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內文：

Abstract

Histological grading 對唾液腺上皮癌的預後是一項很重要的指標，然而因為腫瘤的多樣性與稀有性，對設計具預測性的grading scheme是一種挑戰。

1. Carcinoma ex pleomorphic adenoma
   隨著知識的演進，越來越明顯地，carcinoma ex pleomorphic adenoma並不 如傳統上所認為必然是high grade的腫瘤，這些腫瘤需要進一步根據腫瘤的type/grade以及範圍加以分類，因為intracapsular與minimally invasive carcinomas ex pleomorphic adenoma的行為表現較良好。
2. Adenoid cystic carcinoma
   Adenoid cystic carcinoma(ACC)與mucoepidermoid carcinoma(MEC)是常使用grading scheme的兩種的腫瘤，ACC是根據組織形態pattern作為grading的唯一依據，並以solid component為預後較差的預兆。偶爾ACC會轉化成pleomorphic high grade carcinoma，這類腫瘤有較高比例會產生淋巴結轉移，因此應該列入報告中以提醒臨床醫師。
3. Mucoepidermoid carcinoma
   根據一組條件，MEC被分為三個等級，這些特徵包含cystic component、border、mitoses、anaplasia與perineural invasion。所有的MEC的grading scheme都有點麻煩甚至不明確，但證據顯示使用一種scheme會比憑直覺更具再現性(reproducibility)。在不同的grading systems中，intermediate grade呈現最多差異性，因此在治療上也最矛盾，在AFIP system中，intermediate grade被併入high grade中，而在Brandwein system中，intermediate grade被併入low grade裡。

Introduction

唾液腺上皮癌佔所有的頭頸部惡性腫瘤的3~5%，WHO認可至少有24種不同種類，大部份種類的罕見性與長期結果的不可預測性對治療唾液腺上皮癌形成一種挑戰，如何利用臨床與病理特徵使這些腫瘤轉變成有意義的治療分類(Table 1)，對治療與預後是非常關鍵的。

Table 1 General categories of management of primary salivary gland carcinomas [3]

Surgery alone	Surgery and radiotherapy	Additional neck dissection	Systemic chemotherapy
Negative margins	Close (<2 mm) or positive margins	All cN+	Metastatic or unresectable disease
		cN0 but high grade histology	
Low grade histology	High grade histology	cN0 but high risk (angioinvasive) histologic subtype	
Low risk (non angioinvasive, non infiltrative) histologic subtype	High risk (highly infiltrative) histologic subtype	cN0 but high T stage (T3 or T4)	
Low T stage (T1 or T2)	High T stage (T3 or T4)		
	pN+		
	Perineural invasion[a]		

T = tumor stage in TNM classification, cN? = clinically node positive, cN0 = clinically node negative, pN? = pathologically node positive

[a] Somewhat controversial depending on tumor type

作者回顧文獻發現histological tumor grade的重要性在所有唾液腺上皮癌預後的

預測因子中名列前矛。High grade salivary gland carcinoma 的5年存活率約40% 而low grade與intermediate grade則為85-90%。相當數量的文獻顯示histological grade在multivariate analysis中是一個獨立的預測因子，但它也有與其它因子相關的傾向，例如腫瘤大小與nodal status。現行的grading system仍面臨許多不足與挑戰，無法一直對每一個case都能準確地預測其結果。

Discussion

General grading of salivary gland carcinomas

Grading system 的理想條件如下:

1. Accurately predicate outcome
2. Can be used to stratify patients into distinct management categories
3. Applicable to all sites in which a tumor can be seen
4. Simple criteria
5. Quick and time efficient
6. Reproducible with minimal inter and intraobserver variability

實際上，這樣理想的grade system在唾液腺上皮癌不可能達到，因為沒有足夠的病例數量供人設計出符合上數條件且在統計上有效的系統，各研究的Meta analysis也不具多大意義，因為唾液腺上皮癌的grade system並沒有標準化。大部份的grading system都是以直覺性細胞形態特徵(hyperchromatism、pleomorphism、mitoses)來分類，而且非常個別化。即始有grade system可供使用，也可能一種腫瘤有數種系統，各系統間無法精確的連結。

