Am J Surg Pathol Volume 42, Number 7, July2018

NUT Carcinoma of the Salivary Glands

Clinicopathologic and Molecular Analysis of 3 Cases and a Survey of NUT Expression in Salivary Gland Carcinomas

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背景：

- NUT癌是一种罕见的具有高度侵袭性的低分化癌，常与NUT基因染色体重排相关。
- ICD-O代码：8023/3。
- 早期关于NUT癌的文献报道患病者均为儿童及青年，最新统计显示从儿童到老年都可发生。

背景

- 中线癌的病因尚未明确，已有的研究显示它与EB病毒及人乳头状瘤病毒(HPV)、吸烟及环境因素无关。
- 最常发生的部位：头颈部、纵膈及肺。
- 临床特征：快速增长的肿块引起的非特异性症状。
- NUT预后差，平均总生存率为9.8个月，一些证据表明NUT变异型癌患者预后可能比BRD-NUT癌患者好。

材料和方法

- 作者通过对英文文献的全面回顾，共发现7例来源于涎腺的NUT癌病例报告。
- 作者在此描述3例来自腮腺的新NUT癌病例，并回顾先前报告的病例。
- 通过临床病史、组织学形态特征、免疫组化染色及分子检测来展开研究。

NUT免疫组化判读标准

对NUT免疫组化的判读是基于已发表的数据：

超过50%的肿瘤细胞核有明显的颗粒状（点状或尘埃状）表达视为阳性表现（正常睾丸组织可作为阳性对照）。

临床病史：

case1 ：39岁女性，表现为右侧腮腺快速肿大，在当地被诊断为可能是高级别黏液表皮样癌，行根治性腮腺切除术和右Ⅱ、Ⅲ区淋巴结清扫，并接受放化疗。在术后3个月，出现多发骨（骶骨，第三腰椎，左侧股骨颈和肋骨）、淋巴结和肺部转移。她继续接受姑息治疗，对腰骶骨放疗。为寻求进一步治疗在本中心会诊，病理诊断显示为NUT癌，随后病人接受了姑息性放疗，3个月后建议行临床试验性的靶向治疗，4个月后，死于本病。

case2：35岁，男性，接受了腮腺全切除术及颈部淋巴结清扫，（在国外）诊断为腮腺的未分化大细胞癌（pT3pN2b），术后（3个月后）显示多发性骨转移。从骨盆骨中取活检（无法取回最初的标本以供审查），并开始姑息化疗。

case3：55岁女性，右腮腺迅速增大（最大直径9cm）。她在另一个医院进行了浅表腮腺切除术。三个月后复发并接受全腮腺切除术、面神经切除和颈部淋巴结清扫（pT3pN1），行辅助放化疗，在初步诊断6个月后，出现肺、肝和骨转移，在接受了初次手术后7个月，死于病情进展。

