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# SPATIAL NEGLECT: AN OVERVIEW OF ASSESSMENT, REHABILITATION METHODS, AND CHALLENGES ENCOUNTERED IN CLINICAL PRACTICE

 Nazife İncilay Tirsioğlu<sup>1</sup>,  Melisa Abay<sup>1</sup>,  Rıza Sonkaya<sup>2</sup>,  Necdet Kocabıyık<sup>3</sup>

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## ABSTRACT

Spatial neglect is a syndrome that stems from damage to brain regions that are critical for spatial attention and most commonly occurs post-stroke. Spatial neglect causes a lack of awareness of the contralesional space, affecting sensory perception, motor function, and daily life activities. Conventional paper-and-pencil tasks, the Behavioral Inattention Test, the Catherine Bergego Scale, and the Kessler Foundation Neglect Assessment Process, are the assessment methods used in clinical practice to detect spatial neglect and its impact on functional performance. Rehabilitation strategies, such as prismatic adaptation, non-invasive brain stimulation, and virtual reality, are considered to be promising methods. This review proposes that using a single assessment and a single treatment method still is not ultimately effective. Hence, combining different rehabilitation methods, as well as exploring the potential of artificial intelligence as an assessment and rehabilitation strategy may provide optimized outcomes. In order to overcome the current limitations and remove the ambiguity of long-term results, conducting future randomized controlled trials are critical.

**Keywords:** Functional status, perceptual disorders, rehabilitation, stroke

## INTRODUCTION

Spatial neglect is a syndrome that stems from damage to brain regions critical for spatial attention (1-3). It manifests as a lack of awareness of the contralesional space, which cannot be explained by primary sensory or motor deficits (4, 5). Regardless of diagnostic methodology, time since post-stroke, or location of the lesion in the brain, the prevalence of spatial neglect after unilateral stroke is estimated to be 30% (6).

Common clinical features of patients with spatial neglect encompass failure to respond to stimuli from the contralesional side, reduced movements towards the contralesional side, and diminished use of their contralesional limbs. Patients may be unable to report stimuli on the contralesional side of space, and their body posture may also deviate towards the ipsilesional side (7-10). Some neglect behaviors may manifest during their daily

life routine, such as not being aware of voices arising from the neglected side of the patient, leaving food uneaten on one side of the plate, shaving only one side of their face, and colliding with obstacles on one side (11). These impairments result in patients being more dependent on their daily life activities.

Spatial neglect is more common and more severe in patients with right brain damage than in patients with left brain damage. The severity may be attributed to the fact that neural networks of spatial attention predominantly reside in the right brain hemisphere (2, 6, 7, 12-14). However, spatial neglect after left brain damage is still quite common, with a prevalence of approximately 20% (6). The neglected space may be close to the patient or on their body (personal space), in their arm's reach (peripersonal space), or beyond their arm's reach (extrapersonal space) (8, 15, 16).



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**Assessment of Neglect**

**Paper-and-pencil tasks:** The line bisection and cancellation tasks are two of the most commonly used paper-and-pencil assessments for spatial neglect (17-19). In the line bisection test, the patient is asked to mark the midpoint of a horizontal line (18). In the cancellation task, the patient is required to search for spatially distributed targets (19). Several cancellation task variations exist, such as the letter cancellation task, the bells test, the Behavioral Inattention Test (BIT) letter cancellation, the star cancellation, and Ota's cancellation task (20-23). Despite their widespread use in clinical practice, these assessment tests do not adequately reflect functional performance in daily life activities and may underdiagnose the proprioceptive, auditory, or motor-intentional components of neglect (24).

**The Catherine Bergego Scale (the CBS):** The CBS is a functional assessment tool designed to identify spatial neglect-related impairments that may interrupt neglect patients' performance of everyday chores and compromise their safety (25). The scale aims to evaluate neglect-related disability in daily life by assessing the patient's asymmetric functional body movements (26). During the assessment, patients perform daily life tasks for approximately 15-20 minutes under professional examination (27).

The CBS inclusively assesses the functional performance of the suspected neglect patient in personal (body surface), peripersonal (within arm's reach), and extrapersonal spaces (beyond arm's reach). Hence, the CBS can capture the spectrum of variability in spatial neglect and is more responsive to the neglect detection than traditional paper-and-pencil tests (25, 26).

