中國醫藥大學

臨床醫學研究所

碩士學位論文

雙相正子攝影在食道鱗狀上皮細胞癌之臨床效益評估

Clinical usefulness of dual-time FDG PET-CT in assessment of esophageal Squamous cell carcinoma

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中文：雙相正子攝影在食道鱗狀細胞癌之臨床效益評估

英文：Clinical usefulness of dual-time FDG PET-CT in assessment of esophageal squamous cell carcinoma

本論文係岑榮潤於中國醫藥大學臨床醫學研究所完成之碩士論文，經考試委員審查及口試合格，特此證明。

考試委員

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A 52-year-old man was diagnosed with squamous cell carcinoma in the upper third of thoracic esophagus. The FDG PET/CT scan clearly demonstrated intense FDG uptake suggestive of malignancy in the annually thickened esophagus (arrowheads; SUVmax = 9.6) and a regional lymph node (early SUVmax = 3.4).

中文摘要

背景:

食道癌是台灣男性病患第七常見的癌症，其預後非常差。手術切除是目前對食道癌的主要治療方式，其開刀成功與否是和術前對於腫瘤侵犯深度，局部淋巴結及遠端轉移的正確研判有密切的關係。目前在臨床上最常使用的影像診斷工具包括有 1) 電腦斷層(CT) 2)內視鏡超音波(EUS) 3) 正子射出造影(PET)。正子電腦斷層造影(PET-CT) 是於 2000 年初所發展出來的診斷儀器，其優點是結合了正子掃描的分子生物影像及電腦斷層的解剖結構影像於一身的偵測利器。一般上正子電腦斷層造影的讀值是以最大標準攝取值(SUVmax, standardized uptake value maximum)代表人體細胞所吸收的氟 18 去氧葡萄糖【18F-FDG, FDG(2-[Fluorine-18]Fluoro-2-deoxy-D-glucose)】。由於腫瘤細胞具有高速率的葡萄糖代謝，所以腫瘤細胞會比正常細胞吸收較多的 18F-FDG，而這些正子標記的 FDG 就會偵測出癌細胞的蹤影。

目前臨床使用上，正子電腦斷層造影對於偵測食道癌的靈敏度，特異度及準確性大約是介於 75-95%，常常會有偽

陽性及偽陰性的問題存在。根據一份綜合 40 個研究的統合分析(meta-analysis)報告中發現，惡性腫瘤會隨著時間累積比較多的氟 18F 去氧葡萄糖，發炎與感染疾病剛好相反。因此本研究的主要目的是探討於不同時段進行正子電腦斷層造影分析食道癌細胞對於 18F 去氧葡萄糖吸收的差異性，試圖找出能否提高診斷腫瘤侵犯深度，局部淋巴結及遠端轉移的方式，以協助臨床醫師作出正確的處置。

材料與方法:

首先我們以回溯性的方式進行資料收集和分析，將自 2009 年 10 月至 2010 年 4 月間在中國醫药大學診斷為鱗狀細胞食道癌的患者，全部是男性，合計 26 人收案。全數的病患都接受了手術切除腫瘤和淋巴而且所有的患者在開刀前都有接受了雙相的正子電腦斷層造影檢查。最後我們將會把手術後的病理報告和手術前的 PET-CT 報告及期別作比對分析，以探討雙相正子電腦斷層造影檢查對於原發腫瘤，局部淋巴結及遠端轉移診斷的靈敏度，特異度及準確性是否有提高。我們參考了過去的文獻記載，分別以最大標準攝取值 SUVmax≥2.5 及 Retention index (RI) ≥ 10%為參考基準. Early SUVmax 指的是 FDG 注射到人體 45 分鐘後的最大標準攝取值而 delay SUVmax 為 70 分鐘後的讀值。RI 則是 delaySUVmax 減去 earlySUVmax 值再除以 early SUVmax 值的

差異百分比，其代表意義為細胞是否是惡性(RI≥10%)或者是發炎與感染疾病的可能性。最後將這三種讀值收集後再組合成以下四組的診斷準則:

(1) SUVmax≥ 2.5
(2) RI ≥ 10%
(3) SUVmax 加上 RI ≥ 10%
(4) SUVmax 或者 RI ≥ 10%擇一並進行統計分析

結果

在原發腫瘤部份，當 SUVmax≥ 2.5 或者 RI ≥ 10% 任何一項讀值被選為判定是否為陽性時(腫瘤細胞)，其靈敏度可高達 96.2%，而且是統計上有意義的($p<0.05$)。針對局部淋巴結的部份，當 SUVmax≥ 2.5 加上 RI ≥ 10%時其靈敏度會明顯的提昇到 70%，但是 p 值只有 0.1181。至於在其他不同組合的診斷準則方面，它們均無法有效的提高局部淋巴結的偵測。所有的靈敏度，特異度及準確性均無法達到統計學上的意義。最後在遠端轉移的部份，SUVmax≥ 2.5 無論是否有加上 RI ≥10%與否，其靈敏度及特異度皆相同;分別是靈敏度 16.7% 而特異度則是 100%，兩者均有達到統計學上意義($p<0.05$)。因此我們認為 RI ≥10%可以用來當作一種輔助工具，以提昇食道癌的遠端轉移偵測率。至於在準確性方面，

幾手所有的診斷準則都介於 76.9% -80.8%，無法達到統計學上意義。

結論

本研究的結果發現雙相正子射出電腦斷層造影(Dual-time PET-CT)在臨床診斷食道癌原發腫瘤及局部淋巴結的角色尚未有明確參考價值. 但是從初步報告可發現對於有遠端轉移的食道癌, RI ≥ 10%可以用來當作一個輔助的參考值, 它不但可以提高 PET-CT 的偵測靈敏度及特異度, 同時也可以協助臨床醫師在診療病患時作出適當的處置。

關鍵字:

食道癌 正子電腦斷層造影 氟 18-去氧葡萄糖(F-18FDG) 最大標準攝取值(SUV)

Abstract 英文摘要

Purpose:

We conducted this study to investigate the value of the dual-time 2-[18F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography-computed tomography (PET-CT) in assessmentof the primary tumor, loco-regional lymph node and distant metastasis in patients with esophagealsquamous cell carcinoma.

Methods

Twenty-six patients with histologically proved esophageal squamous cell carcinoma underwent dual-time FDG PET-CT before radical surgery. The standardized uptake values (SUVmax)were obtained including early SUVmax and delayed SUVmax, respectively. The retention index (RI)was also calculated. The results were evaluated retrospectively according to the final pathologic findings.

Four diagnostic criteria including

early SUVmax≥ 2.5 alone

RI ≥ 10% alone
a combination of early SUVmax≧ 2.5 and RI ≧ 10%
a combination of early SUVmax≧ 2.5 or RI ≧ 10%

These results were used for differentiating malignancy from a benign lesion, respectively.