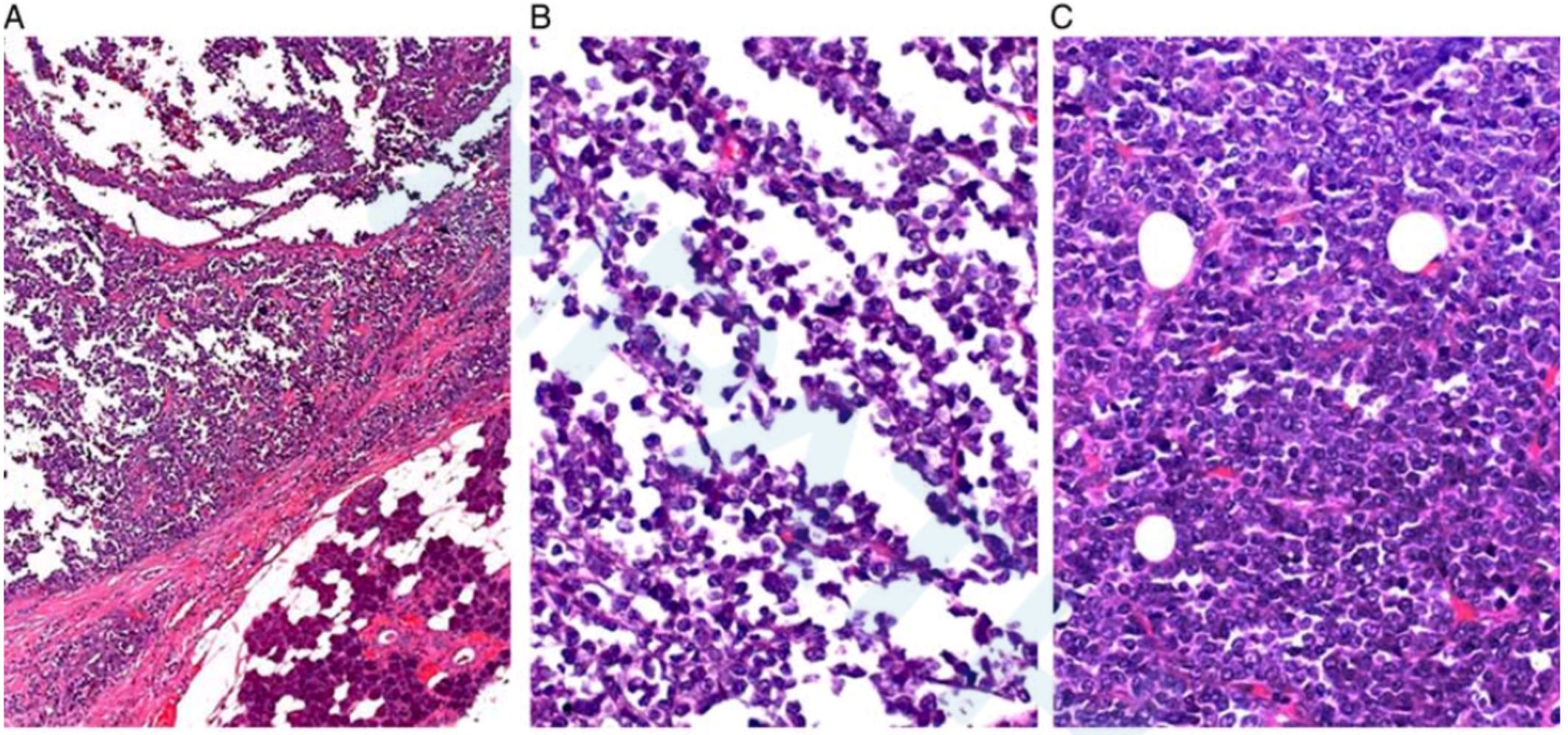
