

DOI: <https://doi.org/10.17816/DD561354>

# Ограничения использования гистологического исследования биоптатов как «золотого стандарта» диагностики на примере аденокарциномы пищевода: описание случая

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## АННОТАЦИЯ

Аденокарцинома пищевода — одно из самых распространённых злокачественных новообразований желудочно-кишечного тракта. Для выявления заболевания на ранних стадиях используют эндоскопические, морфологические, иммуногистохимические методы обследования, однако они требуют не только применения высокоспециализированного оборудования, но и зависят от профессионализма врача-эндоскописта и врача-патоморфолога.

В статье описано клиническое наблюдение пациента с прогрессирующей дисфагией, вызванной опухолью пищевода, распространяющейся на субкардиальный отдел желудка, которую не удавалось патоморфологически верифицировать в течение одного года. Данные эзофагогастродуоденоскопии, выполненной в медицинской организации по месту жительства, компьютерной томографии и рентгеноскопии пищевода с двойным контрастированием не оставляли сомнений в злокачественности новообразования, однако результаты многочисленных гистологических исследований свидетельствовали в пользу аденомы пилорических желёз, аденомы из париетальных, либо онкоцитарных клеток с фокусами дисплазии эпителия высокой степени. Эндоскопическое исследование с таргетированной биопсией в условиях специализированного учреждения позволило доказать злокачественность опухолевого процесса.

Результаты исследования демонстрируют важность клинической картины и инструментальных методов для постановки заключительного диагноза при противоречивых данных патоморфологических исследований и в очередной раз поднимают проблему ограничений гистологического исследования биоптатов как «золотого стандарта» диагностики злокачественных новообразований.

**Ключевые слова:** аденокарцинома пищевода; пищевод Барретта; кардиоэзофагеальный переход; эзофагогастродуоденоскопия; компьютерная томография; биопсия.

## Как цитировать:

Ахмедзянова Д.А., Юцевич О.К., Решетников Р.В., Тащян О.В., Пирогов С.С., Мазурова М.П., Волченко Н.Н., Камалов А.К., Шумская Ю.Ф., Мнацаканян М.Г. Ограничения использования гистологического исследования биоптатов как «золотого стандарта» диагностики на примере аденокарциномы пищевода: описание случая // Digital Diagnostics. 2023. Т. 4, № 4. С. 633–642. DOI: <https://doi.org/10.17816/DD561354>

DOI: <https://doi.org/10.17816/DD561354>

## Tissue sampling and histopathological limitations in esophageal cancer

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### ABSTRACT

Esophageal adenocarcinoma is a common gastrointestinal cancer. Esophagogastroduodenoscopy with biopsy and immunohistochemistry are used to detect the neoplasm at an early stage. Definitive diagnosis requires not only highly specialized equipment but also the skills of the endoscopist and pathologist. We report the case of a 35-year-old man with progressive dysphagia caused by gastroesophageal cancer. Numerous esophagogastroduodenoscopy studies, computed tomography, and barium X-ray swallow revealed an extensive esophageal lesion; however, pathomorphologic examinations did not confirm malignancy within a year. Histological studies showed pyloric gland adenoma and adenoma from parietal or oncocytic cells with high-grade dysplasia. Esophagogastroduodenoscopy with targeted biopsy at a specialized center confirmed the tumor malignancy. This clinical case demonstrates the importance of summing clinical symptoms and using additional instrumental methods to make a definitive diagnosis if biopsy results are ambiguous.

**Keywords:** esophageal adenocarcinoma; Barrett's esophagus; gastroesophageal junction; esophagogastroduodenoscopy; computed tomography; biopsy.

### To cite this article:

Akhmedzyanova DA, Yutsevich OK, Reshetnikov RV, Tashchyan OV, Pirogov SS, Mazurova MP, Volchenko NN, Kamalov AK, Shumskaya YuF, Mnatsakanyan MG. Tissue sampling and histopathological limitations in esophageal cancer. *Digital Diagnostics*. 2023;4(4):633–642. DOI: <https://doi.org/10.17816/DD561354>

Received: 18.07.2023

Accepted: 16.11.2023

Published online: 21.11. 2023

DOI: <https://doi.org/10.17816/DD561354>

## 将活检标本的组织学检查作为诊断“金标准”的局限性：一个例子

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### 简评

食管腺癌是胃肠道最常见的恶性肿瘤之一。为了在早期阶段发现这种疾病，医生采用内窥镜、形态学、免疫组化等检查方法。但是，这些方法不仅需要使用高度专业化的设备，还取决于内镜医师和病理形态学医师的专业水平。

