

The role of Nuclear Medicine in the management of thymomas



Ann. Ital. Chir., 2007; 78: 371-374

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AIM OF THE STUDY: *To evaluate the role of nuclear medicine techniques in the management of patients with thymoma.*

MATERIALS AND METHODS: *The Authors performed a review of the literature about the usefulness of traditional nuclear medicine and positron emission tomography in patients with thymic tumours.*

RESULTS AND DISCUSSION: *Nuclear medicine imaging can provide additional information in cases of thymoma such as in differential diagnosis between thymic tumours, staging and restaging. Thallium-201 (^{201}Tl), $^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin are useful tumour-imaging agent. Another radiopharmaceutical useful in the management of thymomas is ^{111}In -pentetreotide, a somatostatin analogue, used to define the receptor status and the extent of disease in malignant thymomas. Positron emission tomography (PET) is a powerful diagnostic tool for diagnosis, staging and restaging of neoplasms in general. The most used PET radiopharmaceutical is the fluorodeoxyglucose (^{18}F -FDG), a glucose analogue. The uptake of FDG reflects the metabolic activity of organs and neoplasms and correlates with the tumour growth rate. There is a paucity of literature on the use of PET scanning in the diagnosis of thymoma. Further perspective studies with a larger number of cases, considering the development of hybrid imaging PET-CT and new PET radiopharmaceuticals, may increase the role of nuclear medicine in the diagnostic and therapeutic management of thymic neoplasms.*

KEY WORDS: Nuclear medicine, PET, Thymoma.

Introduction

Although considered to have an indolent growth pattern, thymoma has the ability for both local invasion and intrathoracic recurrences. Thymomas typically present in the fourth or fifth decade of life and exhibit no gender predilection. Half of thymomas present asymptotically and are detected incidentally on radiographic imaging, while half will present with symptoms associated with a paraneoplastic syndrome or with symptoms attributable to the local mass effect.

Radiological imaging as x-ray, computed tomography (CT) and magnetic resonance (MR) is an essential part of the workup and in conjunction with history and physical exam is often the only investigation needed prior treatment ¹. CT and MR are helpful in defining a mediastinal mass, its characteristics, its relation to the great vessels, and any involvement of the surrounding structures. Biopsy confirmation is, however, needed to establish the diag-

nosis of thymoma. The diagnosis of malignant thymoma relies on evidence of capsular invasion, cytologic atypia, or distant metastases. Extramediastinal involvement, including extension of tumour into contiguous structures with or without distant metastases, is invaluable information for operative planning and can, potentially, be accessed by imaging ².

Nuclear medicine imaging can provide additional information in cases of thymoma such as in differential diagnosis between thymic tumours, staging and restaging.

Material and methods

Aim of this study is review the literature about the role of nuclear medicine in the management of thymomas.

Results and discussion

Different radiopharmaceuticals are useful in the management of thymomas.

Thallium-201 (^{201}Tl), $^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin are useful tumor-imaging agent.

The limit of scintigraphy with these tumor-seeking agents is the low specificity.

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^{201}Tl uptake is considered to reflect various factors including cellular metabolic activity, regional blood flow and the number of viable cells in the lesion. Accumulation of ^{201}Tl on early and delayed SPECT (Single Photon Emission Computed Tomography) images reflects the histopathologic findings of thymic lesions associated with myasthenia gravis (MG). Normal thymus shows no increase in ^{201}Tl uptake on either early and delayed images, whereas thymic hyperplasia exhibits moderate ^{201}Tl uptake on only delayed images. Moreover, thymoma shows significant (moderate to strong) ^{201}Tl uptake on early and delayed images ³.

Moreover ^{201}Tl scintigraphy permits the evaluation of recurrences after therapy of thymomas ⁴.

Although ^{201}Tl is a useful tumor-imaging agent, it has several physical limitations. Because of a low energy level and a relatively long half-life, ^{201}Tl produces low-quality images and exposes patients to high levels of radiation.

$^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin were developed as myocardial perfusion imaging agents and can also be used to depict tumours. The uptake of these radiopharmaceuticals reflects various factors including cellular metabolic activity, regional blood flow, the number of viable cells in the lesion and mitochondrial density. The accumulation of these tracers may be helpful in localization of primary tumour and metastatic lesions in cases of thymomas. $^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin have also short half-lives and adequate energy to obtain high-quality images.