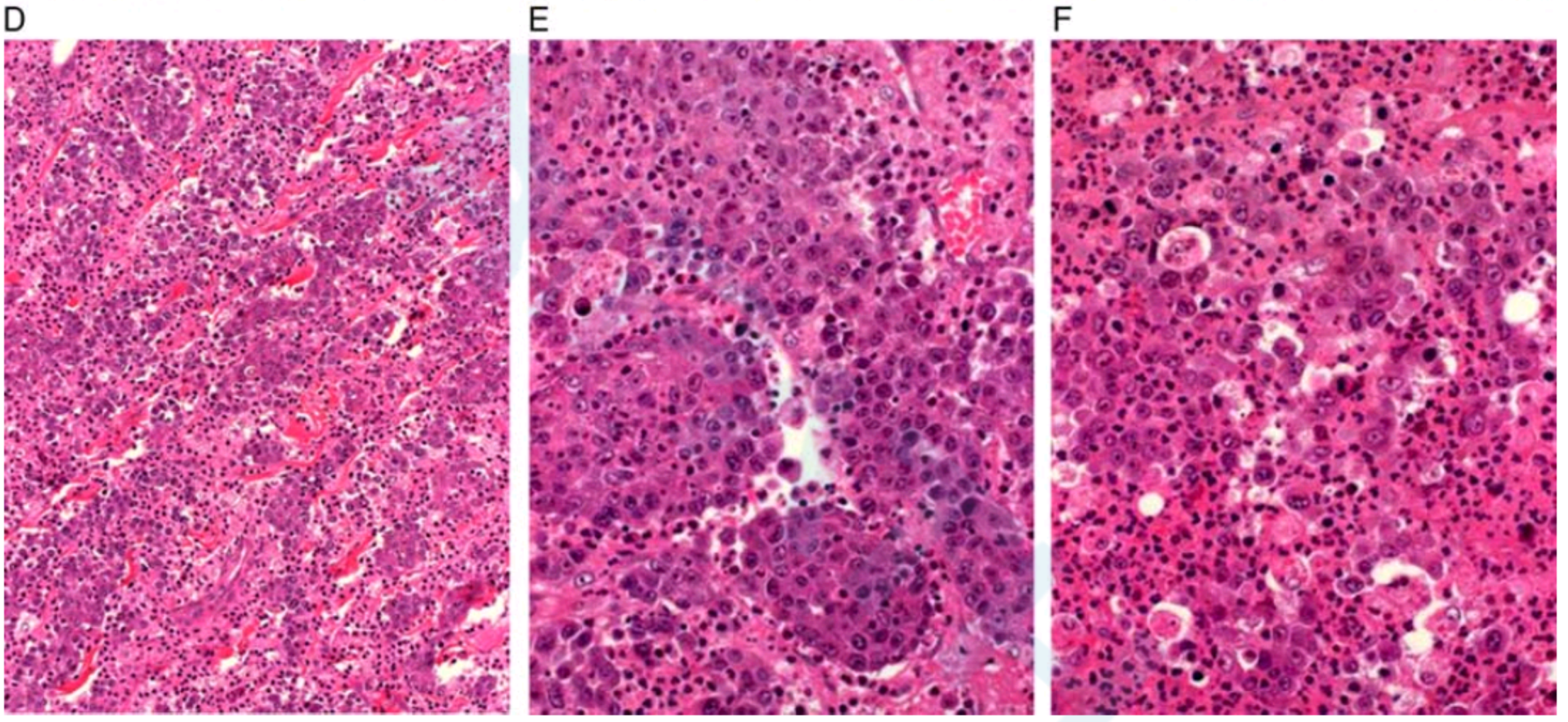