本文描述了对一名进行性吞咽困难患者的临床观察。吞咽困难是由食道肿瘤引起的。肿瘤已扩散到胃的贲门下段。肿瘤在一年内无法进行病理形态学验证。在居住地医疗机构进行的食管胃十二指肠镜检查、电子计算机断层扫描和食管双对比透视检查的数据证实了肿瘤的恶性程度。然而，大量组织学检查的结果都支持幽门腺腺瘤、顶体腺瘤或带有高度上皮发育不良病灶的肿瘤细胞腺瘤。在专业机构的条件下，通过内窥镜检查 and 靶向活检，才有可能证实肿瘤的恶性程度。

研究结果表明，在病理形态学检查数据相互矛盾的情况下，临床表现和仪器方法对最终诊断的重要。这再次提出活检标本的组织学检查作为诊断恶性肿瘤“金标准”的局限性问题的。

**关键词：**食管腺癌；巴雷特食管；食管贲门交界处；食管胃十二指肠镜检查；电子计算机断层扫描；活检。

### 引用本文：

Akhmedzyanova DA, Yutsevich OK, Reshetnikov RV, Tashchyan OV, Pirogov SS, Mazurova MP, Volchenko NN, Kamalov AK, Shumskaya YuF, Mnatsakanyan MG. 将活检标本的组织学检查作为诊断“金标准”的局限性：一个例子. *Digital Diagnostics*. 2023;4(4):633–642.

DOI: <https://doi.org/10.17816/DD561354>

收到: 18.07.2023

接受: 16.11.2023

发布日期: 21.11.2023

## BACKGROUND

Esophageal cancer is the sixth most common cause of cancer deaths worldwide [1], and the incidence of esophageal adenocarcinoma is rapidly increasing in developed countries [2]. This type of esophageal cancer is extremely aggressive, with a 5-year survival rate <20% [3]. Risk factors for esophageal adenocarcinoma and gastroesophageal junction adenocarcinoma include mechanical, chemical, and thermal injury to the esophageal mucosa, male sex, obesity, and smoking [4], with the most significant risk factor being Barrett's esophagus caused by gastroesophageal reflux disease [5]. Prognosis is determined by both the tumor stage and its macroscopic morphology [6–8]. W.R.C. Knight et al. showed that ulcerating tumors were associated with a more favorable prognosis than exophytic or stenotic lesions [9].

Esophageal cancer is commonly diagnosed using radiological methods, specifically with double-contrast upper gastrointestinal radiography and computed tomography (CT) of the chest [10]. These methods allow evaluation of the lesion size, invasion depth, and tumor type. However, these findings must be verified by histopathology [3]. Esophagogastroduodenoscopy (EGD) and transnasal endoscopy are used to diagnose esophageal tumors. They allow visual examination of the organs for abnormalities and obtain biopsy specimens for morphological examination, which is considered the “gold standard” for tumor verification [11]. However, histological findings are dependent on various factors, including the qualifications and experience of the pathologist and endoscopist, quality of reagents used in specimen preservation, and quality of biopsy specimens obtained by endoscopic forceps biopsy. Therefore, biopsy results may not always match the clinical, endoscopic, or radiological findings [12]. Furthermore, diagnosing adenocarcinoma in the setting of Barrett's esophagus is challenging because of its typically endophytic growth pattern, which necessitates a specific biopsy technique [13].

Herein, a case of a patient with progressive dysphagia who was diagnosed with esophageal adenocarcinoma that had spread to the middle third of the esophagus and subcardial stomach is presented. Clinical and instrumental findings were unambiguously indicative of malignancy. However, repeated morphological examinations did not confirm the diagnosis. A definitive diagnosis was made after an EGD-guided targeted biopsy at a tertiary cancer center.

This case report was prepared in accordance with the CARE Case Report Guidelines [14].

## CASE REPORT

### Medical History

Patient N was a 35-year-old man.

In **March 2021**, he experienced a gradual loss of appetite. He did not seek medical advice because he believed that the symptoms were caused by work-related stress.

In **March 2022**, he presented to his primary care physician with symptoms of difficulty swallowing, nausea and vomiting, and a throat lump sensation. At presentation, he was 192 cm tall and weighed 185 kg (body mass index, 50.18 kg/m<sup>2</sup>, class III obesity).

EGD revealed a tumor mass with multiple ulcerations in the esophagus, beginning 30 cm from the incisors and nearly extending to the cardia. No reliable pathological evidence of tumor cells, dysplastic cells, or atypical cells was found in the biopsy specimens.