**Behavioral Inattention Test:** Multiple assessment tests should be used in combination to diminish the likelihood of overlooking some of the neglect-related symptoms (28). The BIT is one of the most frequently used assessment tools (29-32). The BIT consists of nine behavioral tests and six conventional subtests, including the line cancellation test, letter cancellation test, star cancellation test, figure copying, line bisection test, and drawing

test (11, 33). Compared to the line bisection and drawing tests, the score of the cancellation test holds considerable importance by facilitating the detection of recovery in the acute phase (11).

In the standard BIT test, the maximum total score is 146 points, and the threshold score is 129 points; if any of the test scores is below that minimum value, the behavioral test should be considered (11).

**Kessler Foundation Neglect Assessment Process (KF-NAP):** It was found that some additional instructions were required for a more reliable CBS administration (34). Therefore, the KF-NAP method was developed, which delivers comprehensive administration instructions and a scoring chart for the 10 original CBS categories of behavior (26, 35). Certain CBS category labels were transformed for a better demonstration of the aim of an observation, to encompass right-sided neglect symptoms, or to simplify the phrases. For instance, "knowledge of left limbs" on the CBS (36) is revised to "limb awareness" on the KF-NAP (34).

In addition, the KF-NAP incorporates and emphasizes the role of the environment in which the observation is conducted and evaluates the asymmetric performance between the right and left hemispaces. The ultimate goal is to make patients investigate the environment without premeditation and set them in motion, such as moving their gaze and posture. It is significant that both sides of space are assessed by the examiner because at the end of the examination, the scores of the patient should be compared between the right and the left sides (34).

Overall, conventional paper-and-pencil tests are efficient for rapid bedside monitoring owing to their simplicity and standardized scoring. However, functional assessment tools like the CBS and KF-NAP are superior at capturing deficits in daily life activities caused by spatial neglect.

Table 1 provides an overview of clinical assessment tools for spatial neglect in terms of their components and subtests, key features, and utility in clinical practice. Since the diagnostic focus of the assessment tools varies, in clinical practice the tools

**Table 1: Summary of clinical assessment tools for spatial neglect.**

Assessment tool	Components	Key features	Clinical value in practice
Paper-and-pencil tasks	Line bisection and cancellation tasks.	The line bisection test requires marking the midpoint of a horizontal line. The cancellation task requires to search for spatially distributed targets.	They are widely used. Nevertheless, functional performance in daily life activities is not adequately evaluated.
The CBS	Assessment of personal, peripersonal, and extrapersonal spaces.	Patients perform daily life tasks for approximately 15-20 minutes under professional examination.	Evaluates neglect-related disability in daily life by assessing the asymmetric functional body movements.
The BIT	Nine behavioral tests and six conventional subtests.	Multiple assessment tests are used in combination to decline the likelihood of overlooking some of the neglect-related symptoms.	The score of the cancellation test is particularly important for detecting recovery during the acute phase of the injury.
KF-NAP	Comprehensive administration instructions and a scoring chart for the ten original CBS categories of behavior.	Patients' capability of investigation of the environment is highlighted.	Evaluation and comparison of both the right and left hemispaces.

This table comprises the components, key features, and clinical value in diagnostic practice of the assessment tools for spatial neglect. The CBS: The Catherine Bergego Scale, The BIT: The Behavioral Inattention Test, KF-NAP: Kessler Foundation Neglect Assessment Process.

should be chosen considering different clinical needs. The BIT has standardized threshold scores; and the cancellation task, in particular, holds considerable importance for detecting recovery during the acute phase (11). On the other hand, the CBS and KF-NAP, show better performance in capturing the neglect-related deficits in daily life activities (25-27, 34).

### Rehabilitation of Neglect

Because of limitations such as anosognosia, in which patients are not aware of their deficit, and the varying nature of neglect, giving an ultimate verdict on the most effective way of treating spatial neglect patients is still a difficulty for clinicians to overcome (37-39).

Various approaches to spatial neglect rehabilitation have been developed. Some of these methods are mentioned below. However, the authors would like to highlight that given recent findings, prismatic adaptation, non-invasive brain stimulation (NIBS), and virtual reality (VR) are considered as the most promising approaches among them (17).