雖然有這些困難，根據現有資料與臨床的經驗，可將不同種類的腫瘤大致分為low risk與high risk，low risk腫瘤只需將primary tumor切除即可，high risk腫瘤除excision外還需要其它治療，histological grading進一步將同一種類不同grading的腫瘤在這個risk system中分開(Table 2)。

Table 2 Risk stratification of WHO [1] recognized salivary gland malignancies

Low risk	High Risk
Acinic cell carcinoma	Sebaceous carcinoma and lymphadenocarcinoma
Low grade mucoepidermoid carcinoma[a]	High grade mucoepidermoid carcinoma[a]
Epithelial-myoepithelial carcinoma	Adenoid cystic carcinoma[b]
Polymorphous low grade adenocarcinoma	Mucinous adenocarcinoma
Clear cell carcinoma	Squamous cell carcinoma
Basal cell adenocarcinoma	Small cell carcinoma
Low grade salivary duct carcinoma (low grade cribriform cystadenocarcinoma)	Large cell carcinoma
Myoepithelial carcinoma	Lymphoepithelial carcinoma
Oncocytic carcinoma	Metastasizing pleomorphic adenoma
Carcinoma ex pleomorphic adenoma (intracapsular/minimally invasive or with low grade histology)	Carcinoma ex pleomorphic adenoma (widely invasive or high grade histology)
Sialoblastoma	Carcinosarcoma
Adenocarcinoma NOS and Cystadenocarcinoma, low grade[a]	Adenocarcinoma and cystadenocarcinoma, NOS, high grade[a]

a Intermediate grade variants of these tumors are controversial in the assignment of risk. For mucoepidermoid carcinoma this may depend on grading scheme used. For adenocarcinoma NOS, there is little data, but what is present suggests that intermediate grade should be placed in the high risk group

b Adenoid cystic carcinomas are all considered high risk in terms of local recurrence, but only solid adenoid cystic carcinoma (i.e. high pattern grade) is considered high risk for nodal metastasis

並非所有唾液腺上皮癌都需要grading，因為許多腫瘤大部份的病例在組織與生物特性上都是high risk(例如conventional salivary duct carcinoma、squamous cell carcinoma、small cell neuroendocrine carcinoma) 或 low risk(例如epithelial-myoepithelial carcinoma、PLGA)。需要注意的是這些典型的low grade腫瘤會有high grade versions，而典型的high grade腫瘤也會有low grade versions，病理醫師與臨床醫師需要注意這類變異的出現，

1. 這類腫瘤典型的病例不一定需要grading descriptor
2. 不尋常的high 或low grade的變異需要在病理報告中被傳達

這種現象最好的例子是carcinoma ex pleomorphic adenoma。之前與現在的文獻中，carcinoma ex pleomorphic adenoma被自動視為high grade malignancy，大多數的病例中這個觀點是成立的，因為這些大多數病例的carcinoma component為high grade adenocarcinoma NOS與salivary duct carcinoma，然而約有15%為low grade且進展緩慢。最近有證據顯示"intracapsular"carcinoma ex pleomorphic adenoma與minimally invasive(<1.5mm of invasion) carcinoma ex pleomorphic adenoma是low grade，不應被視為等同典型的carcinoma ex pleomorphic adenoma

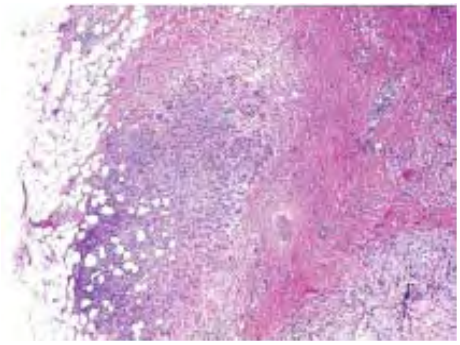

Fig. 1 Minimally invasive carcinoma ex pleomorphic adenoma. The pleomorphic adenoma component with sclerosis is seen on the right, and the minor low grade carcinoma component infiltrates the surrounding adipose tissue. This arcinoma was immunophenotypically a myoepithelial carcinoma (stains not shown).