Moreover $^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin scintigraphy permits the evaluation of recurrences of thymomas after surgery and radiation ⁵.

Another radiopharmaceutical useful in the management of thymomas is ^{111}In -pentetreotide, a somatostatin analogue, used to define the receptor status and the extent of disease in malignant thymomas. In patients with solitary lesions somatostatin receptor scintigraphy (SRS) may identify an occult tumor for surgical excision. In patients with widespread disease SRS may demonstrate somatostatin receptor status and provide potential benefit from "cold" somatostatin therapy, useful in symptomatic control and direct inhibition of tumor growth ⁶.

^{111}In -pentetreotide is avidly concentrated within thymic tumours, but is not concentrated by thymic hyperplasia, which allows differential diagnosis of thymic masses in patients with MG ⁷.

The limit of SRS is that ^{111}In -pentetreotide binds with high affinity to somatostatin receptor subtype 2 (SSR2) whereas in thymoma there is a predominant presence of SSR3 ⁸.

Positron emission tomography (PET) is a powerful diagnostic tool for diagnosis, staging and restaging of neoplasms in general. The most used PET radiopharmaceutical is the fluorodeoxyglucose (^{18}F -FDG), an analogue of glucose. The uptake of FDG reflects the metabolic activity of organs and neoplasms and correlates with

the tumour growth rate. Increased thymic ^{18}F -FDG uptake may represent normal physiologic uptake but may also indicate the presence of thymic hyperplasia, lymphomatous infiltration, primary thymic neoplasms or metastatic disease. Familiarity with the patterns of ^{18}F -FDG uptake that characterize these pathologic conditions is crucial to the interpretations of PET findings in the thymus ⁹.

There is a paucity of literature on the use of PET scanning in the diagnosis of thymoma.

PET cannot diagnose capsular invasion; this inability is not a limitation of PET scanning alone but of all imaging modalities. The basis of classifying a mediastinal mass as an invasive thymoma was based on histopathology.

The usefulness of ^{18}F -FDG PET for evaluating the malignant nature of primary mediastinal tumors ¹⁰ and improving tumour detection in patients with paraneoplastic neurological syndromes has been described ¹¹.

Preliminary results suggest that ^{18}F -FDG-PET is useful in the assessment of the invasiveness of thymic cancer for tumour staging and may have the potential to differentiate thymomas from thymic hyperplasia. ^{18}F -FDG studies showed diffuse uptake in the widened anterior mediastinum in patients with thymic hyperplasia, confined focal ^{18}F -FDG uptake in the non-invasive or less invasive, stage I and II thymomas, and multiple discrete foci of ^{18}F -FDG uptake in the mediastinum and thoracic structures in stage III and IV advanced invasive thymomas. Thymomas have higher ^{18}F -FDG uptake than thymic hyperplasia but no significant difference was found between thymomas in different stage or between thymomas with and thymomas without myasthenia gravis ¹².

^{18}F -FDG PET was considered to be useful in the differential diagnosis between thymic cancer and thymoma: a high FDG uptake was observed in thymic cancer, whereas a moderate FDG uptake was seen in invasive thymoma and non-invasive thymoma. These results can be explained considering that thymic cancer is a highly malignant tumor in comparison with thymoma.

FDG uptake in invasive thymoma was not different from that in non-invasive thymoma; this result suggests that FDG uptake cannot possibly reflect the invasive features of thymoma ¹³.

The recent development of integrated PET-CT overcomes to a large extent the lack of precision of PET in terms of anatomic landmark identification, and the PET-CT combination based on the integrated approach is not additive but, in fact, highly synergistic.

Integrated PET-CT was found to be useful for differentiating subgroups of thymic epithelial tumours. The ^{18}F -FDG uptake of high-risk thymomas (type B2 and B3) and low-risk thymomas (type A, AB and B1) are significantly lower than those of thymic carcinomas, but no difference is observed between low-risk and high-risk thymomas. The homogeneous uptake was observed more frequently in thymic carcinomas, whereas heterogeneous

uptake was observed more frequently in thymomas. An irregular contour and mediastinal fat invasion were seen more often in thymic carcinoma than low-risk thymomas and mediastinal fat invasion is more frequent in high-risk thymomas than in low-risk thymomas.