Results

The sensitivity of FDG PET-CT in detecting the primary tumor with combination of early SUVmax≧ 2.5 or RI ≧ 10% was 96.2%. It was statistically significantly higher than the results using the other three criteria ($p < 0.0001$). For loco-regional lymph node detection, there was no significant difference among the 4 criteria. For distal metastases, the significantly higher specificity (100%) was found when using combination of early SUVmax≧ 2.5 and RI ≧ 10% or using early SUVmax≧ 2.5 alone than using the other two criteria ($p = 0.0058$). With regard to accuracy, no significant correlations were observed among primary tumor, loco-regional lymph nodes and distant

metastasis($p > 0.05$).

Conclusion

The preliminary result of this study demonstrated that dual-time point FDG PET-CT had limited value in detection of primary tumor and loco-regional lymph nodes metastasis. For the distant metastasis, the sensitivity and specificity would be improved if RI $\geqq$ 10% is used as a supplemental criterion. Efforts should be made to improve the ability of the dual-time FDG PET-CT technique to assess of primary tumor and loco-regional lymph nodes metastasis.

Keywords:

2-[18F]fluoro-2-deoxy-d-glucose (FDG)

Positron emission tomography–computed tomography

(PET–CT)

Esophageal squamous cell carcinoma

Standardized uptake value (SUVmax)

Retention index (RI)

Chapter 1

Introduction

背景 Background

近年來癌症已成為國人最重要的死亡原因，依據統計，平均每 7 分 10 秒就有人罹患癌症; 每 3 人死亡中，更有 1 人因癌症喪命。每年不知有多少家庭因為有家屬罹患癌症而飽受折磨。雖然近年來各種癌症的診斷及治療技術有不錯的突破，但國人仍然是"談癌色變"。

根據行政院生署國民健康局癌症登記相關資料顯示，自民國七十一年起，癌症即躍居國人十大死因第一位，迄今約二十餘年。且其發生及死亡的情形，皆有呈現逐年攀升的趨勢。在民國 99 年國人共有 7 萬多人被診斷為癌症，並有 4 萬餘人死於癌症，當中以食道癌為例，它是台灣男性病患第七常見的癌症，占男性癌症死亡率的第八位。食道癌好發於 50 到 60 歲居多，發生的部位以食道中下段居多，幾乎都是鱗狀上皮細胞癌，腺癌佔少數，其比例為 9 比 1。

食道癌為胃腸道癌症中預後最不好的一種，與胃或腸癌相比，存活率是較差的一種。其原因是因為當發生有症狀

時，大多數為期已晚，能夠早期發現的比率不高。根據目前一般的文獻報告，外科切除的食道癌其五年存活率是相當不好的，報告從 5%至 30%不等，但若是較早期的食道癌患者則可能有 65-90% 的五年存活率。相對於比較晚期的病患如果無法以手術處理其五年存活率大部份則少於 5%.

食道癌的診斷並不困難，但大部份已有相當明顯的症狀，病人約 90%是因為吞嚥問題而來，只有少數在作例行健康檢查而早期發現。手術切除是目前對食道癌治療的主要方式，其開刀成功與否是和術前對於腫瘤侵犯深度，局部淋巴結及遠端轉移的判斷有著密切的關係。目前在臨床上最常使用的影像診斷工具包括有

1）電腦斷層(CT)

2）內視鏡超音波(EUS)

3）正子射出造影(PET) 。

以食道內視鏡超音波檢查(EUS)為例，它是可以偵測腫瘤侵犯的深度及其周邊淋巴結是否有轉移的情形。正常的食道超音波圖像是由五層強弱不同，境界清楚的回音波相間所組成，由內向外為(圖一)

1）第一層回音區代表探頭與球束之間的界面

2) 第二層低回音區為粘膜層及粘膜下層內半部構成

3) 第三層粘膜下層外半部為一強回音波

4)第四層代表肌層的低回音波

5)第五層代表外膜的強回音波。

在 EUS 中正常的縱膈腔淋巴結大多為直徑小于 5mm 的軟組織，呈現橢圓或三角形、邊界模糊的強回音光團。因此，內視鏡超音波能依據淋巴結的大小及內部狀態的變化來判斷腫瘤的淋巴結是否有轉移。(圖二)

判斷縱膈腔淋巴結是否受侵犯的標準為：

1)直徑大於 10mm

2)圓形輪廓清楚

3)內部回音不均或呈現弱回音光團

4)局限性食道外膜壓迫推移。

一般說來，電腦斷層(CT)，通常是使用在食道內視鏡後而且確診的病人所做的進一步檢查。由於電腦斷層攝影能清楚地顯現食道癌腫瘤的位置，也容易觀察腫瘤是否已有侵犯至食道周圍之組織及器官，是否有淋巴結轉移及遠處轉移等。因此它是目前食道癌的分期的重要檢查，更常藉以決定

治療方式，或放射線治療，甚至手術方法的主要的根據。

根據目前研究報道，內視鏡超音波在診斷腫瘤侵犯深度的準確性約 52%～92%，淋巴結轉移的準確性則有 70%～90%。有不少的文獻報告就以內視鏡超音波和電腦斷層對食道癌行分期的比較認為，在腫瘤侵犯深度和區域淋巴結轉移方面內視鏡超音波是優於電腦斷層；而判斷遠處轉移則以電腦斷層優越於內視鏡超音波。

至於正子射出造影 (Positron Emission Tomography, PET)，它是核子醫學近年所發展出來的斷層造影技術。PET 的原理是將正子蛻變(positron/B decay)的同位素示蹤劑(tracer)注入人體內，當正子蛻變會伴隨發生互毀反應(annihilation reaction)，所產生的兩個 511keV 高能光子將會往相反方向激發，再由一部偶合偵測高能光子的儀器偵測到訊號，再經由電腦影像重組，就可以得到正子放射核種在人體內分佈的資訊。

FDG(2-[Fluorine-18]Fluoro-2-deoxy-D-glucose)目前是臨床使用上最常使用的同位素示蹤劑。一般上 PET 的讀值是以 SUV (Standardized uptake value) 為代表人體細胞所吸收的放射性葡萄糖衍生物。大多數的癌症腫瘤會進行的

無氧解糖作用(Anaerobic glycolysis)，比正常組織為高，而呈現異常的葡萄糖代謝。FDG 是葡萄糖的同功異構物(analogue)，也會和葡萄糖一樣，被腫瘤組織攝取，但不會再行糖解而滯留在人體細胞內，再以正子射出斷層造影偵測放射性 F-18 FDG 的分佈資料，作為診斷依據。由於腫瘤細胞具有高速率的葡萄糖代謝，所以腫瘤細胞就會比正常細胞吸收較多的 18F-FDG，因此在影像上就會以高 SUV 值來顯現。