**Prismatic Adaptation:** The neglect patient is expected to point at the target while wearing prismatic goggles. Because of the visual shift caused by the prismatic goggles, the patient experiences a mismatch between the actual location of the target and the pointed location. After initial errors, with the help of visual feedback, adaptation occurs, and performance improves (17).

Assessed by paper-and-pencil tasks, some studies suggest that prismatic adaptation helps to show improvement in neglect behavior (40-42).

**Non-Invasive Brain Stimulation:** The symptoms shown by neglect patients are not only due to the decreased activity of the damaged brain area but also the increased activity of the homologous area of the other brain hemisphere. Therefore, making the lesioned area more active while reducing the overstimulated activity of the other hemisphere is the expected outcome of this type of rehabilitation (17, 43, 44). The lack of consensus about the NIBS parameters, as well as the significant heterogeneity, likely resulting from variations in NIBS protocols and the small sample sizes, represent limitations that should be considered regarding this rehabilitation method (45).

**Virtual Reality:** In a randomized controlled trial, VR was

used for the rehabilitation of neglect (46). The results of the experimental group, which used VR for the tasks, were compared with a control group that was rehabilitated by the standard methods. Both groups improved their performance as a result of the treatment phase, while the experimental group showed better performance in both the star cancellation test and the CBS (46).

Nevertheless, several limitations such as lack of information regarding the underlying neuroplastic changes responsible for the observed improvements, inherent heterogeneity of neglect patient populations, variations in VR intervention protocols, and generally small sample sizes should be acknowledged (47). Even so, it is suggested that VR may have a powerful potential as a spatial neglect rehabilitation method (47). Further studies are needed to be done focusing on the efficiency of the VR technique in the rehabilitation of neglect patients.

Table 2 provides an overview of rehabilitation methods for spatial neglect in terms of their mechanism of method and clinical outcomes. VR is considered as a rehabilitation method that still requires further research and demonstrates superior efficacy in both the conventional task (the star cancellation test) and the CBS (46). On the other hand, the prismatic adaptation method optimizes sensorimotor deficits in paper-and-pencil tasks, while NIBS method stands out by effectively addressing inter-hemispheric imbalance (17, 40-44).

### CONCLUSION

All these tools and methods discussed in this review, have unique aspects and are significant for overall neglect assessment and rehabilitation processes. Nevertheless, the remaining challenges should not be ignored. Although noteworthy improvements have been made in acknowledging and treating spatial neglect, inability to fully capture the extent of neglect in daily scenarios and lack of a treatment that works for every patient are remaining challenges.

In light of the findings discussed, this review proposes these three key clinical considerations in terms of assessment and rehabilitation methods of the spatial neglect.

First of all, conventional paper-and-pencil tests should be complemented by the functional tests such as the CBS and KF-NAP in order to better capture the deficits in neglect patients'

**Table 2: Summary of rehabilitation methods for spatial neglect.**

Rehabilitation method	Mechanism of method	Clinical outcomes
Prismatic adaptation	Usage of prismatic goggles to cause a mismatch between the actual location of the target and the pointed location, leading performance to get better with the help of visual feedback.	Associated with improvement in neglect behavior, assessed by paper-and-pencil tasks.
NIBS	Restoring the decreased activity of the damaged brain area and the increased activity of the contralateral brain hemisphere.	Regulation of the interhemispheric balance.
VR	Usage of VR during the tasks.	Experimental VR group showed better performance in both the star cancellation test and the CBS.

This table encompasses the underlying mechanisms and clinical outcomes of the rehabilitation methods for spatial neglect. NIBS: Non-invasive brain stimulation, VR: Virtual reality, The CBS: The Catherine Bergego Scale.

daily activities. Another point is that, since using a single treatment method still is not ultimately effective, combining different rehabilitation methods, and exploring the potential of artificial intelligence as an assessment and rehabilitation method may improve clinical outcomes. Finally, in order to overcome the current limitations and remove the ambiguity of long-term results, especially in NIBS and VR, conducting future randomized controlled trials are critical.

Future studies are likely to become milestones by overcoming these current challenges encountered in assessment and rehabilitation processes of the spatial neglect.

#### Ethics

**Ethics Committee Approval:** The authors declare that this manuscript is a review of previously published literature. Since the study does not involve primary data collection from human participants or animals, and no identifiable private information was used, and therefore, ethical approval was not required.