In **April 2022**, the patient visited a gastroenterologist and underwent EGD at follow-up. The examination revealed a significantly narrowed lumen in the middle and lower thirds of the esophagus, which was caused by a circumferential tumor with focal destruction. The tumor's proximal and distal edges were visualized at 25 and 45 cm from the incisors, respectively. Submucosal tumor infiltration was observed in the subcardial stomach. Repeated biopsy of the ulcerations demonstrated fragments of a villous tumor lined with columnar epithelium with low-grade dysplasia. Another EGD-guided biopsy revealed no signs of atypical cells.

**Preliminary diagnosis.** The observed pathological changes were consistent with the presentation of a pyloric gland adenoma with focal high-grade dysplasia arising from parietal or oncocytic cells that were highly suspicious of malignancy. Histological findings were inconsistent with clinical presentation and endoscopy. To address the inconsistencies between the endoscopic and histological findings, the tumor immunophenotype was examined by immunohistochemistry, which correlated with the pyloric tumor expressing gastric superficial-foveolar epithelial mucins and pyloric gland mucins. No *p53* mutation was detected in the tumor cells, which did not exhibit high proliferative activity. Because the malignant nature of the tumor could not be conclusively established through immunohistochemistry, the mass was considered a pyloric gland adenoma. A local gastroenterologist suggested a dynamic follow-up.

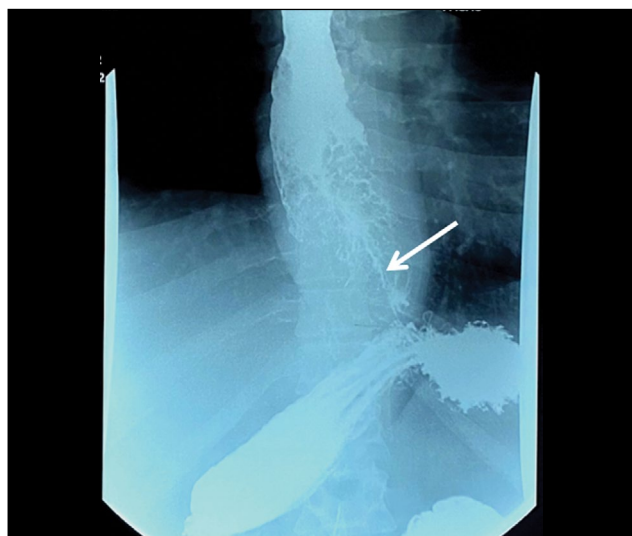
In **May 2022**, the patient presented to a gastroenterologist with worsening symptoms of impaired food passage from the mouth to the stomach and a weight loss of 15 kg over the past 3 months (body mass index, 46.12 kg/m<sup>2</sup>). The patient was admitted to the gastroenterology department for examination and diagnosis verification.

### Laboratory Data

Blood chemistry revealed hyperuricemia (uric acid, 634.8 mmol/L; normal range, 154–357 mmol/L) and high levels of nonspecific inflammatory markers:

- Erythrocyte sedimentation rate: elevation to 50 (normal range, 2–20) mm/h
- Fibrinogen: elevation to 4.81 (normal range, 1.8–4) g/L
- C-reactive protein: elevation to 11.4 (normal range, 0–5) mg/L.

Latent iron deficiency was also found:



**Fig. 1.** Upper GI X-ray. Circumferential narrowing of the esophagus; a thin passage of barium leakage (arrow).

- Hemoglobin: 147 (normal range, 132–180) g/L
- Color index: 0.9
- Iron: 5.9 (normal range, 10.7–32.2) mmol/L

**Imaging Studies**

Barium-contrast upper gastrointestinal X-ray findings were suggestive of an extended mass lesion in the middle and lower thirds of the esophagus with luminal stenosis (Fig. 1).

Chest CT showed a 186-mm esophageal tumor that had extended to the cardia. The esophageal walls had a polypoid

thickening of up to 41 mm, and a significant narrowing of the esophageal lumen to 2 mm was observed. Signs of regional lymph node involvement were also visible (Fig. 2).

Abdominal CT did not reveal any distant metastases. The results demonstrated a locally advanced malignant esophageal tumor involving the cardia.