FIGURE 1. Salivary NCs were centered within salivary parenchyma (A) and displayed poorly cohesive sheets of small-sized to medium-sized cells arranged into pseudoalveolar (B), solid (C), corded (D), or nested (E) pattern. The nucleoli ranged from inconspicuous (C) to prominent (F), note extensive granulocytosis in F (A, B, C from case 3; D, E, F from case 1).



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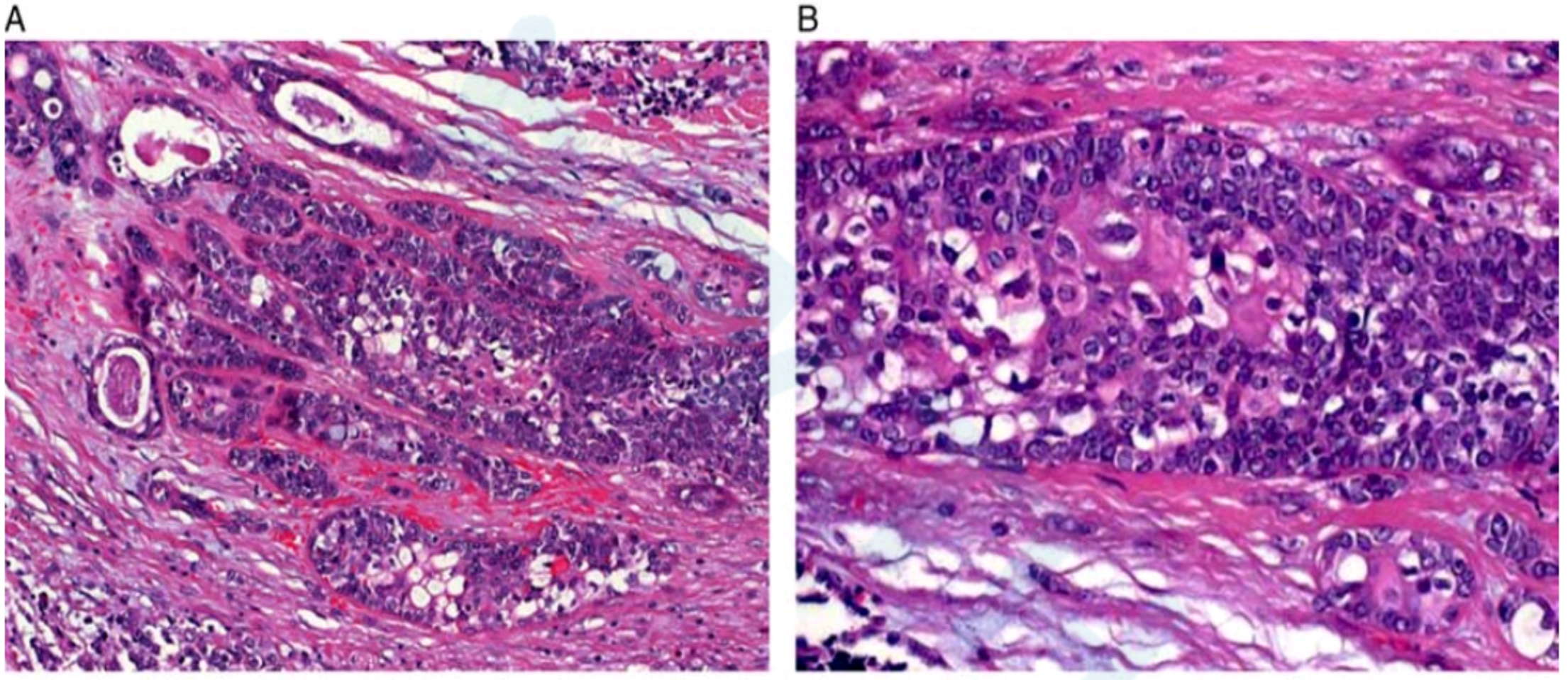
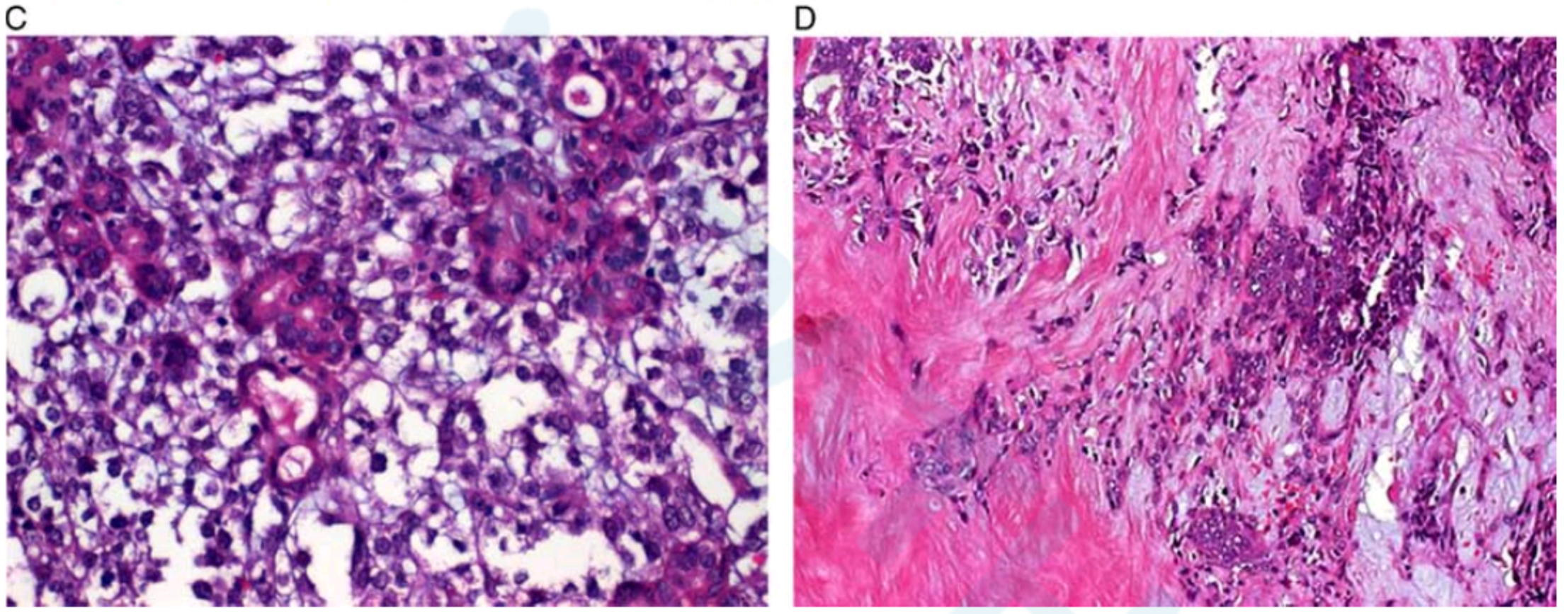


FIGURE 2. Foci of abrupt (clear cell) keratinization were seen in all 3 cases. Potentially misleading features included florid ductular proliferations (A, C) with entrapped of rare goblet cells (A, midlower field) and myxohyaline stromal changes reminiscent of pleomorphic adenoma (D). A to D from case 3.



