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內文：

Introduction

1. Oral SCC and oropharyngeal SCC 的治療依據 tumor size, infiltration of surrounding tissue and the absence or presence of metastases 這幾點而有不同，正確的對腫瘤分期對於適當的治療病人，將可能的 treatment-related morbidity 降到最低非常重要。通常對 Oral SCC and oropharyngeal SCC 的分期依靠臨床檢查、CT、MRI、Ultrasound with or without guided fine needle aspiration cytology。
2. Fluorine-18 fluorodeoxyglucose (¹⁸FDG) positron emission tomography (PET) 已被證實對診斷 Oral SCC and oropharyngeal SCC 是一項很有效的技術，特別是在偵查 locoregional and distant metastases。最近對將 ¹⁸FDG PET 當作診斷 Oral SCC and oropharyngeal SCC 的 primary imaging technique 的支持越來越多。
優點：(1) sensitivity and specificity 可與 conventional imaging 比擬甚至更好
(2) 可在同一次檢查中同時評估 locoregional and distant metastases
缺點：(1) 缺乏解剖細節
(2) relative low resolution
以上缺點已藉由 combined PET/CT imaging 改善了。
3. 成為 primary imaging technique 除了 sensitivity and specificity 要好之外，同一觀察者 (intraobserver) 不同時間的解讀與不同觀察者 (interobserver) 的解讀之間的 consistency 也是必須的，這項品質條件與 PET 有否合併 CT 無關。要有效且一致地判讀 oral and oropharyngeal SCC ¹⁸FDG PET images 是否需要一定程度的專業能力，這個答案很重要，但令人意外的是對頭頸 SCC ¹⁸FDG PET images inter- and intraobserver agreement 大家的了解很少。技術發展的速度比評估 observer properties 以及他們對影像判讀的影響要快，所以本研究的目的
(1) to evaluate the inter- and intraobserver agreement of the interpretations of ¹⁸FDG PET images
(2) to assess the influence of observer experience, tumor localization and tumor size on the agreement and sensitivity and specificity

Patients and Methods

1. Patients

數量：80, female: 31, male: 49, mean age: 61.3

Oral SCC: 62, Oropharyngeal SCC: 18

狀態：(1) newly diagnosed SCC of the oral cavity and /or oropharynx, 在 1999~2004 期間做過 ¹⁸FDG PET 的檢查，在檢查前已經病理檢查確診為 SCC

(2) TNM staging

Table 1. POST-TREATMENT TN CLASSIFICATION OF PRIMARY TUMORS

Stage	N0	N1	N2	Total
T1	16	1	0	17*
T2	11	4	4	19
T3	5	3	2	10
T4	9	10	15	34
Total	41	18	21	80

Presence or absence of nodular involvement determined by histologic examination (n = 50), cytologic examination (n = 10), or clinical follow-up (n = 20).

*Two tumors were completely excised by excision biopsy before fluorine-18 fluorodeoxyglucose positron emission tomography.

T: 由histological findings決定(全部)

N: 由histological findings決定(n=50, N+=23, 28 neck sides)

其次由cytological findings決定(n=10, N+=5, 5 neck sides)

以上皆無者由影像檢查(CT, MR, US etc)與clinical follow up(至少1.5年)結果決定(n=20, N+=11, 18 neck sides)

N(+): 39 cases, 51 neck sides

M: ?, 頭頸以外的 malignancy: lung cancer(n=4), thyroid tumor(n=1), skeletal tumor(n=1), infraclavicular metastasis(n=1), esophagus carcinoma(n=1)

治療：(1) Primary Surgery (n=56)

– Surgery only (n=28)

Surgery + supplementary RT (n=38)

Neck dissection (n=50, 68 neck sides)

SND (39 neck sides)

Modified ND (28 neck sides)

RND (1 neck sides)

(2) Primary RT (n=19)

– RT only (n=12)

RT+C/T (n=7)

(3) No therapy (n=5)

2. ¹⁸FDG PET study

(1) 病人禁食至少4小時，IV注射FDG後90分鐘開使拍攝

(2) 使用相機

ECAT 951 – 31 planes/10.9-cm field, resolution: 6 mm full width at max.

