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Macroscopy predicts tumor progression in gastric cancer: A retrospective patho-historical analysis based on Napoleon Bonaparte's autopsy report

Heather Dawson[a,b,*], Alexander Novotny[c], Karen Becker[d], Daniel Reim[c], Rupert Langer[a,b], Irene Gullo[e,f], Magali Svrcek[g], Jan H. Niess[h], Radu Tutuian[h], Kaspar Truninger[i], Ioannis Diamantis[j], Annika Blank[a,b], Inti Zlobec[b], Robert H. Riddell[k], Fatima Carneiro[e,f], Jean-François Fléjou[g], Robert M. Genta[l,m], Alessandro Lugli[a,b]

[a] *Clinical Pathology Division, Institute of Pathology, University of Bern, Bern, Switzerland*
[b] *Translational Research Unit, Institute of Pathology, University of Bern, Bern, Switzerland*
[c] *Department of Surgery, Klinikum Rechts der Isar, Technische Universität München, Germany*
[d] *Institute of Pathology, Klinikum Rechts der Isar, Technische Universität München, Germany*
[e] *Centro Hospitalar de São João/Medical Faculty of Porto, Porto, Portugal*
[f] *Institute of Molecular Pathology and Immunology of the University of Porto/i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal*
[g] *Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine, Service d'Anatomie Pathologique, Paris, France*
[h] *University Clinic of Visceral Surgery and Medicine, Inselspital Bern, Switzerland*
[i] *Gastroenterologie Oberaargau, Langenthal, Switzerland*
[j] *Privatklinik Linde, Biel, Switzerland*
[k] *Department of Pathology and Laboratory Medicine, Mount Sinai Hospital and University of Toronto, Toronto, ON, Canada*
[l] *Miraca Life Sciences, Research Institute, Irving, TX, United States*
[m] *University of Texas Southwestern Medical Center, Dallas, TX, United States*

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ABSTRACT

Background: The cause of Napoleon Bonaparte's death remains controversial. Originally suggested to be gastric cancer, whether this was truly neoplastic or a benign lesion has been recently debated.
Aims: To interpret findings of original autopsy reports in light of the current knowledge of gastric cancer and to highlight the significance of accurate macroscopy in modern-day medicine.
Methods: Using original autopsy documents, endoscopic images and data from current literature, Napoleon's gastric situation was reconstructed. In a multicenter collection of 2071 gastric cancer specimens, the relationship between tumor size and features of tumor progression was assessed.
Results: Greater tumor size was associated with advanced pT, nodal metastases and Borrmann types 3–4 ($p < 0.001$). The best cut-off for predicting pT3-4 tumors was 6.5 cm (AUC 0.8; OR 1.397, 95% CI 1.35–1.446), and 6 cm for lymph node metastases (AUC 0.775; OR 1.389, 95% CI 1.338–1.442). The 6 cm cut-off of had a positive predictive value of 0.820 for nodal metastases and a negative predictive value of 0.880 for distant metastases.
Conclusion: This analysis combines Napoleon's autopsy with present-day knowledge to support gastric cancer as his terminal illness and emphasizes the role of macroscopy, which may provide valuable information on gastric cancer progression and aid patient management.

1. Introduction

In 1815, after his final defeat at the battle of Waterloo, Napoleon Bonaparte was sent into exile to the remote South Atlantic island of St. Helena, where he was held captive until his death on May 5, 1821, at age 51. The autopsy was performed by Dr. Francesco Antommarchi, assisted by the surgeon Archibald Arnott and

* Corresponding author at: Clinical Pathology Division, Institute of Pathology, University of Bern, Murtenstrasse 31, P.O. Box 62, CH-3010 Bern, Switzerland. Fax: +41 31 632 4995.
E-mail address: heather.dawson@pathology.unibe.ch (H. Dawson).

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overseen by several British physicians who had been sent to St. Helena to follow Napoleon's health. Two original autopsy reports were produced, one by Antommarchi himself and one by the British physicians Thomas Shortt, Archibald Arnott, Charles Mitchell, Francis Burton and Matthew Livingstone. Antommarchi's book '*Les Derniers Moments de Napoleon*', published in 1825, includes a second autopsy report with details not originally described. In 2006, this report was found to have striking similarities with an article published in the French medical journal *Archives Générales de Médecine* in 1823 [1,2], and since then has been considered highly suspicious of plagiarism. This discovery has questioned the credibility of used sources [3,4] in previous manuscripts [5,6].

Although both original reports describe an ulcerated and perforated 'scirrhous' tumor in the stomach (the word 'scirrhous' was used in the 19th century to describe a cancerous growth), a recent publication questioned whether Napoleon's lesion was indeed gastric cancer or a benign gastric ulcer on a background of gastritis [3]. The resolution of this matter, which would be simple if histologic examination were possible, must rest on macroscopic description alone. This mirrors the importance of expert macroscopic evaluation of gastric lesions in modern-day medicine to distinguish between gastritis, benign ulcers and gastric cancer. In gastric cancer, most current treatment algorithms for advanced tumors combine neo-adjuvant therapy and radical resection. Hence, preoperative assessment of tumor extent, especially its depth and lymph node involvement is critical to plan further treatment. If additional reliable macroscopic indicators of tumor progression could be gathered at endoscopy, they could become integral elements in guiding management decisions.