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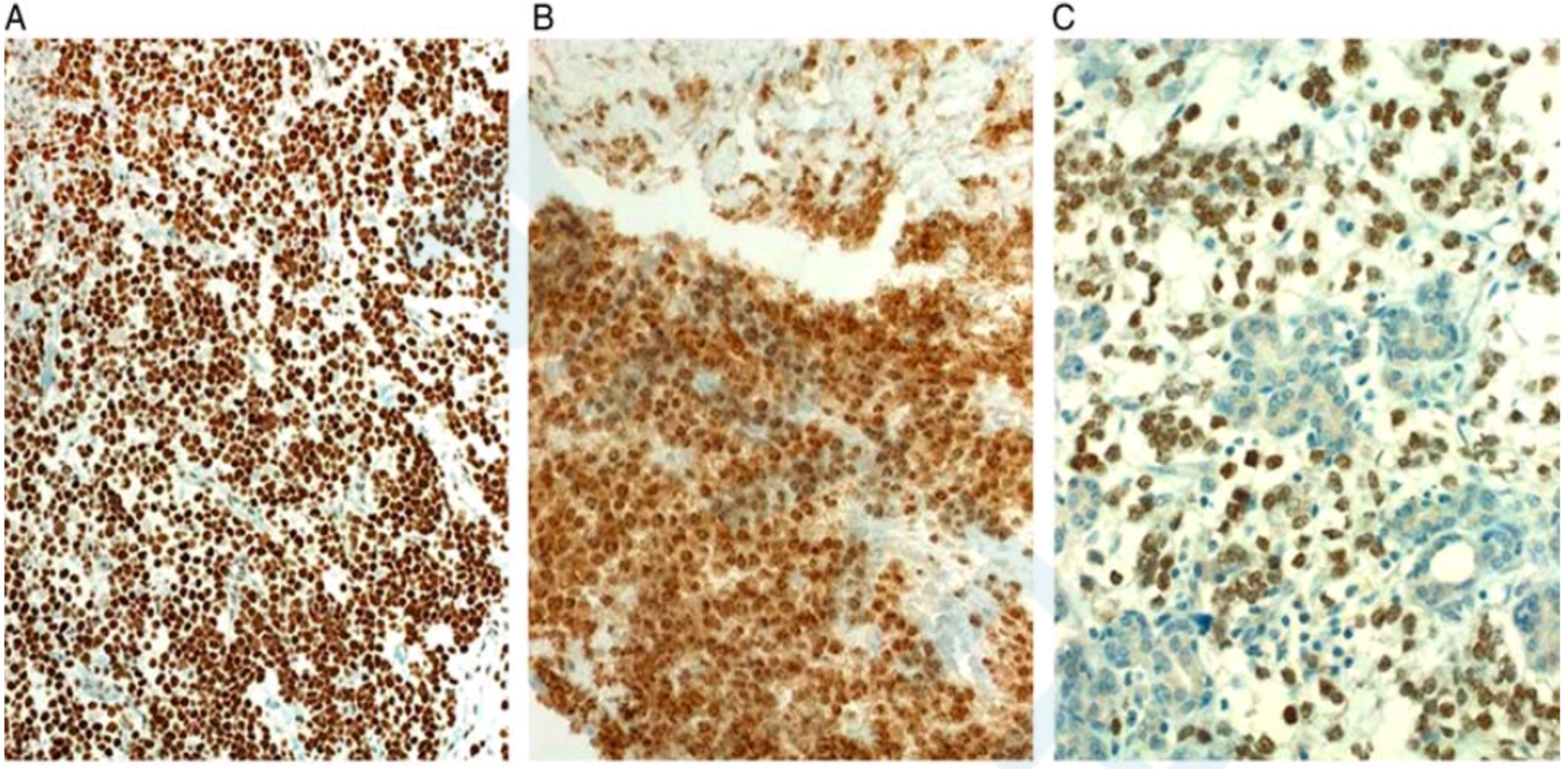

FIGURE 3. IHC showed consistent expression of p63 (A, case 3) and NUT protein (B, case 2). The NUT immunostain highlighted the neoplastic cells amid native salivary tissue (C, case 3). FISH analysis using the *NUT* probe (D) and *BRD4* probe (E) showed break-apart signals indicating a *NUT/BRD4* translocation (image from case 1).