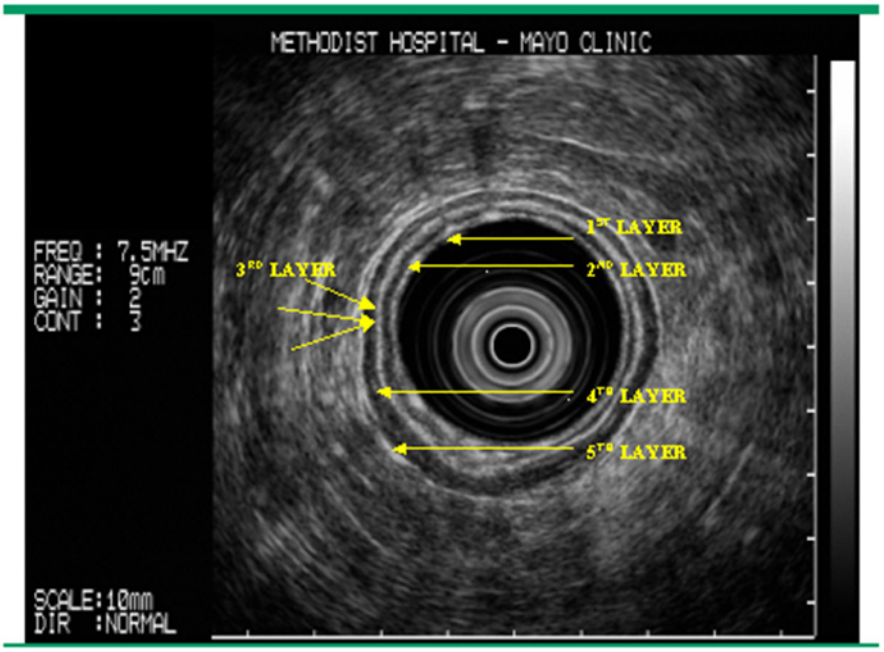
正子射出造影(PET)相較於電腦斷層，雖然 PET 能精確的找到腫瘤，然而對於相關解剖位置則不易呈現，缺點就是 PET 在判斷時必須和電腦斷層作同步比對，有時候 SUV 相對於解剖部位會有誤差，而造成誤判。所以最近發展出正子電腦斷層造影(PET-CT)，同時結合 PET scan 對腫瘤偵測的準確及 CT scan 對解剖位置清析的雙重優點，有效的克服了 PET Scan 對於相關解剖位置不易呈現的缺點。正子電腦斷層造影是於 2000 年由美國匹茲堡大學所發展出來的最新醫療儀器，其優點是不但可以同時偵察功能性和解剖結構影像，也藉由 CT 提供清楚的解剖定位，配合 FDG 就可以清楚判定確實的病灶區，大大提高了 PET-CT 在腫瘤診斷和分期

的準確度。

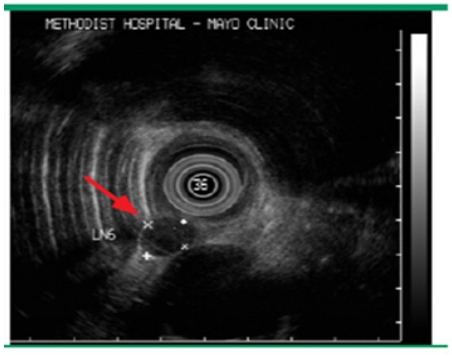
一般食道癌的治療，是依據病灶形態、淋巴結大小，是否有遠端轉移來認定病變波及的範圍，如果在術前的評估不精確，就會錯失早期轉移，輕判病程而致不當的手術。目前多項回遡性的研究發現，對於偵測食道癌的靈敏度，特異度及準確性不管用何種檢查工具大都介於 65-90%，有一些小型的報告即使是最新的 PET-CT，其差異性也只是相差約 5-10%。除此以外特別是對於淋巴結轉移有否，其靈敏度，特異度及準確性和 CT 及 EUS 相差不遠，因此常常會衍生偽陽性及偽陰性的問題存在。

目前有一些學者發現除了藉由詳細的病史分析、理學檢查與其他臨床資料來做鑑別診斷之外，亦可利用當日前後兩次正子造影（PET）的最大標準攝取值數值變化來輔助診斷，即所謂的雙相正子造影（dual-time-point PET)。原則上在許多的報告中發現，惡性腫瘤會隨著時間累積比較多的氟 18 去氧葡萄糖，發炎與感染疾病剛好相反。在一份綜合 40 個研究的統合分析（meta-analysis）報告中，氟 18 去氧葡萄糖正子造影對於 1474 個單一肺結節診斷為肺癌的敏感度(sensitivity)與特異度(specificity)各為 91.2%

與 85.6%，表示 F-18 去氧葡萄糖正子造影對於單一肺結節極具價值。然而，肺結核、霉菌感染、類肉瘤與矽肺症等肉芽腫疾病，在 F-18 去氧葡萄糖正子造影亦可能呈現類似惡性結節的影像表徵。由於現有大部份的正子造影(PET)文獻都是以肺癌和單一肺結節為主，相對於使用在食道癌的診斷只有一篇報導，更何況如果以正子電腦斷層造影(PET-CT)來做檢查的則是掛零。因此本研究的主要目的是探討於不同時段進行正子電腦斷層造影分析食道癌細胞對於 18F-FDG 吸收的差異性，試圖找出能否提高診斷腫瘤侵犯深度、局部淋巴結及遠端轉移的方式，以協助臨床醫師作出正確的判斷和處置。



（圖一）食道內視鏡超音波檢查



	Benign	Malignant
Size (width)	< 10 mm	> 10 mm
Shape	Elongated	Round
Border	Irregular	Smooth
Echogenicity	Echorich	Echopoor

（圖二）食道內視鏡超音波檢查良惡性淋巴結的大小及內部狀態。

Appendix:

Esophageal cancer is a lethal malignant cancer with a poor prognosis. The 5 -year survival rate for most cases diagnosed in the advanced stage is only 10 – 30% for resectable tumors and 5% for unresectable ones. Information regarding tumor invasion depth, lymph node involvement, and distant metastasis is important in deciding the appropriate treatment for esophageal cancer. Accurate assessment of tumor extent and nodal involvement is essential for curative resection. Various imaging tools, such as computed tomography scan (CT) and, Endoscopic Ultrasonography (EUS) are widely used in routine clinical practice. These imaging tool are useful for evaluating the extent of the disease but have limitations when determining lymph nodes metastasis. In the past, computed tomography (CT)scanning was the major staging method, but recently,2-[18F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)scanning has become more widely used. The FDG PET is used for diagnosis, initial staging, restaging, prediction, and monitoring of treatment response,

surveillance, and prognostication in a variety of cancers. However, FDG PET does not allow for the precise localization of landmarks, making it difficult to identify the foci of the increased FDG uptake. The role of FDG PET in the detection of nodal metastasis is still controversial and its efficacy far from ideal. Integrated FDG PET-CT is a new functional and metabolic imaging tool. Many reports indicate that FDG PET-CT is more sensitive and specific in the diagnosis and staging of several types of malignancies than FDG PET. However, FDG uptake is not tumor specific. Traditionally, a threshold for a single time point standardized uptake value (SUV) of 2.5-3.5 has been proposed as the optimal threshold for distinguishes between benign and malignant lesion in various literatures. Many researchers found that when SUV is measured, there is a correlation between the FDG uptake and time. In tumor, the uptake of FDG uptake continues to increase for several hours after FDG injection whereas such prolonged period of FDG uptake is rare in inflammatory/infectious or normal tissues. This may be related to the graded concentration

of FDG in tumor cells, low glucose-6-phosphatase activity, and increase glucose uptake through glucose transporter in these cells.