Integrated PET-CT is also useful for staging the extent of disease. In a recent study PET-CT helped the detection of lymph node metastases, which were not identified on stand-alone CT, because of their small or normal sizes. Extrathoracic organ metastases were equally and correctly detected on integrated PET-CT and stand-alone CT. PET-CT may also be useful for the evaluation of pleural seeding ¹⁴.

Moreover, about the staging of disease, a PET study can provide additional information in cases of thymoma such as extramediastinal involvement, which may be helpful in surgical planning ².

PET is also helpful in evaluating the response at surgical therapy and/or chemotherapy and/or radiotherapy in various neoplasms such as thymomas. Furthermore PET permits the differentiation between recurrence of disease in which there is an increased uptake of ¹⁸F-FDG and fibrosis in which the uptake of ¹⁸F-FDG is absent ¹⁵.

A recent study suggested the potential role of ¹¹C-Acetate PET in the diagnosis of thymomas. In fact, this tracer of oxidative metabolism tends to accumulate prevalently in slow-growing tumours ¹⁶.

¹¹C-Methionine (MET) is a PET radiopharmaceutical used to measure the amino acid metabolism in vivo, and thus a high ¹¹C-MET uptake in tumor cell is thought to reflect an increase in either the transport mechanism of amino acids or protein synthesis. Questions still exist regarding ¹¹C-MET uptake in thymic tumours. In ¹¹C-MET PET intense MET uptake was observed in thymic cancer and thymomas without a significant difference of uptake between these tumours; ¹¹C-MET PET is therefore unable in differentiating between benign and malignant thymic tumours. MET uptake is lower than ¹⁸F-FDG uptake in thymic cancer and higher than ¹⁸F-FDG uptake in thymoma, probably suggesting a different origin of these tumours ¹³.

Further perspective studies with a larger number of cases, considering the development of hybrid imaging PET-CT and new PET radiopharmaceuticals, may increase the role of nuclear medicine in the diagnostic and therapeutic management of thymic neoplasms.

Riassunto

OBIETTIVO: Lo scopo del lavoro è di valutare il ruolo delle metodiche medico-nucleari nella gestione dei pazienti con timoma.

MATERIALE DI STUDIO: È stata effettuata una revisione della letteratura sul ruolo delle tecniche di *medicina nucleare tradizionale e della tomografia ad emissione di positroni (PET)* nel timoma.

RISULTATI E DISCUSSIONE: Le tecniche di medicina nucleare tradizionali sono utili nella diagnosi differenziale delle masse timiche (timoma, carcinoma timico, iperplasia), nella stadiazione e nella valutazione della risposta al trattamento dei tumori timici. Il Tallio-201 (²⁰¹Tl), il ^{99m}Tc-sestamibi e il ^{99m}Tc-tetrofosmin, traccianti di metabolismo e di vitalità cellulare, sono i traccianti oncotropi più frequentemente impiegati, mentre l'¹¹¹In-pentetreotide, un analogo della somatostatina, è utilizzato per definire lo stato recettoriale. Sono pochi i lavori in letteratura sul ruolo della PET nel timoma. Recentemente sono stati sviluppati apparecchi ibridi PET-TAC che integrano i dati morfologici (tomografia computerizzata) con quelli funzionali (PET) al fine di ottenere una migliore localizzazione anatomica delle lesioni. La maggior parte degli studi è stata effettuata utilizzando come tracciante il fluoro-deossiglucosio (¹⁸F-FDG), un analogo del glucosio, il cui accumulo nelle cellule è direttamente proporzionale alla velocità di crescita tumorale. I recenti progressi della radiochimica hanno portato allo sviluppo di nuovi radiofarmaci PET per studiare aspetti diversi del metabolismo cellulare e per la diagnosi dei tumori a lenta crescita che accumulano poco ¹⁸F-FDG.