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# PERIPHERAL FACIAL PARALYSIS DEVELOPING AFTER A BEE STING: A CASE REPORT

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## ABSTRACT

Bee stings usually cause mild local reactions; however, rare neurological complications, including peripheral facial paralysis, may occur. We present a case of peripheral facial paralysis following a bee sting. A 62-year-old male presented with left-sided facial asymmetry two days after being stung in the left infraorbital and preauricular region. Neurological examination revealed left-sided House-Brackmann grade II peripheral facial paralysis without additional neurological deficits, and central causes were excluded clinically. The patient had well-controlled diabetes mellitus. Oral methylprednisolone and supportive therapy were initiated. Significant clinical improvement was observed on day ten, and complete recovery was achieved by the third week. Inflammatory edema, neurotoxic effects, and microvascular ischemia may contribute to the pathogenesis. Bee sting should be considered a rare cause of peripheral facial paralysis, and early corticosteroid therapy may result in complete recovery.

**Keywords:** Bee sting, case report, corticosteroid, facial palsy, peripheral facial paralysis

## INTRODUCTION

Bee stings are highly prevalent insect stings in humans. In the 16-65 year age group, the cumulative lifetime prevalence of bee stings is between 61% and 95% (1). Complications developing after bee stings are classified as early and delayed reactions. While early reactions may range from mild local allergic responses to severe anaphylactic shock, delayed reactions may occur up to ten days later and patients may present with different clinical manifestations depending on the affected system. The clinical course and severity of these reactions may vary depending on the type of immune response and the patient's sensitivity. Various mediators such as histamine, proteases, and thromboxanes play a role in this process. Antihistamines, corticosteroids, adrenaline, and venom immunotherapy, when necessary, are used in treatment (2).

Facial paralysis has a wide etiological spectrum, including infectious, neurological, congenital, neoplastic, traumatic,

systemic, and iatrogenic causes (3). Peripheral facial paralysis (PFP) is the most prevalent form of facial paralysis and is caused by the impairment of the facial nerve along its pathway from the brainstem to the peripheral branches. The estimated incidence is 20-30 cases per 100,000 population, with approximately 40,000 new cases each year worldwide (4). Regardless of etiology, the management of facial paralysis requires a multidisciplinary approach, and the prognosis varies depending on the degree of nerve injury (5).

In this case report, a rare case of PFP that developed following a bee sting is presented.

## CASE REPORT

A 62-year-old male patient presented with the complaint of deviation in the left half of the face two days after a bee sting. Following the bee sting, the patient applied ice to the affected area to manage localized erythema, increased warmth, edema,



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and tenderness. No medical treatment was administered. According to the patient's history bee stings occurred in the left infraorbital and preauricular region (Figure 1). In the patient's medical history, the patient had no other known history of allergies, there was diabetes mellitus under regular follow-up, and it was stated that glycemic control was regular.

In the otorhinolaryngological examination, otoscopic and nasopharyngeal evaluation were unremarkable. In the neurological examination, findings compatible with left-sided House-Brackmann grade II (Table 1) PFP were observed (6). There was mild weakness in eye closure (Figure 2), flattening of the nasolabial sulcus (Figure 3) and slight weakness to wrinkle the forehead (Figure 4).

No additional neurological deficit was detected. In the clinical evaluation performed to exclude central pathology, no central nervous system findings were observed.

Methylprednisolone (prednol) treatment was initiated at a dose of 1 mg/kg/day (80 mg/day). As supportive treatment, citicoline, benfotiamine (benexol) 2x1, and pantoprazole 1x1 were prescribed. A three-week course of treatment was planned. There was no indication for hospitalization.

During follow-up, significant clinical improvement was observed starting from the tenth day, and complete recovery was achieved at the end of the third week. Informed oral consent was obtained from the patient for the publication of this case report and the accompanying clinical images.