Therefore, recognition of these imaging pitfalls is an important step in patient assessment. Various cell types exhibit varying rates of FDG uptake. Dual-time-point scanning of FDG PET has been widely applied in many kinds of cancers. Most of them seem useful in differentiating between inflammation and malignancy because of the additional qualitative and quantitative information derived from these scans. Hence, the method has been routinely used in all FDG PET scans of our institute. However, poor discriminability of dual-time-point method has also been found in few studies. Nevertheless, the efficacy of such method for esophageal cancer is seldom reported or discussed in the literature. Thus, the purpose of current study is aimed to analyze the relation between findings of dual-time-point FDG PET-CT and clinical/pathological results of the primary tumor, lymph nodes and distant metastasis of the esophageal cancers retrospectively, and tries to discuss the

potential use of dual-time-point method in such circumstance.

Chapter 2

Materials and Method

材料與方法:

首先我們以回溯性的方式進行資料收集和分析，將自2009年10月至2010年4月期間在中國醫藥大學診斷為鱗狀上皮食道癌的患者，全部是男性，合計26人收案(表一)。所有的病患都接受了手術切除腫瘤和淋巴結，而且所有的患者在手術前都接受了雙相的正子電腦斷層造影(PET-CT)檢查。最後我們將手術後的病理報告和手術前的PET-CT報告及期別作比對分析，以檢測雙相的正子電腦斷層造影檢查對於原發腫瘤、局部淋巴結轉移及遠端轉移偵測的靈敏度、特異度及準確性是否有提高。我們所採取的癌症期別是根據AJCC第6版，同時本研究是經過中國醫藥大學人體實驗委員會審查通過。(DMR-99-IRB-010)

我們所使用的正子電腦斷層是由美國奇異公司(Discovery STE, GE Medical Systems, Milwaukee, WI, USA)所生產的儀器。檢查前病患禁食至少4小時，血糖不超過120mg/dl。約10毫居里(mCi)或370百萬貝克(MBq)的氟18-去氧葡萄糖(FDG)經靜脈注射後，受檢者被要求靜躺休息45

分鐘，以便 FDG 在腫瘤內能夠充分聚積，在正常組織中能充分排除，並經由腎臟、膀胱排泄。當 45 分鐘後，開始進行檢查，一般自頭部掃瞄至大腿上三分之一約需一小時。當 70 分鐘的時候，我們將再施作一次全身性正子電腦斷層掃描。當所有影像重組後，就會由二位核子醫學科的醫師進行判讀（圖三）。

SUV 的定義是"mean selected region of activity/injected dose/body weight"。FDG uptake 的區域指的是放射性物質吸收較高的地方，一般上是針對超過週邊背景值或組織的區域如血管，食道，淋巴結及其他在電腦斷層上可辨識的器官(圖四)。

統計與分析:

我們參考過去的文獻記載發現，目前大多數的學者判定腫瘤是否為惡性的 SUV 值大多介於 2.5-3.5 之間。最終我們決定採用 Hu Q et al.於 2009 年所發表的文章，分別以最大標準攝取值 SUVmax≥ 2.5 及 Retention index (RI) ≥10%作為本次實驗的參考值 (cutoff value)。每位病患在術前都會接受兩次的全身正子電腦斷層掃描，因此就會取

得兩組不同時間內的 SUVmax 值；Early SUVmax 及 Delay SUVmax。Early SUVmax 指的是 FDG 注射到人體 45 分鐘後的最大標準攝取值而 delay SUVmax 為 70 分鐘後的讀值;而 RI 則是 delay SUVmax 值減去 early SUVmax 值再除以 early SUVmax 值的百分比，其代表意義為判別細胞是否是惡性(RI≥10%)或者只是發炎與感染疾病的可能性。將這 3 種讀值收集後再組合成以下 4 組的診斷標準(Diagnostic criteria):

(1) SUVmax≥ 2.5

(2) RI ≥ 10%

(3) SUVmax 加上 RI ≥ 10%

(4) SUVmax 或 RI ≥ 10%擇一，並進行統計分析。

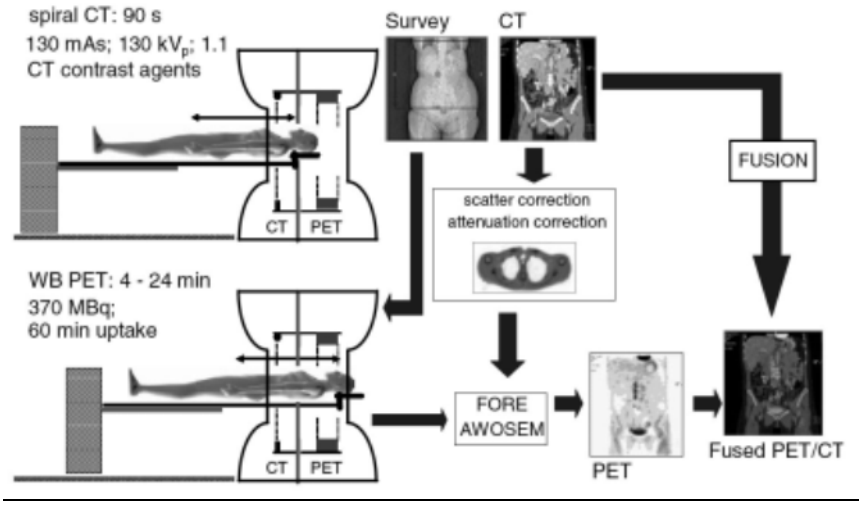
我們所使用的統計方法及軟體分別是 Fisher’s exact test 及 SPSS 12 版，同時採取 p 值< 0.05 為統計上有意義。

（表一）

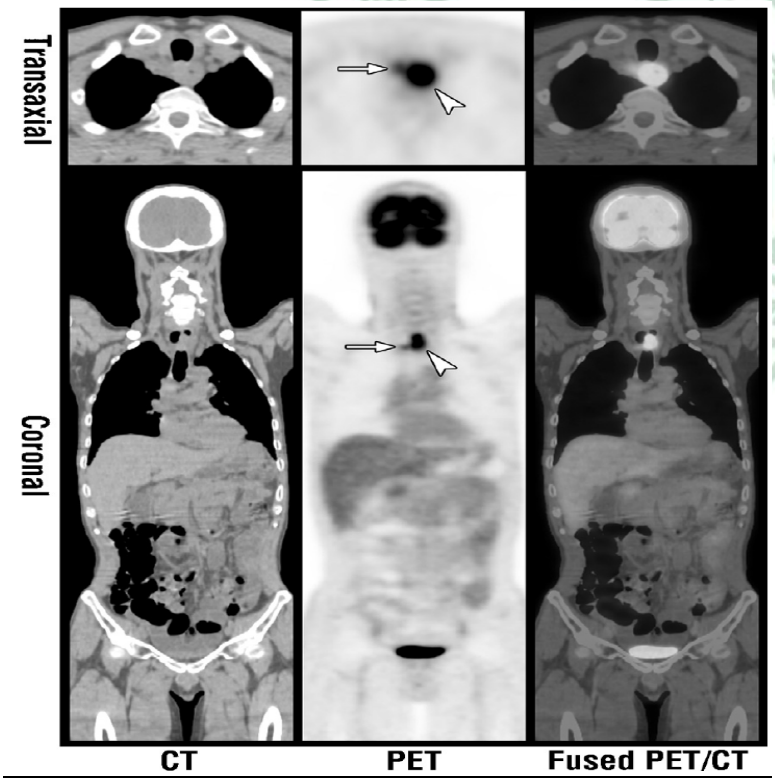
Tumor staging, SUV_{max} and RI of the primary tumor, loco-regional lymph node and distant metastasis.