References

- 1) Nishino M, Ashiku SK, Kocher ON, Thurer RL, Boisselle PM, Hatabu H: *The thymus: A comprehensive review*. Radiographics, 2006; 26:335-48.
- 2) Bagga S, Bloch EM: *Imaging of an invasive malignant thymoma on PET scan: CT and histopathologic correlation*. Clin Nucl Med, 2006; 31:614-16.
- 3) Higuchi T, Taki J, Kinuya S, Yamada M, Kawasuji M, Matsui O, Nonomura A, Bunko H, Tonami N: *Thymic lesions in patients with myasthenia gravis: characterization with Thallium 201 scintigraphy*. Radiology, 2001; 221:201-06.
- 4) Ohta H, Taniguchi T, Watanabe H, Komibuchi T, Nakade M, Kohno K: *Tl-201 and Tc-99m HMPAO SPECT in a patient with recurrent thymoma*. Clin Nucl Med, 1996; 21:902-03.
- 5) Kim SJ, Kim IJ, Kim YK: *Tc-99m MIBI, Tc-99m Tetrofosmin and Tc-99m (V) DMSA accumulation in recurrent malignant thymoma*. Clin Nucl Med, 2002; 27:30-33.
- 6) Lin K, Nguyen DB, Ettinger DS, Chin BB: *Somatostatin receptor scintigraphy and somatostatin therapy in the evaluation and treatment of malignant thymoma*. Clin. Nucl Med, 1999; 24:24-28.
- 7) Lastoria S, Vergara E, Palmieri G, Acampa W, Varrella P, Caraco C, Bianco RA, Muto P, Salvatore M: *In vivo detection of malignant thymic masses by indium-111-DTPA-D-Phe1-octreotide scintigraphy*. J Nucl Med, 1998; 39:634-39.
- 8) Ferone D, Van Hagen MP, Kwekkeboom DJ, van Koetsveld PM, Mooy DM, Lichtenauer-Kaligis E, Schönbrunn A, Colao A, Lamberts SWJ, Hofland LJ: *Somatostatin Receptor subtypes in human thymoma and inhibition of cell proliferation by octreotide in vitro*. J Clin Endocrinol Metab, 2000; 85:1719-726.
- 9) Ferdinand B, Gupta M, Kramer EL: *Spectrum of thymic uptake at ¹⁸F-FDG PET*. Radiographics, 2004; 24:1611-616.

- 10) Kubota K, Yamada S, Kondo T, Yamada K, Fukuda H, Fujiwara T, Ito M, Ido T: *PET imaging of primary mediastinal tumours*. Br J Cancer, 1996; 73:882-86.
- 11) Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, Ternamian PJ, Trouillas P, Honnorat J: *FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes*. Brain, 2004; 127:2331-338.
- 12) Liu RS, Yeh SH, Huang MH, Wang LS, Chu LS, Chang CP, Chu YK, Wu LC: *Use of fluorine-18 fluorodeoxyglucose positron emission tomography in the detection of thymoma: a preliminary report*. Eur J Nucl Med, 1995; 22:1402-07.
- 13) Sasaki M, Kuwabara Y, Ichiya Y, Akashi Y, Yoshida T, Nakagawa M, Murayama S, Masuda K: *Differential diagnosis of thymic tumors using a combination of ^{11}C -Methionine PET and FDG PET*. J Nucl Med, 1999; 40:1595-1601.
- 14) Sung YM, Lee KS, Kim BT, Choi JC, Shim YM, Yi CA: *^{18}F -FDG PET/CT of thymic epithelial tumours: usefulness for distinguishing and staging tumor subgroups*. J Nucl Med, 2006; 47:1628-634.
- 15) Kudva GC, Maliekal K, Kim HJ, Naunheim KS, Stolar C, Fletcher JW, Puri S: *Thymoma and myotonic dystrophy: Successful treatment with chemotherapy and radiation: case report and review of the literature*. Chest, 2002; 121:2061-63.
- 16) Ohtsuka T, Nomori H, Watanabe K, Naruke T, Suemasu K, Kosaka N, Uno K: *Positive imaging of thymoma by ^{11}C -Acetate Positron Emission Tomography*. Ann Thorac Surg, 2006; 81:1132-134.