Carcinoma ex pleomorphic adenoma不足以成為一個單獨的診斷，建議在報告中應列出:

1. Histological type/grade
2. Percentage of carcinoma
3. Extend of invasion of the carcinomatous component(intracapsular、minimally invasive、invasive)

普遍使用grading system的兩種腫瘤為ACC與mucoepidermoid carcinoma，adenocarcinoma NOS與cystadenocarcinoma也會被分級，雖然這兩種腫瘤並不常見所以不足以產生一個正式的分級系統。Acinic cell adenocarcinoma的分級有一些矛盾存在，這個腫瘤與其它low risk腫瘤相比，淋巴結轉移的機率較高。組織學研究顯示確實有能力根據cytomorphologic grading parameters將這些腫瘤分類，這暗示了對這些腫瘤而言，grading system確實有其必要性。

Adenoid cystic cacinoma

ACC特性

1. 是一種biphasic的唾液腺惡性腫瘤(由duct與basal/myoepithelial cells所組成)，
2. 分為三種組織形態tubular、cribriform與solid pattern，通常是monomorphic。
3. 行為上發展緩慢卻不間斷，5年存活率約75-80%，而15年存活率僅35%。局部侵襲性強，所以被歸為high risk，需要輔以radiotherapy。淋巴轉移低，約5%，許多機構因此不進行neck dissection，如果臨床上為node negative。

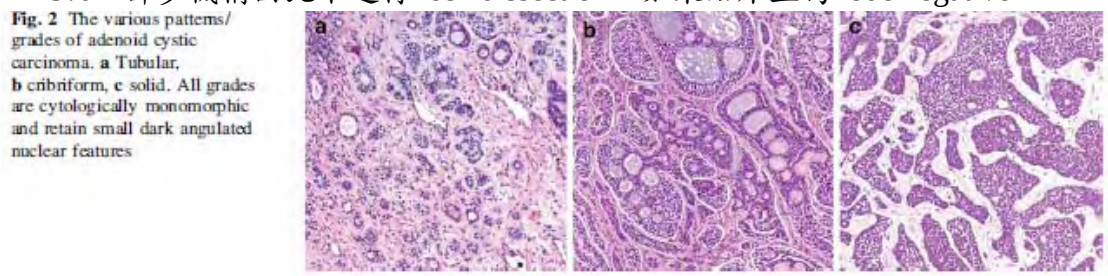

Fig. 2 The various patterns/grades of adenoid cystic carcinoma. **a** Tubular, **b** cribriform, **c** solid. All grades are cytologically monomorphic and retain small dark angulated nuclear features

數個研究指出ACC的grading對預後的預測確實有用，不像其它腫瘤的grading system，ACC只根據growth pattern來分類。早在1958年，Patey與Thackray

就發現solid pattern顯示較差的預後，在這之後，ACC的分級就演進為以growth pattern來分為三級
Grade 1: tubular
Grade 2: cribriform
Grade 3: solid
一般而言，若solid pattern佔整個腫瘤的30%以上即歸類為grade 3，solid growth pattern的比例與預後呈現線性相關(linear relationship)，設定比率門檻作為分級依據(例如30%)可能是隨意的，WHO目前只依形態名稱分類，並沒有給予數字分級

ACC的矛盾之一為ACC的grading對預後預測的能力與tumor stage無關，Spiro et al的研究認為這個觀點並不正確，然而更近的研究(da Cruz Perez)發現，在multivariate analysis中，grade是一項獨立的預後預測因子。

Table 3 Comparison of common pattern grading schemes in adenoid cystic carcinoma

Grade	Perzin et al. [10], Szanto et al. [11]	Grade	Spiro et al. [8]
1	Predominantly tubular, no solid component	1	Mostly tubular or cribriform (no stipulations on minor solid components)
2	Predominantly cribriform, solid component <30% acceptable		
3	Solid component >30%	2	50% solid
		3	Mostly solid