Patient	Tumor location	Pathology tumor staging (AJCC 6)			SUV of positive PET-CT finding						PET-CT staging		
		pT	pN	pM	Primary tumor		Locoregional LN		Distant Metastasis		T	N	M
					SUV early	RI (%)	SUV early	RI (%)	SUV early	RI (%)			
1	M/3	2	0	0	2.4	13.9	2.3	4.7	Absent	NA	X	1	0
2	M/3	2	0	0	4.3	2.2	0.8	20.8	Absent	NA	X	0	0
3	U/3	3	0	1a	9.1	16.8	1.3	8.5	1.3	11.0	X	1	1a
4	L/3	3	1	1a	11.8	5.6	1.6	−15.1	2.0	−13.8	X	0	1a
5	U/3	3	0	0	6.3	6.9	1.3	−3.8	Absent	NA	X	1	0
6	U/3	3	1	0	10.0	3.8	1.2	−0.3	Absent	NA	X	1	0
7	U/3	4	1	0	10.3	0.3	0.6	91.7	1.7	11.3	X	1	1a
8	M/3	3	1	1b	3.5	5.4	Absent	NA	3.5	12.3	X	0	1b
9	U/3	1	0	0	3.9	37.2	0.8	67.6	Absent	NA	X	1	0
10	M/3	4	1	1a	4.1	55.6	1.1	54.1	1.5	1.3	X	1	1a
11	U/3	3	1	0	9.1	9.3	3.3	81.9	Absent	NA	X	1	0
12	U/3	3	1	0	12.6	13.8	3.3	28.3	1.8	39.1	X	1	1b
13	M/3	2	0	0	14.9	12.2	1.4	11.1	Absent	NA	X	0	0
14	U/3	3	0	0	8.2	30.6	2.6	15.5	Absent	NA	X	0	0
15	U/3	3	0	0	3.4	3.5	1.5	−8.2	Absent	NA	X	1	0
16	U/3	4	1	0	11.2	10.4	1.0	30.4	Absent	NA	X	1	0
17	M/3	1	0	0	1.8	38.0	1.1	−0.1	Absent	NA	0	0	0
18	M/3	1	0	0	4.3	23.9	1.5	16.8	Absent	NA	X	0	0
19	L/3	3	1	0	13.4	18.4	0.9	26.0	Absent	NA	X	1	0
20	M/3	3	0	0	8.4	19.0	2.1	−4.4	Absent	NA	X	0	0
21	M/3	1	0	0	3.1	12.7	1.1	1.1	Absent	NA	X	0	0
22	M/3	3	0	0	7.7	14.6	1.4	15.0	1.6	22.9	X	1	1b
23	M/3	3	0	0	9.0	7.6	0.8	14.5	Absent	NA	X	0	0
24	U/3	4	0	1b	2.1	8.3	0.9	−12.5	Absent	NA	X	0	0
25	L/3	3	0	1b	9.0	36.6	Absent	NA	1.7	63.7	X	0	1b
26	U/3	3	1	0	9.6	2.4	3.4	4.1	Absent	NA	X	1	0

NA: not applicable. X: representing positive for malignancy but difficult to denote T stage.



（圖三） PET-CT scanner and procedure



(圖四) Example of an FDG PET/CT scan.

Appendix:

2.1 Patient Population

Twenty-six patients (all men; age range, 42 - 72 years old; mean age, 60.4 years)who underwent preoperative FDG PET-CT scan and subsequent surgical resection of esophageal cancer between October 2009 and April 2010 in China Medical University Hospital were retrospectively included in this study. All patients histologically proved to have squamous cell carcinoma and had received esophageal resection and regional lymph nodes dissection. Surgical pathology results were used to provide the final diagnosis with which the FDG PET-CT results were compared, including those with distant metastases. The visual interpretation of the FDG PET-CT and surgical pathology stage was classified according to the sixth edition of the AJCC Cancer Staging System. This study was approved by the Ethics Committee of the China Medical University Hospital (DMR-99-IRB-010).

2.2 FDG PET-CT Imaging protocol, Interpretation and Calculation of Related Parameters

All patients were asked to fast for at least 4 hours before FDG PET-CT imaging. Imaging was performed with a PET-CT scanner (Discovery STE, GE Medical Systems, Milwaukee, WI, USA). Whole - body FDG PET-CT images were acquired approximately 45 minutes after intravenous injection of 370 MBq (10 mCi) of FDG. Delayed FDG PET-CT images were obtained approximately 70 minutes after FDG injection. PET emission images were acquired after CT scans at 2 minutes per field of view (FOV) in the 3 - dimensional acquisition mode. The CT images were reconstructed onto a 512×512 matrix with a section thickness of 3.75 mm, then reconstructed onto a 128×128 matrix, and converted into 11-keV-equivalent attenuation factors for attenuation correction of the corresponding PET emission images. The suspected tumoral FDG uptake was defined as focally increased radioactivity, greater than those in the surrounding background or blood pool, in the esophagus, lymph node or other recognizable

morphological lesional sites on the CT component of FDG PET-CT by visual interpretation. A semiquantitative parameter, standardized uptake value (SUV), was defined as “tracer activity in the tumor per unit mass divided by amount of injected radioactivity per unit body mass”, and calculated from each region of interest with increased FDG radioactivity in the suspected tumoral region. The maximum standardized uptake value (SUVmax) of esophageal cancer and metastasis on early and delayed FDG PET-CT images were measured. The retention index (RI) based on the measured SUVmax was calculated as 100% × (delayed SUVmax－ early SUVmax) ÷ early SUVmax. Early and delayed PET images were reviewed on the computer monitor in the trans-axial, coronal, and sagittal planes along with maximum-intensity-projection images. Two experienced nuclear medicine physicians in dependently evaluated FDG uptake both visually and semiquantitatively. The evaluating physicians were unaware of the clinical history and the PET images were compared with the corresponding CT images for accurate anatomic identification of the tumor. Any difference of

opinion was resolved by consensus.