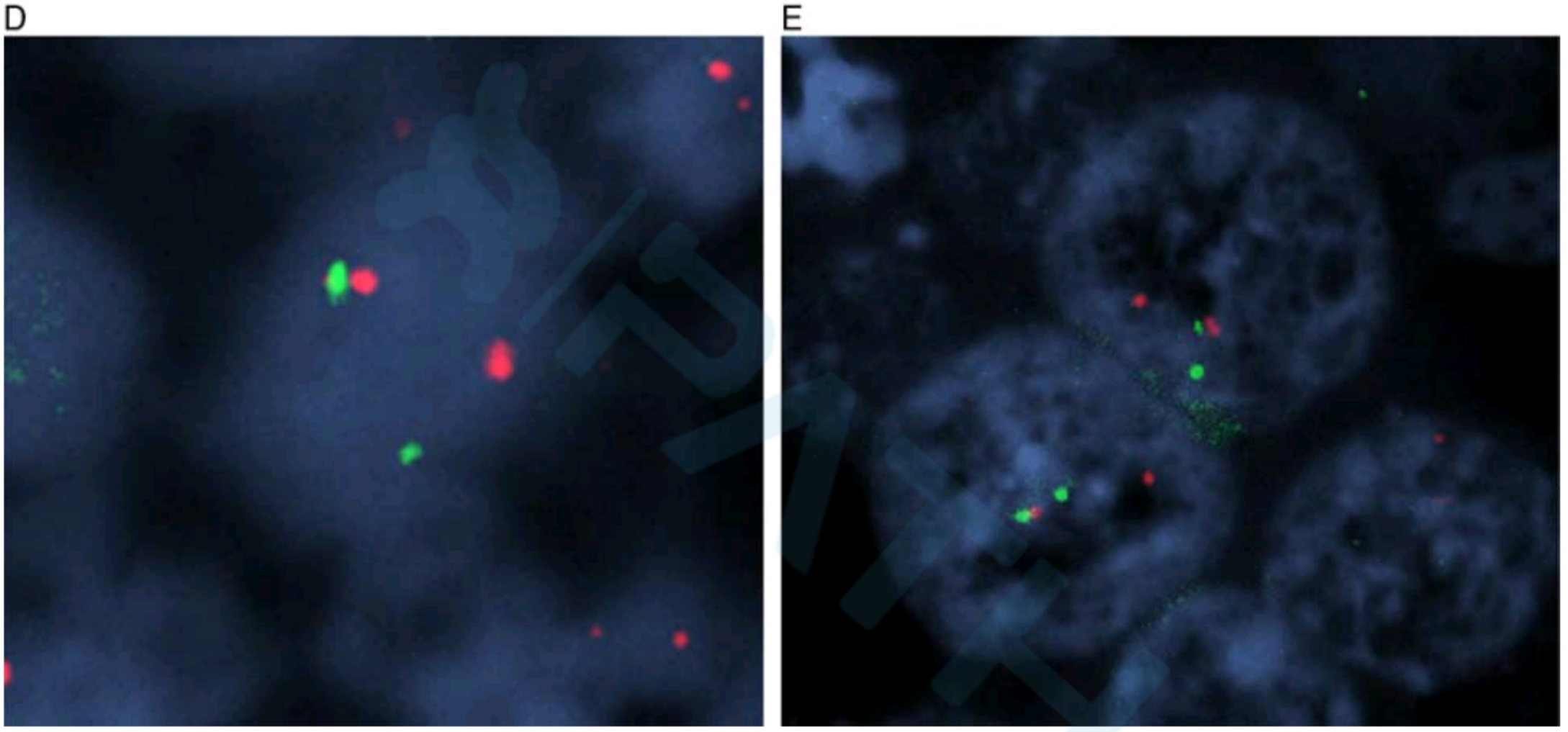

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TABLE 2. Clinicopathologic Features of Reported NUT Carcinomas of the Salivary Glands (n = 10)