兩個grade system的主要差別在solid pattern的比例設定，兩者的轉換有困難。有研究顯示Spiro system在不同觀察者(interobserver)得到的結果差異較小(reproducibility較好)。

Grade對預測預後有用，但對Patient management是否有用則不明確，不論任何grade，所有的ACC都以手術加上RT來治療，因為ACC局部侵犯性屬於high risk，而是否要進行neck dissection也不是根據grade來判定，雖然有一些證據表示solide/grade 3 ACC有較高的淋巴轉移機率。

ACC high grade transformation

1. 定義:A pleomorphic mitotically active high grade carcinoma arising in an otherwise conventional adenoid cystic carcinoma of any pattern/grade
2. 通常轉化形成的component 為單純的ductal phenotype，有solid或cribriform的外觀。傳統的ACC的特徵為small、hyperchromatic、monomorphic nuclei與稀少的細胞質，轉化的component的nuclear size與chromatin 有明顯的多樣性，普遍的特色包括fibrocellular desmoplasia、abundant mitoses 、necrosis、and microcalcifications，high grade transformation單獨的特徵有micropapillary與squamoid growth。但是在傳統的solid ACC與high grade transformation之間仍有morphologic overlap，這之間的過渡(transition)常是漸進的(gradual)。
3. 基本上，傳統的solid ACC與high grade transformation所共有的aggressive nuclear、stromal、architectural與immunohistochemical特徵，在high grade transformation variant中都比較嚴重。Table 4出兩者的差異。

這些轉化腫瘤的預後差，平均存活時間為12~36個月比solid/grade 3 ACC更差，淋巴轉移的機率超過50%，因此neck dissection對治療這個variant可能是必要的

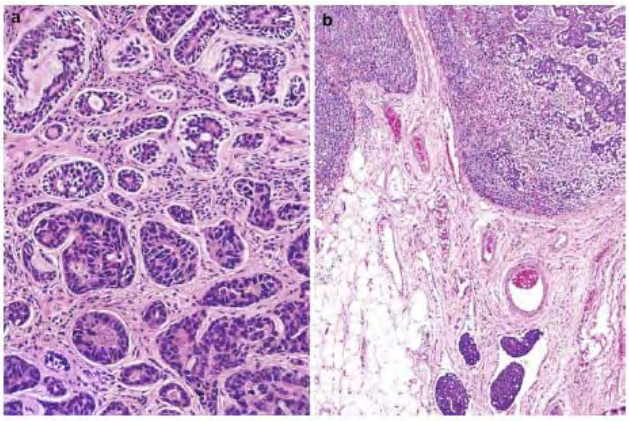

Fig. 3 Adenoid cystic carcinoma with high grade transformation. **a** A conventional cribriform component with monomorphic nuclei on top transitions to a pleomorphic highly atypical adenocarcinoma on bottom. **b** The transformed component metastasized to a cervical lymph node

Table 4 Comparison of solid conventional adenoid cystic carcinoma and high grade transformation[a]

Features	Solid conventional adenoid cystic carcinoma	Adenoid cystic carcinoma with high grade transformation
Chromatin	Dark, homogeneous	Vesicular or heterogeneously dispersed
Nuclear membranes	Delicate	Thickened or irregular
Nucleoli	Present but indistinct	Prominent central
Nuclear size	**At most twice the size of grade I-II ACC nuclei. Uniform size distribution**	**At least 2–3 times the size of grade I-II ACC nuclei (typically more). At least 2 fold nuclear variation**
Cytoplasm	Scant to nearly absent	Scant to moderate
Growth	**Solid nests, rarely spanning more than a 40× high power field**	**Solid confluent nests to sheets often filling a 40× high power field**
Stroma	**Paucicellular myxoid or hyaline**	**Fibrocellular desmoplastic**
Comedonecrosis	Focally present, usually punctuate	Often present, punctuate to large zones
Microcalcifications	Rarely present	Often present
Unique features		**Micropapillae, squamoid areas**
Mitoses	Generally <10/hpf	Usually >10/hpf
Abluminal cell layer presence by immunohistochemistry	**Present and complete**	**Incomplete and at least focally absent**
Ki-67	<50%	>50%
p53 overexpression (strong reactivity in >50% of cells)	**Rare**	**Common**