The patient was referred to a tertiary cancer center. Endoscopy at the cancer center showed the proximal edge of esophageal tumor infiltration at a site 24 cm from the incisors. The tumor appeared as multiple whitish-red merging lesions that spread circumferentially to the subcardial stomach. Deep ulcers covered with fibrin and necrotic plaque were observed. A fistula opening was found in the tumor tissue at a site 36 cm from the incisors, with the creamy opalescent contents flowing into the lumen. The esophageal lumen was significantly narrowed by the exophytic component of the tumor (Fig. 3). The tumor tissue was dough-like in texture and bled easily upon contact. The circumferentially infiltrated cardioesophageal junction was visualized at a site 44 cm from the incisors. The tumor infiltrated along the posterior wall to the subcardia (Fig. 4).

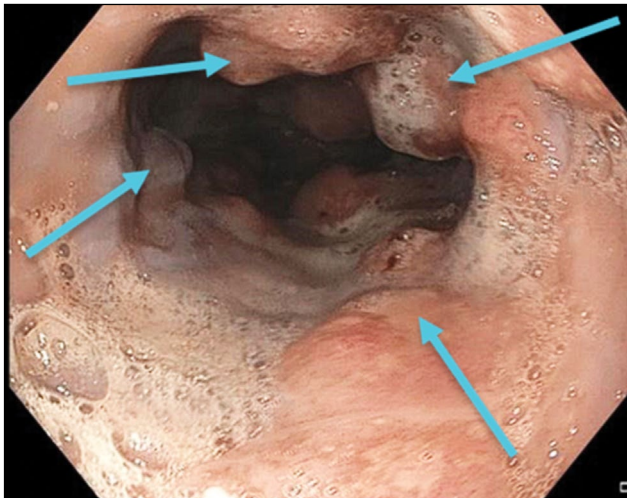
Targeted stepwise biopsy of the non-necrotic regions was performed. The pathology results indicated low-grade esophageal adenocarcinoma progressing from Barrett's esophagus.

**Diagnosis and Treatment**

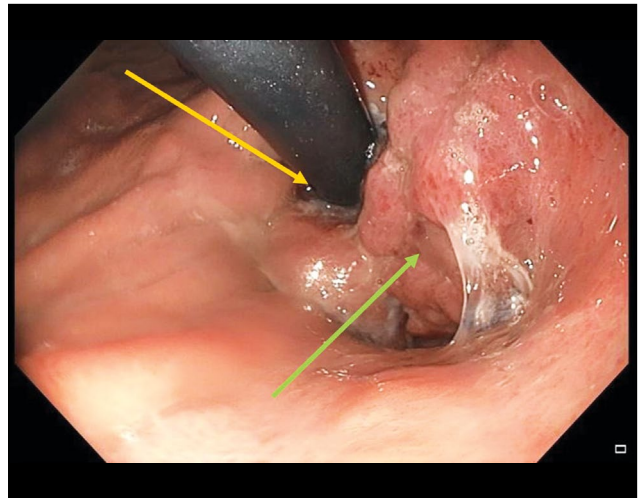
The patient was diagnosed with low-grade cT3N1M0 adenocarcinoma progressing from Barrett's esophagus. The



**Fig. 2.** Computed tomography of the chest. The white arrows show pathological changes: *a*, a 186-mm esophageal tumor extending to the cardia; *b*, massive invasion of the tumor tissue with narrowed lumen in the middle third of the esophagus; *c*, tumor involvement of the regional para-aortic lymph node; *d*, luminal narrowing to 2 mm in the lower third.



**Fig. 3.** Endoscopic image. Stenosing adenocarcinoma progressing from Barrett's esophagus. The circumferential tumor is indicated by the blue arrows.



**Fig. 4.** Endoscopic image. Stenosing adenocarcinoma progressing from Barrett's esophagus. The yellow arrow shows the endoscope located at the stomach entrance, and the green arrow shows the tumor tissue.

tumor had spread to the cardia and was complicated by an esophageal–mediastinal fistula.

Given the patient's young age and absence of long-term tumor metastasis, radical surgical treatment was deemed appropriate. In July 2022, the patient underwent single-step surgery including thoracoscopic esophageal resection, esophageal repair with a pedicle flap composed of a segment of the greater curvature of the stomach, cervical anastomosis formation, and 2S lymphadenectomy. During the surgical intervention, an esophageal–mediastinal fistula was also removed.

Pathological examination of the surgical specimen confirmed a low-grade esophageal adenocarcinoma progressing from Barrett's esophagus with necrotic sites and surface ulceration. The tumor had infiltrated the mucous membrane and the submucosal muscle layer of the esophageal wall and had spread to the cardia. Tumor metastases were detected in 4 of 11 esophageal lymph nodes and 4 of 6 lymph nodes along the lesser curvature of the stomach.