References	Age (y)/ Gender	Site	Size (cm)	Symptoms/ Duration	Initial nodal /M Status	Treatment	MTS/Duration	Outcome
den Bakker et al[11]	15 M	Right parotid gland	1.5 (6 at surgery 8 mo later)	Mass	N+M0	Surgery+aRCT	No	ANED (7 mo)
Ziai et al[12]	15 M	Left submandibular gland	2.5	Mass and pain, 3 mo	N+M0	Surgery+aRT	No	ANED (14 mo)
Park et al[13]	12 M	Right parotid gland	2.4	Mass	N+M0	Surgery+aRCT	2 recurrences within 12 mo	DOD (24 mo)
Vulsteke et al[14]	32M	Left parotid gland	3.8	Rapidly growing mass	N0M0	Surgery+aRT, then CT for MTS	Disseminated bone MTS (1 mo)	DOD (4 mo)
Andreasen et al[15]	40 F	Right sublingual gland	4	Swelling, meal-related pain (1 mo)	N0M0	Surgery, palliative RCT	Wide-spread bone +cervical nodes (1 mo)	DOD (5.5 mo)
Klijanienko et al[16]	21 F	Left parotid gland	5	Mass	N+M0	Surgery, RT	Subcutaneous and liver (2 mo)	DOD (2 mo)
Seim et al[17]	26 M	Right sublingual gland	3	Pain, swelling, otalgia	N+M0	Surgery, palliative RCT	Extensive lung +bone MTS (2 wk)	DOD (1 mo)
Current series	39 F	Right parotid gland	3.6	Rapidly growing mass	pN2b M0	Surgery+aRCT BET inhibitor	Disseminated bone, nodes and lung (3 mo)	DOD (7 mo)
Current series	35 M	Parotid gland	NA	Mass	N+M0	Surgery, then palliative CT	Bone (postoperative)	AWD (3 mo)
Current series	55 F	Right parotid gland	9	Mass	N+M0	Surgery, then RCT	Live, lung and bone (6 mo)	DOD (7 mo)

a indicates adjuvant; ANED, alive with no evidence of disease; AWD, alive with disease; CT, chemotherapy; DOD, died of disease; F, female; NA, not available; M, male; mo, months; MTS, metastasis; RCT, radiochemotherapy; RT, radiotherapy.

表2总结

- 包括我们的3个案例，总共有10个涎腺发生的NC病例，男:女（M:F比率=1.5:1），年龄范围为12岁-55岁（中位，29 y），9名患者40岁以下，有3/10的病例是儿童。原发性肿瘤的起源是腮腺（n=7）、舌下腺（n=2）和下颌下腺（n=1）。6例肿瘤位于右边，3例位于左边，1例未知。（8/10）有局部淋巴结受累。所有患者均行手术治疗，并辅以放射治疗/化疗，大多数患者术后迅速发生多发转移。中位随访5个月（1-24月;），7/10患者死于疾病，中位数为5.5个月（1到24个月）。1个患者在姑息性治疗后多发转移带病生存，只有2名患者在随访7月和14个月时无病生存。

TABLE 3. Histopathologic, Immunohistochemical, and Molecular Findings in Salivary NUT Carcinomas (n = 10)

Cases	Histologic Pattern	Unusual Features	Original Diagnosis	Pan-CK	p63	CK7	SYN	Ch-A	CD56	INI1	NUT IHC	Genotype
1	Poorly cohesive basaloid cells, squamoid islands	Foci of cartilage	Poorly differentiated carcinoma (FNA)	+	+	NA	—	—	+	NA	+	*NUT-BRD4*
2	Poorly cohesive basaloid cells, squamoid islands	No	Not specified	+	+	NA	—	—	—	NA	NA	*NUT*-variant (other than *BRD4*/*BRD3*)
3	Basaloid with desmoplasia, no squamous islands	No	Poorly differentiated SCC	+	+	NA	—	—	—	NA	+	NA
4	Poorly cohesive large cells	No	Myoepithelial carcinoma with neuroendocrine features	+	+	NA	+F	NA	+	NA	+	*NUT-BRD4*
5	Poorly cohesive basaloid cells, squamoid islands	No	Poorly differentiated basaloid SCC	+	+	+	< 1%	—	—	NA	+	*NUT-BRD4*
6	Poorly cohesive basaloid cells	No	Poorly differentiated AdCC (FNA)	+	+	NA	—	—	—	NA	+	*NUT-BRD4*
7	Poorly cohesive large cells	No	Undifferentiated carcinoma	NA	NA	NA	NA	NA	NA	NA	NA	*NUT-BRD4*
8	Poorly cohesive large cells, squamoid islands	Prominent granulocytes	High-grade tumor, favor MEC	+	+	+	—	—	—	Intact	+	*NUT-BRD4*
9	Poorly cohesive basaloid cells, squamoid islands	No	Undifferentiated large cell carcinoma	+	+	NA	—	—	—	Intact	+	*NUT*, partner unknown (FISH failed)
10	Poorly cohesive basaloid cells, squamoid islands	No	Undifferentiated tumor	—	+	—	—	—	—	Intact	+	*NUT-BRD4*

AdCC indicates adenoid cystic carcinoma; Ch-A, chromogranin A; F, focal; FNA, fine needle aspiration; MEC, mucoepidermoid carcinoma; NA, not available; pan-CK, pancytokeratin; SYN, synaptophysin.