Bold = Major Features

[a] Adapted from Seethala et al. [15]

Summary recommendations for grading of ACC

1. Report predominant growth pattern(tubular、cribriform、solid)
2. If any solid component is present give rough estimate of percentage
   - ■ It may be reasonable to indicate in a comment that a solid component >30% correlates with aggressive behavior
3. If evidence of high grade transformation is present, this should be reported and quantitated
   - ■ A comment regarding the unusually high propensity for lymph node involvement is recommended

Mucoepidermoid carcinoma

MEC的簡介

1. 最常見的唾液腺上皮癌
2. 組織學特徵: mucus cells、intermediate cells 與squamoid (epidermoid) cells的混合，也會有clear cell、oncocytic 或columnar cells出現
3. MEC的grading對預後與治療很重要，

   預後: 5年存活率 low grade - 92~100%
   intermediate grade - 62~92%
   high grade - 0~43%

   治療: low grade – only surgical treatment
   intermediate grade – controversy
   high grade – surgical treatment + adjuvant RT and neck dissection

Grading system

1945年Stewart et al.記錄兩種MEC的種類—"benign"與"malignant"相當於今日的low與high grade，發展至今日MEC被分為三級— low、intermediate、high grade，最受歡迎的grading system有三種

— The AFIP grading system
The modified Healey system
The Brandwein system

所有的systems都運用類似的參數，包括cytomorphologic與architectural，也包含了perineural 與angiolymphatic invasion。AFIP與Brandwein系統都以分數為基礎，給各種不同的histological parameters指定分數，分數高歸入high grade。Modified Healey system被認為是最適合的分類系統—特定的histologic parameters代表一種特定的grade，而一個腫瘤是根據它的主要形態特色來分級。

Table 5 Comparison of Grading Systems for Mucoepidermoid Carcinoma

Modified Healey [22] Qualitative	AFIP [21] Point based	Brandwein [23] Point based
Low grade	Intracystic component <20% = 2pts	Intracystic component <25% = 2pts
Macrocysts, microcysts, transition with excretory ducts	Neural invasion present = 2pts	Tumor invades in small nests and islands = 2pts
Differentiated Mucin producing Epidermoid Cells, often in a 1:1 ration; minimal to moderate intermediate cell population	Necrosis present = 3pts	Pronounced nuclear atypia = 2pts
Daughter cyst proliferation from large cysts		
Minimal to absent pleomorphism, rare mitoses		
Broad-front, often circumscribed invasion		
Pools of extravasated mucin with stromal reaction		
Intermediate grade	Mitosis (4 or more per 10 HPF) = 3pts	Lymphatic and/or vascular invasion = 3pts
No macrocysts, few microcysts, solid nests of cells	Anaplasia = 4pts	Bony invasion = 3pts
Large duct not conspicuous		>4mitoses per 10 HPF = 3pts
Slight to moderate pleomorphism, few mitoses, prominent nuclei and nucleoli		
Invasive quality, usually well difined and uncircumscribed		
Chronic inflammation at periphery, fibrosis separates nests of cells and groups of nests		
High grade		Perineural spread = 3pts
No macrocysts, predominantly solid but may be nearly all glandular		Necrosis = 3pts
Cell constituents range from poorly differentiated to recognizable epidermoid and intermediate to ductal type adenocarcinoma		
Considerable pleomorphism, easily found mitoses		
Unquestionable soft tissue, perineural and intravascular invasion		
Chronic inflammation less prominent, desmoplasia of stroma may outline invasive clusters	*Low grade = 0–4 pts* *Intermediate grade = 5–6 pts* *High grade = 7–14 pts*	*Low grade = 0 pts* *Intermediate grade = 2–3 pts* *High grade = 4 or more pts*