ECAT HR+ -- 63 planes/15.5-cm field, resolution: 6 mm full width at max.

3. Study design

(1) Observer – 4個

2 experienced nuclear medicine physicians (NMP)

– 15 years of experience (NMP I) and 5 years experience (NMP II)

2 residents in nuclear medicine

– 4 years of experience (R I) and 2 years experience (R II)

(2) 除了診斷為oral and oropharyngeal SCC 以外，進行檢查時其它資訊都沒有提供

(3) 所有observer判讀影像時都是以任意(random order) 順序進行兩次，兩次之間間隔3週，進行第二次判讀時第一次的結果並不會顯示出來，採用visual assessment，

- (4) 評估 primary tumor 與有無 cervical 及 distant metastases，對 abnormally increased ¹⁸FDG uptake 使用標準評分量表 (5-point scale) – definitely benign, probably benign, equivocal, probably malignant, 與 definitely malignant.
- (5) 為統計分析，將 definitely benign 與 probably benign 視為 negative for malignancy 而其餘視為 positive for malignancy

4. Statistical analysis

(1) Inter- and intraobserver agreement

依 primary tumor, cervical metastases per neck side 與 distant malignancy 三項判讀結果分析這4位自身與彼此間判讀結果的一致性。以 absolute agreement 與 Cohen's kappa 來進行統計分析

Absolute agreement – the ratio of the finding in which agreement exists with the total findings

Cohen's kappa – the ratio between chance-corrected observed agreement and chance-corrected perfect agreement

- < 0.21 → poor
- 0.21 ~0.4 → fair
- 0.41~0.6 → moderate
- 0.61~0.8 → good
- > 0.8 → almost perfect agreement

以第一次判讀的結果來比較 NPM I 與 NPM II, R I 與 R II interobserver agreement, 以第一次和第二次判讀結果來比較四位 observer 的 intraobserver agreement, 為了解經驗是否會影響此 agreement, 以 95% confidence interval analysis 來分 NMP 與 R 的結果是否有顯著差異。

(2) Influence of tumor localization and tumor size

分析4位 observer 對原發腫瘤位置、大小與頸部轉移的評估，藉此了解 tumor localization 與 tumor size 對 interobserver agreement 的影響

(3) Sensitivity 與 specificity

以4位 observer 第一次判讀結果比對 histological findings, 或 cytological findings (若沒有前一項), 或 follow-up 結果 (若前兩項皆無) 來計算 sensitivity 與 specificity, 並比較 NMP 與 R 的結果以了解經驗是否會影響 sensitivity 與 specificity

Sensitivity = true positive / (true positive + false negative)

Specificity = true negative / (true negative + false positive)

Results

1. Inter- and intraobserver agreement (table 2)

Variable	Interobserver Agreement				Intraobserver Agreement							
	NMPI and NMPII		RI and RII		NMPI		NMPII		RI		RII	
	P ₀	κ	P ₀	κ	P ₀	κ	P ₀	κ	P ₀	κ	P ₀	κ
Primary tumor	0.91	0.58	0.76	0.29	0.90	0.54	0.94	0.58	0.91	0.19	0.85	0.64
Cervical metastases	0.94	0.83*	0.86	0.54*	0.94	0.83	0.94	0.86	0.93	0.81	0.93	0.71
Distant metastases/second primary tumor	0.85	0.53	0.78	0.26	0.95†	0.84	0.88	0.66	0.79†	0.52	0.94	0.42

Abbreviations: NMPI, nuclear medicine physician I; NMPII, nuclear medicine physician II; RI, resident I; RII, resident II; P₀, absolute agreement; κ, Cohen's kappa.

*Significant difference between κ values of NMPs and residents.