2.3 Statistical analysis

We used 4 diagnostic criteria to evaluate the sensitivity, specificity and accuracy of dual-time FDG PET-CT in differentiating malignancy from a benign lesion among the primary tumor, loco-regional lymph nodes, and distant metastases. The 4 criteria included (1) early SUVmax ≧ 2.5 alone, (2) RI ≧ 10% alone, (3) combination of early SUVmax ≧ 2.5 and RI ≧ 10%, and (4) combination of early SUVmax ≧ 2.5 or RI ≧ 10%. Fisher's exact test was applied to compare each difference in the sensitivity, specificity and accuracy. SPSS software was used for the analysis. A p-value of less than 0.05 was considered statistically significant.

Chapter 3

Results

第三章 研究結果

在原發腫瘤部份，當 SUVmax≥ 2.5 或者 RI ≥ 10% 任何一項讀值被選為判定是否為陽性時(腫瘤細胞)，其靈敏度可提高到 96.2%，而且是统計上有意義的 (p<0.05)(表二)。

針對局部淋巴結的部份，當 SUVmax≥ 2.5 加上 RI ≥ 10% 時靈敏度會明顯的提昇到 70%，但是 p 值却只有 0.1181。至於在其他不同組合的診斷準則方面也都無法有效提高對局部淋巴結的偵測，所有的靈敏度，特異度及準確性均無法達到統計學上的意義 (表三)。

最後在遠端轉移的部份，SUVmax≥ 2.5 無論是否有加上 RI ≥10%，其靈敏度及特異度皆相同;分別是靈敏度 16.7% 而特異度則是 100%，均有達到統計學上意義(p<0.05)。至於在準確性方面所有的診斷準大都介於 76.9-80.8%，無法達到統計學上意義 (表四)。

（表二）

Table 2
Sensitivity of different diagnostic criteria in the detection of primary tumor.

Diagnostic criteria	Sensitivity (%)
SUV early ≧ 2.5	88.5
RI ≧ 10%	57.7
SUV early ≧ 2.5 and RI ≧ 10%	50.0
SUV early ≧ 2.5 or RI ≧ 10%	96.2[a]

[a] Stastitically significantly higher than the other 3 criteria.

（表三）

Table 3
Sensitivity, specificity and accuracy of different diagnostic criteria in the detection of loco-regional lymph node metastasis.

Diagnostic criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
SUV early ≧ 2.5	30.0	93.8	69.2
RI ≧ 10%	60.0	56.3	57.7
SUV early ≧ 2.5 and RI ≧ 10%	20.0	93.8	65.4
SUV early ≧ 2.5 or RI ≧ 10%	70.0	56.3	61.5

（表四）

Table 4
Sensitivity, specificity and accuracy of different diagnostic criteria in the detection of distant metastasis.

Diagnostic criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
SUV early ≧ 2.5	16.7	100.0[a]	80.8
RI ≧ 10%	50.0	85.0	76.9
SUV early ≧ 2.5 and RI ≧ 10%	16.7	100.0[a]	80.8
SUV early ≧ 2.5 or RI ≧ 10%	50.0	85.0	76.9

[a] Stastitically significantly higher than the other 2 criteria.

Appendix:

Results

3.1 Primary tumor

The sensitivity of FDG PET-CT in detecting the primary tumor site with combination of early SUVmax≧ 2.5 or RI ≧ 10 % was 96.2%. It was statistically significantly higher than the other 3 criteria. The p value of Fisher's exact test was <0.0001 and it was statistically significant (Table 2).

3.2 Regional lymph nodes

The sensitivity of early SUVmax≧ 2.5 alone was 30.0%, but it increased to 70% when combination of early SUVmax≧ 2.5 or RI ≧ 10% was used. However, the p value was only 0.1181 and hence not significant. For the specificity, the result was reversed. When using early SUVmax≧2.5 alone, it was 93.8% but it decreased dramatically to 56.3% when combination of early SUVmax≧ 2.5 or RI ≧ 10% was used. Similarly, the p value was not significant (p = 0.0756) (Table 3). With regard to accuracy, there was no significant correlation among the four

diagnostic criteria. (p>0.05).

3.3 Distant Metastasis

When using combination of early SUVmax≧ 2.5 and RI ≧ 10%, the sensitivity and specificity were 16.7% and 100%, respectively. The same result was found when early SUVmax≧ 2.5 was used alone. However, when RI ≧ 10% was used alone, the sensitivity increased dramatically to 50% but the specificity dropped to 85%. Furthermore, a similar poor result was found when combination of early SUVmax or RI ≧ 10%, was used (Table 4). A significantly higher specificity was found when using combination of early SUVmax≧ 2.5 and RI ≧ 10% or using early SUVmax alone than using the other 2 parameters (p = 0.0058 by using Fisher's exact test). The sensitivity, however, was somewhat different (p = 0.4906). For the accuracies, the detection rate was between 76.9% and 80.8%, which did not reach statistical significance (p > 0.05).

Chapter 4

Discussion

第四章討論

正子電腦斷層攝影是一種非侵入性的影像檢查，目前廣範的使用在癌症病人身上。在臨床應用範圍方面，PET-CT 除了可協助醫師更早期地診斷癌症及決定治療方法，它也具備了迅速而清晰辨識腫瘤特質，精確判斷腫瘤是否是良性或惡性或者是否已經轉移。雖然如此，PET-CT 在臨床使用上也會有些盲點存在，譬如 FDG 除了會被癌細胞吸收外，一些發炎細胞也會有 FDG 的吸收，而造成偽陽性。所以為了減少誤判，我們必須找到合適的檢測方式以提高 PET-CT 的準確率。

針對如何提高 PET-CT 的偵測率，許多學者發現在不同時段所進行的正子電腦斷層檢查，其 SUVmax 值會有不同的走勢;良性的細胞大約在 FDG uptake 60 分鐘後會漸漸下降，反之在惡性腫瘤其 SUVmax 值可以持續 120-180 分鐘甚至上昇。有鑑於此，許多研究人員會安排病患當日進行前後兩次不同時段(雙相)的全身正子掃描，並觀察及記錄其 FDG uptake 的變化，以提高靈敏度及特異性。目前這些雙相正子掃描的研究大部份是針對肺部單一肺結節和肺癌的鑑別診

斷，相對於使用雙相正子掃描(dual time PET-CT)在食道癌的診斷的文章則只有一篇報導。除此以外還有一個更重要的議題要討論就是對於 SUVmax 值的標準值(cutoff value)，要取决於那一個讀值，各學者專家到目前為此也還沒有一個定論。

在本研究中我們參考了以往的報告，以 SUVmax> 2.5 來界定良性與惡性的標準值，同時加入了 Retention Index (RI)，也即是 70 分鐘和 45 分鐘 SUVmax 值的變化百分比，作為另一個參考值以提高診斷食道原發腫瘤，淋巴結及遠端轉移的靈敏度，特異度及準確性。根據本研究的最後統計，如果單獨使用 early SUVmax> 2.5 為診斷準則的話，其靈敏度可達到 88.5%，這和其他報導過的文獻很接近。當 RI > 10% 納入為其中一個診斷準則 (SUVmax> 2.5 or RI > 10%)，其靈敏度會上昇到 96.2%。所以我們認為 RI>10%對於診斷食道原發腫瘤有很大的臨床參考價值。