MEC的grading system並非沒有缺點，最明顯的缺點是應用困難，特別是分數基礎的系統。用這些系統來進行分級是有點麻煩且耗費時間的，尤其是有些條件定義並不清楚，許多病理學家傾向不使用這類正式的系統因為耗時且缺乏userfriendliness，然而證據顯示使用非正式或個人化grading system，再現性(reproducibility)比使用標準grading system差。

所有的系統對預測預後都是有用的，甚至獨立於 tumor stage之外，然而這些系統與結果的連結方式不同。AFIP系統常會將腫瘤降級(down grade)，而Brandwein系統則會將腫瘤升級(up grade)，這些差別對預後預測影響小，對治療卻有很重要的指示。臨床對low grade MEC的期望為low risk，只會進行手術治療，而且lymph node metastasis機率小可忽略，AFIP系統會將侵犯性較強的腫瘤歸入low grade因而增加了low risk tumor治療失敗率。相反地，aggressive MEC需要輔助治療與neck dissection，Brandwein 系統會將某些進展緩慢的腫瘤歸入high risk，使病人接受不必要的治療。

Grading system的差異因為intermediate grade而加大，因為它無法對應出一

個明確的治療方式。Aro et al.使用AFIP system進行分析結果顯示intermediate grade MEC cluster with high grade MEC，應採用類似的治療方法，而Nance et al.使用Brandwein system 得到相反結果，他們認為intermediate grade cluster with low grade MEC，Healey system雖然沒有上述限制，文字上使用intermediate表示其行為介於low與high之間，在治療上會比使用其它系統更不明確。

MEC的其它類型如clear、oncocytic與sclerosing variants無法適用於傳統的grading system，有限的證據顯示以傳統grading system對oncocytic variant進行分級應屬於high grade，其臨床表現可能是進展緩慢的，目前仍無足夠的證據對這些variants設計或建議適合的grading scheme。

目前對MEC的grading建議如下:

1. Utilize a standard scheme，rather than an intuitive approach
2. Regarding which system to use, understanding of the clinical expectations is necessary. 在美國，low grade tumor臨床上表現出高侵襲性比high grade tumor臨床上表現進展緩慢更令人無法接受，因此the Healey system與Brandwein system較受歡迎。
3. Variants should still be graded in a similar fashion although limited evidence suggests that some variants may behave more indolently even if technically high grade.

Conclusion

1. Salivary gland carcinoma的grading system雖然有缺點但確實具有預測價值。
2. Carcinoma ex pleomorphic adenoma不該再被視為一個診斷，而要視為一個類別，carcinoma的部份應該被分類、分級與量化以得到預測預後與治療結果的資料。
3. ACC以growth pattern來分級，solid growth pattern為預後差的預兆。罕見地，ACC會經歷high grade transformation，這類種瘤的淋巴轉移機率較傳統的ACC高。
4. MEC標準化的grading system再現性比較高，但較麻煩且耗時。Intermediate grade的結果非常依賴所使用的grading system，因此其預後與治療也最具爭議。AFIP系統會將tumor 降級造成intermediate grade表現出更強侵襲性，而Brandwein system會將tumor升級造成intermediate grade表現出進展緩慢的行為模式。

題號	題目
1	下列那一種唾液腺腫瘤組織病理特徵不是雙相性(biphasic)? (A) Pleomorphic adenoma (B) Adenoid cystic carcinoma (C) Canalicular adenoma (D) Mucoepidermoid carcinoma
答案(C)	出處：Oral and maxillofacial Pathology, Neville, 3rd ed., P484
題號	題目
2	下列何者不屬於malignant mixed tumor 的分類? (A) Carcinoma ex pleomorphic adenoma (B) Polymorphous low-grade adenocarcinoma (C) Carcinosarcoma (D) Metastasizing pleomorphic adenoma
答案(B)	出處：Oral and maxillofacial Pathology, Neville, 3rd ed., P484