†Significant difference between P₀ of NMPI and RI.

- (1) The interobserver agreement between NMPs was greater than the interobserver

- agreement between of Rs, 但只有cervical metastases達到顯著差異
- (2) The intraobserver agreement of NMPs was greater than Rs, 但只有一個數值達到顯著差異
- (3) 兩個PET cameras之間沒有差異

2. Influence of tumor localization and tumor size (table 3 and table 4)

(1) Tumor localization

當更精確的描述解剖位置被要求時，不論是primary tumor (oral cavity or oropharynx) 或cervical metastases (level I-V)，其interobserver agreement都下降(只有level I cervical metastases absolute agreement 例外)。Level 5無kappa值因為只有一個observer發現這個level的metastases。

(2) Tumor size

其中2個病例在檢查前其tumor就已經completely removed，其餘78個scan中，有7個病例NMPs對其腫瘤的存在沒有共識，其中6個為stage T1，tumor 最大直徑為20 mm，侵犯深度為5 mm，剩下1個為stage T2，最大直徑為31 mm，侵犯深度為4 mm。Cervical metastases的size對interobserver agreement並沒有影響，在10個不同意見的neck sides中只有一個neck side出現metastases，這個lymph node 為25 mm。Sensitivity會隨tumor size增加而增加。

Table 3. INTEROBSERVER AGREEMENT BETWEEN NUCLEAR MEDICINE PHYSICIANS FOR LOCALIZATION OF PRIMARY TUMOR AND CERVICAL METASTASES

Variable	P ₀	κ
Primary tumor	0.91*	0.58*
Oral cavity	0.76	0.44
Oropharynx	0.75	0.21
Cervical metastases	0.94*	0.83*
Level I	0.98	0.76
Level II	0.89	0.51
Level III	0.86	-0.06
Level IV	0.95	0.53
Level V	0.94	—

Abbreviations as in Table 2.

*For easy comparison, p₀ and κ values from Table 2 included.

Table 4. ABSOLUTE INTEROBSERVER AGREEMENT AND SENSITIVITY OF NUCLEAR MEDICINE PHYSICIANS STRATIFIED BY TUMOR SIZE

Variable	T1		T2		T3-T4	
Primary tumor stage	T1		T2		T3-T4	
Ag	88%	88%	88%	88%	88%	88%
Se	91%	91%	91%	91%	91%	91%
Cerv	Cerv		Cerv		Cerv	
Ag	98%	98%	98%	98%	98%	98%
Se	95%	95%	95%	95%	95%	95%
Abn	Abn		Abn		Abn	
Ag	94%	94%	94%	94%	94%	94%
Se	94%	94%	94%	94%	94%	94%

3. SENSITIVITY AND SPECIFICITY OF ISO-BET INTEROBSERVATION FOR INTEROBSERVATION

- (1) 經驗最少的R II 三項的sensitivity都比較其它三人低
- (2) 因為正確地偵查到的malignancy少，false-positive results少，所以在cervical metastases與distant metastases/ second primary tumor 的specificity R II 比其它人高

Discussion

1. Inter- and intraobserver agreement

本研究顯示¹⁸F-FDG PET在檢查oral 與oropharyngeal SCC有高 inter- and intraobserver agreement in SCC。

2. NMPs與Rs的經驗

NMPs的 inter- and intraobserver agreement 普遍比Rs高，雖然Rs的表現也在fair到good之間，但經驗在intraobserver agreement 並沒有造成兩者間的差異，這表示observer的經驗對判讀相同影像所發揮的影響是有限的。同樣在sensitivity and specificity, 經驗所扮演的角色也是有限的，在NMP之間並沒有差異，儘管兩人之間有10年的資歷差別，而資深R的表現趨近於NMP，由於這個研究為cross-sectional所有沒辦法呈現¹⁸F-FDG PET scans真實的學習曲線，資淺R的sensitivity確實比其他三人低，所以本篇作者認為a short learning phase是存在的，在此之後就達可接受的水準。其它的技術 (US-guided fine needle aspiration cytology, MRI, and CT)則被認為更加的依賴observer的經驗。對observer與經驗依賴度較低可說是判讀¹⁸F-FDG PET影像一項優點。