在局部淋巴結的部份，在許多不同的報告中有很大的差異性，靈敏度從 22% 到 72% 都有人在報導。至於在特異度方面，大部份的報告都是介於 50-85%之間。在本次研究中我們在局部淋巴結的靈敏度及特異度所測得的數據分別是

70% 和 56.3% ，這和以往的 PET 報告相差不遠。檢討分析後我們認為可能和淋巴結太小或者只有顯微的侵犯，所以葡萄糖的吸收會比較低。同時如果局部的淋巴結與原發腫瘤太接近或者患者的胸部呼吸太大都會影响到判讀。除此以外，如果在手術中所切除的淋巴結數不夠或被忽略掉，淋巴結和原腫瘤術後無法完全分陶檢查，食道複雜的淋巴系統及太微小的淋巴結都會影响到最後的判讀結果。總括以上各項因素，我們認為雙相正子攝影在偵測食道癌局部淋巴結轉移的角色尚未有定論。

最後針對遠端轉移部份，我們發現如果使用雙相正子電腦斷層攝影檢查，其特異度會高達 85%-100%，這和現有的報導比較並不遜色。相反如果只單獨使用 SUVmax 為單一判讀準則，其靈敏度會比同時/或加上 RI 值來得低。最後我們的結論是在診斷食道癌的遠端轉移時建議可以把 RI 值加上作為一項參考指標，以提高其準確度。

Appendix:

FDG PET-CT is widely used with cancer patients. Its role as a non –invasive imaging modality has been widely investigated but the exact SUVmax cutoff value for esophageal cancer remains controversial. To accurately distinguish malignant from benign lesion is challenging because FDG is taken up not only by tumor cells but by inflammatory cells as well.

Although the potential of dual-time FDG PET in evaluating various cancers has been reported, the diagnostic value of this technique for esophageal cancer has not been fully investigated. To our knowledge, only one report has demonstrated the potential of dual–time FDG PET in evaluating the loco-regional lymph nodes in esophageal cancer. Furthermore, there have been few reports on the sensitivity, specificity and accuracy of dual–time FDG PET-CT in evaluation of primary tumor and distant metastasis.

In our study, we assessed whether dual-time FDG

PET-CT would have more value than conventional FDG PET-CT imaging in differentiating between malignant and benign esophageal lesions. An arbitrary cutoff as SUVmax of 2.5 has been used in various malignancies, most in lung cancers. Nevertheless, the frequent effective discriminability with this arbitrary value among those previous studies results infrequent citations in newly conducted studies for various tumors, especially in the initial applications. Therefore, the current preliminary study assumed that a SUVmax of2.5 might be a potential useful cutoff for differentiation of esophageal cancer in addition to the visual interpretation. Various studies have shown that the FDG uptake in inflammatory lesions normally reached a peak at approximately 60minutes after injection. However, in some malignant lesions the uptake continuously increased for 120 - 180 minutes. In order to increase the detection rate, we proposed using the percentage of change in the lesion between early SUVmax and delayed SUVmax as an alternative in the diagnosis of esophageal cancer (RI > 10%). We also hypothesized that the sensitivity, specificity and

accuracy would increase if the SUVmax and retention index were used simultaneously. Statistically, when using early SUVmax≧ 2.5 alone as the diagnostic criterion, the sensitivity for the primary tumor was approximately 88.5%,which is consistent with the finding of other recently published reports. When combination of early SUVmax≧ 2.5 or RI ≧ 10% was used as the diagnostic criteria for imaging reading, the sensitivity reached 96.2% and that was significantly higher than with the other three criteria. Therefore, we conclude that combination of early SUVmax≧ 2.5or RI ≧ 10% is a reliable tool in detecting the primary site of esophageal carcinoma.

For loco-regional lymph node involvement, many studies reported that sensitivity varied, ranging from 22% and 72%. In a retrospective study, Hsu et al. reported sensitivities and specificities rates for regional lymph node involvement of, 57.1% and 83.3%, respectively. In comparison, our data demonstrate that the combination of early SUVmax≧ 2.5 or RI ≧ 10% produced an sensitivity of 70% and specificity of 56.3%. When compared with the usual FDG PET results, these

results were unsatisfactory. This could be related to the relatively low glucose utilization of the small lymph node or a limited microscopic spread. Tracer uptake in physiologic structures at the thoracic cage, motion or high FDG uptake in the adjacent primary tumor can lead to an underestimate of the FDG uptake of the regional lymph nodes. Furthermore, the size and morphology of the lymph nodes, a complicated lymphatic drainage network, an uneven margin between the tumor and the nodal extension, inadequate surgery and failure to detect peri-tumoral nodes during resection may also influence the final histology finding. The number of lymph nodes examined must also be taken into account when assessing the results. In conclusion, we believe that the ability of dual-time FDG PET-CT to detect loco-regional lymph node metastasis using different diagnostic criteria remains to be demonstrated.

In our study, high specificities were achieved in the detection of distant metastasis of esophageal carcinoma using dual-time FDG PET-CT, in a range from85% to 100%. Our results are in agreement with those of several FDG PET studies.

In contrast, the low sensitivities of early SUVmax≧ 2.5 alone as the single diagnostic criteria in recognizing metastatic lesions might be due to variable volumes of the metastatic lesions. When RI is applied, significantly improvement was noted. Therefore, based on our study, we recommend combination early SUVmax≧ 2.5 and/or RI ≧ 10% in order to increase the accuracy. One limitation of this study was the small number of cases. This may have affected the statistical calculations. Therefore, studies with a larger number of patients should be conducted to determine the appropriate cutoff values of SUVmax and RI for esophageal cancer. Besides, short interval of follow up may also cause some false negative results. However, on the basis of the data reported, to some extent, the dual-time point FDG PET-CT has more value than standard PET imaging for detecting esophageal cancer. Therefore, we recommend that FDG PET-CT be considered in routine examination prior to the treatment of esophageal cancer in orderto guide optimal clinical management for possible distal metastases to avoid unnecessary operation.