表3总结

- 所有的肿瘤呈现为快速增长的肿块。
- （6/9）原始诊断提示为未分化或低分化鳞癌/癌。其余3例分别诊断为肌上皮癌、腺样囊性癌、粘液表皮样癌。
- 免疫组化：广谱CK（8/9）阳性表达，p63（9/9）弥漫阳性，神经内分泌标记（2/9）灶性表达，其余7例均阴性。
- 所有NUT抗体染色的8个病例均为（核）阳性，9个病例通过基因检测显示NUT重排。融合的基因是BRD4（n=7），非BRD4/3（n=1），FISH失败（n=1）。

TABLE 1. Summary of the Salivary Gland Tumors Tested for NUT Immunoexpression in This Study

Tumor Type	+/Total No. Cases Tested
Adenoid cystic carcinoma (7 high grade)	0/50
Mucoepidermoid carcinoma	0/41
Salivary duct carcinoma*	0/62
High-grade adenocarcinoma/NOS*	0/35
Acinic cell carcinoma	0/32
Poorly differentiated SCC†	0/28
Myoepithelial carcinoma	0/17
Polymorphous carcinoma‡	0/13
Undifferentiated/rhabdoid carcinoma	0/05
Basal cell adenocarcinoma	0/07
Oncocytic carcinoma	0/04
Epithelial myoepithelial carcinoma	0/04
Primary malignant mixed tumor	0/04
Poorly differentiated neuroendocrine carcinoma	0/02
Cystadenocarcinoma	0/02
Total	0/306

*This group includes also some carcinoma ex pleomorphic adenoma cases.

†This group includes tumors without detectable other primary at time of clinical workup but many likely represent metastases from others, for example previous skin carcinomas, occult primaries, etc.

‡All cases belong to the old category of polymorphous low-grade adenocarcinoma.

讨论：

- NC大多发生于头颈部及胸腔等中线器官，但是即便在这些特征性的部位，这种罕见的疾病可能仍被忽视。唾液腺NC的报告中，绝大多数病例最初的诊断没有考虑到NC，诊断主要是在分子检测后确诊。这主要是由于该肿瘤表面上与传统的SCC或其他低分化的癌形态学相似，以及作为鳞状细胞标志的p63的一致性表达。因此将NUT IHC和/或分子检测纳入到唾液腺NC的鉴别诊断中是必要的。

讨论：

- 虽然NC被一些作者认为是SCC的变异体，但它与传统的SCC的关系尚不清楚。与传统SCC的高度异质性相比，在NC中缺乏其他分子改变，BRD-NUT融合是这种罕见疾病的唯一驱动因素。针对该基因融合，制定新的治疗策略可能是一个很有前景的选择。

讨论：

- 涎腺癌中NC的发生率尚不清楚。在鼻腔鼻窦，NC在低分化/未分化癌中占10%。在本研究筛选的306例涎腺癌中缺乏NUT免疫表达。因此建议在未分化癌的检查中和唾液腺的鳞状细胞癌中列入NUT IHC。
- 虽然基因检测不是诊断必须的，但建议确定融合基因，为了更好地了解和描述这种罕见的侵袭性疾病。有初步的证据表明BRD4-NUT和NUT变异型的预后差异，后者可能与更长的整体存活率有关。

讨论：

- 涎腺NUT癌应与多种原发和转移性肿瘤相鉴别，包括低分化鳞状细胞癌和多种涎腺癌的高级别或去分化癌，包括肌上皮癌、粘液表皮样癌、基底细胞腺癌、上皮性肌上皮癌等。基于这些鉴别诊断，并考虑到异质性和非特异性的NUT癌形态，建议将NUT癌纳入低分化和未分化涎腺恶性肿瘤的鉴别诊断中，并建议使用NUT 免疫组化。

总结

总之，这是关于涎腺NC的第一个小综述，强调将这种罕见疾病纳入低分化涎腺癌的鉴别诊断中的重要性，特别是在可推测涎腺起源或未知来源的低分化鳞状细胞癌和高级别肌上皮癌中。

Thank you !

謝謝！