3. Tumor localization

當對malignancy的位置要更精確的描述時，interobserver agreement就下降，只有neck level I顯示有高interobserver agreement，這可能是因為這個區域在影像上較易辨識的緣故，這種結果並不令人意外，因為¹⁸F-FDG PET影像缺乏解剖細節。這項結果支持combining PET與CT(PET/CT)的附加價值，PET/CT比單獨PET有更好的tumor localization又保有原PET的優點。

4. Tumor size

Tumor size 會影響 interobserver agreement 與 sensitivity of NMPs. The agreements increased with tumor size, with the exception of metastases smaller than 1 cm. These small cervical metastases showed high interobserver agreement despite the very low sensitivity. The high interobserver agreement resulted from the nondetection of the small metastases by both observers. Missing metastases 5 mm or smaller was not surprising against the background of the limited resolution of the PET camera.

5. Distant metastases or malignancy

¹⁸F-FDG PET for the initial staging of head and neck cancer is the possibility of evaluating the whole body for malignancy. All distant metastases/second primary tumors were detected by both NMPs, except for one small superficial esophagus carcinoma. Disagreement, mostly for suspected malignancy in the lung or mediastinum, was present in 12 scans, all without proven second primary tumors or distant metastases, highlighting the known false-positive risk of ¹⁸F-FDG PET.

6. Limitation of this study

(1) Most notably for our study, the drawback was the influence of the distribution of malignancy. The kappa values tend toward lower values when the distribution is asymmetric. In the present study, the presence of malignancy in the head and body was very asymmetrically distributed: 98% and 10%, respectively. Thus, despite the high absolute agreement for detecting primary tumor and distant metastases, comparable to the agreement for detecting

cervical metastases, the kappa values of the primary tumor and distant metastases were lower than those for cervical metastases.

- (2) The histologic findings of the surgical specimens were used to determine the tumor size. However, for some patients with malignancy, surgical specimens were not obtained. For these patients, the tumor size was determined by CT, MRI, or US performed at diagnosis of the malignancy. The measured diameter was used as the malignancy size. Thus, it is possible that the measurements for these malignancies were somewhat overestimated.

7. PET/CT與PET alone

It could be argued that an analysis of PET data is superfluous in the PET/CT era. However, PET/CT is a combination of 2 imaging techniques, each with its own characteristics. To understand the added value of the combination, the value of each of the components should be known. The results of our study have revealed that the interpretation of PET data is relatively observer experience independent; however, 18F-FDG PET is lacking for locating a tumor. As such, the present study provides a strong argument for the use of PET/CT in the evaluation of SCC of the head and neck.

Conclusion

- (1) ¹⁸F-FDG PET images of SCC of the oral cavity or oropharynx在偵測malignancy方面表現出良好的inter-與intraobserver agreement
- (2) Observer的經驗對observer agreement的影響有限
- (3) 即使是在困難的頭頸區域，所得到的影像仍可被可靠地的判讀
- (4) 若要更精確描述tumor anatomic localization，則observer agreement會下降
- (5) Observer agreement 與sensitivity隨tumor size 增加而增加，與經驗無關，這表示在偵測small cervical metastases ¹⁸F-FDG PET得能力有限。

題號	題目
1	下列何種檢查非利用放射線? (A) Whole body Bone scan (B) PET (C) MR (D) Scintigraphy
答案(C)	出處：
題號	題目
2	Oral SCC TNM 分期下列何者正確? (A) Tumor size > 6 cm為T4 (B) 同側多個lymph node轉移, 小於6 cm為N2b (C) 對側lymph node 轉移為N2a (D) Carcinoma in situ 為T0
答案(B)	出處：