Therefore, the aim of this work is twofold: (1) to interpret the findings of original autopsy reports in light of our current knowledge on the macroscopy of gastritis, benign gastric ulcers and gastric cancer. If we could conclude that the controversial lesion was likely a malignant tumor of the stomach, then we could substantiate the hypothesis that an upper gastrointestinal bleed occurring in or as a consequence of gastric cancer was the most probable cause of Napoleon's death. (2) To evaluate the role of macroscopic features as predictors of gastric cancer progression.

2. Methods

2.1. Historical data

Descriptions of Napoleon's stomach from original autopsy reports, namely Antommarchi's original report and the British physician's report were reviewed (excerpts in Supplementary File S1). Observations from Napoleon's entourage were not taken into account due to probable bias.

2.2. Gross pathology analysis

To compare the size range of benign inflammatory and malignant gastric lesions, images from 14 cases of therapy-naïve pangastritis (Fig. 1), 10 benign ulcers (Fig. 2) and 9 gastric adenocarcinomas (Fig. 3) from endoscopies performed between 2009–2015 at the Clinic of Gastroenterology, Inselspital, University Hospital of Bern and 2 private practices (Gastroenterologie Oberaargau and Privatklinik Linde) were reviewed. A literature search on macroscopic appearances of gastric cancer, benign ulcers and pangastritis was performed including peer-reviewed articles and established printed works [7–10]. In an attempt to visualize the extent of Napoleons gastric lesion, macroscopic findings as described in original autopsy reports were reconstructed.

Macroscopically, autoimmune atrophic gastritis can be recognized by the atrophic border and distinct transition from antral to oxyntic mucosa [10]. *Helicobacter pylori* gastritis may take on a wide variety of appearances ranging from normal to erosive gastritis with ulcers, but common findings include antral nodularity (caused by lymphoid follicles), thickened gastric folds and abnormal pattern of mucosal collecting venules [11]. Chemical gastritis or reactive gastropathy is often characterized by erythematous antral mucosa with varying degrees of congestion and edema; erosion and ulcers may also be present [12].

Careful macroscopic examination allows the distinction between benign and malignant ulcers in most cases. Helpful features include the appearance of the mucosa at the margin of the ulcer. Benign ulcers are relatively small, well-circumscribed, 'punched out' lesions while any gastric ulcer with irregular, firm, and raised margins and thickening of the surrounding mucosa should be considered highly suspicious for malignancy [8–10]. Furthermore, associated erythema in carcinoma tends to be severe and diffuse, whereas in benign ulcers, stippled, raised red dots with intervening white lines may be seen [9]. The craters of ulcerated carcinomas are typically filled with necrotic debris, whereas benign ulcers tend to have a clean base that may be covered with an adherent grayish-white fibrinous exudate [10]. Both benign and malignant gastric ulcers often bleed and blood clots may fill the ulcer crater [7,10].

Macroscopic growth patterns in advanced gastric carcinoma (infiltration of at least the lamina muscularis propria) are classified according to Borrmann [13,14]:

- Type 1: Polypoid carcinomas
- Type 2: Excavating carcinomas with sharply demarcated and raised margins
- Type 3: Ulcerated carcinomas without definite limits, infiltrating into the surrounding wall
- Type 4: Diffusely infiltrating carcinomas, in which ulceration is usually not a prominent feature.

2.3. Correlation of tumor size and clinicopathological features

For a correlation between the size of gastric cancers and the extent of disease, clinicopathological data including tumor size, Borrmann classification, histological tumor type and tumor grade (WHO), Lauren classification, pT, pN and M stage were retrieved from reviewed pathology reports of gastric cancer patients having undergone primary resection (Institute of Pathology, Technische Universität München, $n = 2199$ (1983–2013), Centro Hospitalar de São João/Medical Faculty of Porto, $n = 93$ (2005–2013), Institute of Pathology, University of Bern, $n = 80$ (1995–2007) and Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine, Service d'Anatomie Pathologique, France, $n = 20$ (2006–2008)). A total of 321 cases were excluded because of incomplete information regarding tumor size, pN and pT status. Thus, 2071 patients were included in the final analysis (Table 1), none of whom had received neo-adjuvant therapy. The use of this completely anonymized non-genetic health-related data does not require review or approval by an ethics committee in any of the participating centers. The 6th edition of the UICC/AJCC (2002) had been used for tumor classification [15].

2.4. Statistical analysis

Based on the distribution of tumor size, Mann–Whitney-*U* test was performed to evaluate associations between tumor size and clinicopathological features. ROC-analysis was used to determine tumor size cut-offs for predicting tumor stage and histopathological features. Chi-square test was used to determine the association of determined cut-offs with TNM features. Statistical analysis was

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