**The final diagnosis was** stage III pT4N1M0 esophageal adenocarcinoma progressing from Barrett's esophagus.

The postoperative period was complicated by a tracheoesophageal fistula, which was epithelialized after 3 weeks of endoscopic vacuum therapy. Given the advanced stage of the primary tumor, the high risk of disease recurrence, and young patient age, he received nine cycles of adjuvant FOLFOX (calcium folinate, fluorouracil, and oxaliplatin).

Follow-up examinations in December 2022 and April 2023 showed no signs of local tumor recurrence or progression.

## DISCUSSION

This clinical case report discloses several problems associated with the endoscopic and pathological diagnosis of a malignant tumor progressing from Barrett's esophagus.

Histological confirmation of the tumor process and its type is vital before surgery, or other treatments can be performed. The decision to use chemotherapy or combined chemoradiotherapy, either as an adjuvant or neoadjuvant treatment, depends on both the tumor stage and its histological pattern. In this case, the main issue was the inconsistency between the endoscopy and radiology results and the histological findings.

Advanced endoscopic equipment provides high-resolution imaging of the mucous membrane of hollow organs. The primary principle should be to perform a comprehensive examination of the entire organ and identify the most suspicious regions of the mucous membrane. This is a more labor-intensive and time-consuming manipulation. The decision to perform a targeted biopsy should only be made after a detailed endoscopy. Targeted biopsy differs from blind biopsy and classic forceps biopsy by taking specimens from the most suspicious regions using more specific techniques such as narrowed-spectrum endoscopy combined with near-focus mode [15].

Early-stage adenocarcinoma progressing from Barrett's esophagus is most commonly characterized by a flat growth pattern within the metaplasia segment [16]. In our case, the esophageal carcinoma was accompanied by massive adenomatous tissue growth, which delayed the malignancy verification because adenomatous tissue samples were taken in multiple nontargeted biopsies. The diagnosis was established accurately through a targeted, stepwise biopsy of the non-necrotic regions.

A study reported that only 35% of patients experience correct detection and preoperative staging of esophageal adenocarcinomas [17], a finding supported by this case. One reason for this is the insufficient accuracy of forceps biopsy as a means of obtaining pathology specimens. If esophageal malignancy is suspected, endoscopic mucosal resection is warranted [18]. The value of a biopsy is increased when at

least five tissue fragments are obtained. This increases the likelihood of detecting atypical tumor cells, even incidentally, in one of the fragments [19, 20].

Pathologists may disagree on whether the changes detected in the biopsy specimens are caused by dysplasia or signs of a malignant tumor. According to A.H. Ormsby et al., pathologists specializing in gastrointestinal tissues frequently disagree on the diagnosis of high-grade dysplasia versus adenocarcinoma, even when evaluating total resection specimens [21]. The authors suggested revising treatment strategies that differentiate between severe dysplasia and intramucosal adenocarcinoma based on histological differences using a limited number of biopsies.

## CONCLUSION

This case report demonstrates the significance of a clinician's critical approach to pathology results. The diagnosis should also be based on the clinical presentation and instrumental findings. However, in cases of unclear histological findings, biopsy samples from the tumor sites with the highest quality or volume are recommended, even if multiple biopsies are required.

## ADDITIONAL INFORMATION

**Funding source.** This article was prepared by a group of authors as a part of the research and development effort titled "Opportunistic

screening of high-profile and other common diseases", No. 123031400009-1", (USIS No. 123031400009-1) in accordance with the Order No. 1196 dated December 21, 2022 "On approval of state assignments funded by means of allocations from the budget of the city of Moscow to the state budgetary (autonomous) institutions subordinate to the Moscow Health Care Department, for 2023 and the planned period of 2024 and 2025" issued by the Moscow Health Care Department.

**Competing interests.** The authors declare that they have no competing interests.

**Authors' contribution.** All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. D.A. Akhmedzyanova — concept, collection and processing of data, data analysis, manuscript writing; O.K. Yutsevich — collection and processing of data, manuscript writing; R.V. Reshetnikov — concept, manuscript editing; O.V. Tashchyan, S.S. Pirogov, M.P. Mazurova, N.N. Volchenko, A.K. Kamalov, Y.F. Shumskaya — manuscript editing, preparation of illustrative material; M.G. Mnatsakanyan — final editing, manuscript approval.

**Consent for publication.** Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript in Digital Diagnostics Journal.

**Acknowledgments.** The authors express their gratitude to Ivan A. Blokhin for his support in the text editing.

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