Chapter 5

第五章

Conclusion 結論

結論

本研究的結果發現雙相正子射出電腦斷層造影(Dual-time PET-CT)在臨床診斷食道原發腫瘤及局部淋巴結的角色尚未有明確的參考價值。但是從初步報告可以發現對於有遠端轉移的食道癌病患，RI > 10%可以用來當作一個輔助的參考值，它不但可以提高 PET-CT 偵測的靈敏度及特異度，同時也可以協助臨床醫師作出適當的處置。

建議

最後在檢討改進中，我們認為由於本研究的病人數只有 26 人，以致於在統計上或實務上都無法證實雙相正子電腦斷層攝影有顯著的臨床價值。但是將來如果有更多的病患人數納入，追踪的時間也夠長，同時可考慮使用不同的 SUVmax 值和 Retention Index 值，我們相信結果可能就會不一樣。

總括來說，透過本次研究的初步結果，我們認為雙相

正子電腦斷層攝影對於診斷食道癌及其分期上是具有臨床參考的價值。因此我們建議，所有的食道癌病患在手術前都必須施做雙相正子電腦斷層攝影，以提供外科醫師適當的資訊來評估是否要以開刀來處理或者接受其他的治療方式。

Appendix:

The preliminary result of this study demonstrated that dual-time point FDGPET-CT had limited value in detection of primary tumor and loco-regional lymph node metastasis. For the distant metastasis, the sensitivity and specificity would be improved if RI ≧ 10% was used as a supplement criterion. Efforts should be made to improve the ability of the dual–time FDG PET-CT technique to assess primary tumor and loco-regional lymph nodes metastasis.

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Reference 參考文獻及附錄

[1] Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241-52.

[2] Okada M, Murakami T, Kumano S, et al. Integrated FDG-PET/CT compared with intravenous contrast-enhanced CT for evaluation of metastatic regional lymph nodes in patients with resectable early stage esophageal cancer. Ann Nucl Med2009;23:73-80.

[3] Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neo-adjuvant chemoradiotherapy. J Thorac Cardiovasc Surg 2005;129:1232-41.

[4] Swisher SG, Maish M, Erasmus JJ, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. Ann ThoracSurg2004;78:1152-60; discussion -60.

[5] Kato H, Kuwano H, Nakajima M, et al. Comparison between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. Cancer 2002;94:921-8.

[6] Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. N Engl J Med 2006;354:496-507.

[7] van Westreenen HL, Westerterp M, Bossuyt PM, et al. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J ClinOncol2004;22:3805-12.

[8] Erasmus JJ, Munden RF. The role of integrated computed tomography positron-emission tomography in esophageal cancer: staging and assessment of therapeutic response. Semin Radiat Oncol 2007;17:29-37.

[9] Kato H, Kimura H, Nakajima M, et al. The additional value of integrated PET/CT over PET in initial lymph node staging of esophageal cancer. Oncol Rep2008;20:857-62.

[10] Yuan S, Yu Y, Chao KS, et al. Additional value of PET/CT

over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. J Nucl Med 2006;47:1255-9.

[11] Yamada S, Kubota K, Kubota R, Ido T, Tamahashi N. High accumulation offluorine-18-fluorodeoxyglucose in turpentine-induced inflammatory tissue. J Nucl Med 1995;36:1301-6.

[12] Demura Y, Tsuchida T, Ishizaki T, et al. 18F-FDG accumulation with PET for differentiation between benign and malignant lesions in the thorax. J Nucl Med 2003;44:540-8.

[13] Charest M, Hickeson M, Lisbona R, Novales-Diaz JA, Derbekyan V, TurcotteRE. FDG PET/CT imaging in primary osseous and soft tissue sarcomas: a retrospective review of 212 cases. Eur J Nucl Med Mol Imaging 2009.

[14] Straver ME, Aukema TS, Olmos RA, et al. Feasibility of FDGPET/CT to monitor the response of axillary lymph node metastases to neoadjuvant chemotherapy in breast cancer patients. Eur J Nucl Med MolImaging;37:1069-76.

[15] Kumar R, Loving VA, Chauhan A, Zhuang H, Mitchell S, Alavi A. Potential of dual-time-point imaging to improve breast cancer diagnosis with (18)F-FDGPET. J Nucl Med 2005;46:1819-24.

[16] Hamberg LM, Hunter GJ, Alpert NM, Choi NC, Babich JW, Fischman AJ. The dose uptake ratio as an index of glucose metabolism: useful parameter or over simplification? J Nucl Med 1994;35:1308-12.

[17] Lodge MA, Lucas JD, Marsden PK, Cronin BF, O'Doherty MJ, Smith MA. APET study of 18FDG uptake in soft tissue masses. Eur J Nucl Med1999;26:22-30.

[18] Matthies A, Hickeson M, Cuchiara A, Alavi A. Dual time point18F-FDG PET for the evaluation of pulmonary nodules. J Nucl Med2002;43:871-5.

[19] Kubota K, Itoh M, Ozaki K, et al. Advantage of delayed whole-body FDG-PET imaging for tumour detection. Eur J Nucl Med 2001;28:696-703.

[20] Tian R, Su M, Tian Y, et al. Dual-time point PET/CT with F-18 FDG for the differentiation of malignant and benign

bone lesions. Skeletal Radiol2009;38:451-8.

[21] Laffon E, de Clermont H, Begueret H, et al. Assessment of dual-time-point18F-FDG-PET imaging for pulmonary lesions. Nucl Med Commun2009;30:455-61.

[22] Zhuang H, Pourdehnad M, Lambright ES, et al. Dual time point 18F-FDG PET imaging for differentiating malignant from inflammatory processes. J Nucl Med 2001;42:1412-7.

[23] Bakheet SM, Powe J. Benign causes of 18-FDG uptake on whole body imaging. Semin Nucl Med 1998;28:352-8.

[24] Hu Q, Wang W, Zhong X, et al. Dual-time-point FDG PET for the evaluation of loco-regional lymph nodes in thoracic esophageal squamous cell cancer. Eur J Radiol 2009;70:320-4.

[25] Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of Positron emission tomography in lung nodules. J Clin Oncol 1998;16:1075-84.

[26] Hellwig D, Graeter TP, Ukena D, et al. 18F-FDG PET for mediastinal staging of lung cancer: which SUV threshold makes sense? J Nucl Med 2007;48:1761-6.

[27] Hsu WH, Hsu PK, Wang SJ, et al. Positron emission tomography-computed tomography in predicting locoregional invasion in esophageal squamous cell carcinoma. Ann ThoracSurg2009;87:1564-8.

[28] Cerfolio RJ, Bryant AS. Maximum standardized uptake values on Positron emission tomography of esophageal cancer predicts stage, tumor biology, and survival. Ann Thorac Surg 2006;82:391-4; discussion 4-5.

[29] Choi JY, Jang HJ, Shim YM, et al. 18F-FDG PET in patients with Esophageal squamous cell carcinoma undergoing curative surgery: prognostic implications. J Nucl Med 2004;45:1843-50.

[30] Choi JY, Lee KH, Shim YM, et al. Improved detection of individual Nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. J Nucl Med2000;41:808-15.

[31] Hofstetter W, Correa AM, Bekele N, et al. Proposed modification of nodal status in AJCC esophageal cancer staging system. Ann ThoracSurg2007;84:365-73;discussion

74-5.

[32] Wren SM, Stijns P, Srinivas S. Positron emission tomography in the Initial staging of esophageal cancer. Arch Surg 2002;137:1001-6; discussion 6-7.

[33] Liberale G, Van Laethem JL, Gay F, et al. The role of PET scan in The preoperative management of oesophageal cancer. Eur J SurgOncol2004;30:942-7.