL, Anderson JR, Crist WM, et al. *Indications for radiotherapy and chemotherapy after complete resection in rhabdomyosarcoma: a Report from the Intergroup Rhabdomyosarcoma Studies I to III*. J Clin Oncol 1999;17:3468-75.

Received: September 17, 2008 - Accepted: April 4, 2009

Address for correspondence: Dr.ssa B. Pittore, Ospedale “Santissima Trinità”, ASL 8 Cagliari, via Is Mirrionis 92, 09100 Cagliari, Italy. Fax: +39 070 6095789. E-mail: barbarapitt@tiscali.it