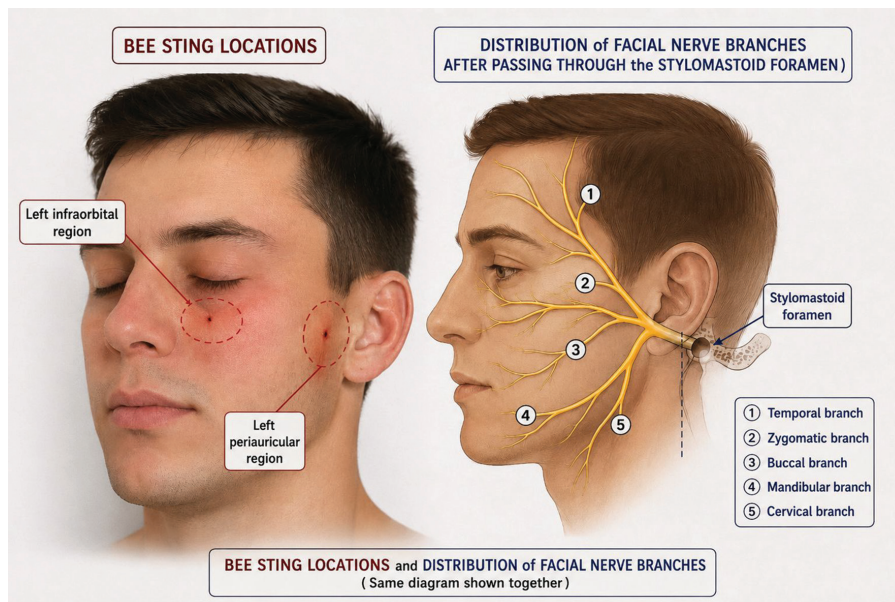


Figure 1: Diagram explaining bee sting locations and the distribution of facial nerve branches (the figure has been generated by ChatGPT on 16.05.2026).

Table 1: The House-Brackmann grading scale (6).

Grade	Description	Gross	At rest	Motion	Estimated function (%)
I	Normal	Normal	Normal	Normal	100
II	Mild dysfunction	Slight weakness noticeable on close inspection, may have very slight synkinesis	Normal symmetry & tone	Forehead: moderate to good function; eye: complete closure w/minimum effort; mouth: slight asymmetry	80
III	Moderate dysfunction	Obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, and/or hemifacial spasm	Normal symmetry & tone	Forehead: slight to moderate movement; eye: complete closure w/effort; mouth: slightly weak w/ maximum effort	60
IV	Moderately severe dysfunction	Obvious weakness and/or disfiguring asymmetry	Normal symmetry & tone	Forehead: none; eye: incomplete closure; mouth: asymmetric w/ maximum effort	40
V	Severe dysfunction	Only barely perceptible motion	Asymmetry	Forehead: none; eye: incomplete closure; mouth: slight movement	20
VI	Total paralysis	No movement	Asymmetry	No movement	0

w/: with.



Figure 2: Mild weakness in eye closure.



Figure 4: Slight weakness to wrinkle the forehead.



Figure 3: Flattening of the nasolabial sulcus.

## DISCUSSION

Both strong allergic reactions and the direct toxic effects of bee venom contribute to the pathophysiology of bee sting injuries. The venom's phospholipase enzyme is the primary source of allergic responses (7). Honeybees, wasps, and hornets are the primary stinging species of bees, which are members of the Hymenoptera order (8). The venom gland is linked to the bee stinger. Toxins from the venom gland are injected into the skin by the stinger during a sting, resulting in either systemic or

local reactions. Honeybee stings usually cause regional edema without a systemic reaction. Venom from all hymenoptera species induce localized pain and swelling, and affected individuals usually notice that they are stung, unlike venomous spider bites. The local reaction includes edema, erythema, and discomfort, represents a non-immunoglobulin E (IgE)-mediated response that resolves spontaneously within 24 hours. The amount of venom in a bee sting is directly correlated with its clinical symptoms, which can be fatal in extreme circumstances. The chemical composition of venom varies among bee species. Wasp venom is alkaline, while honeybee venom is acidic. The stinger withdraws from the human body following a hornet sting, whereas it stays in the body following a honeybee sting. Histamine, various enzymes, formic acid, neurotoxins, and hemolytic toxins are among the complex components of bee venom. Toxic symptoms occur when bee venom enters the human body. The location of the sting, the quantity of venom entering the body, and the existence of an allergic reaction all affect the toxic reaction brought on by bee venom (9, 10).

Although PFP has a broad etiology spanning from infections to injuries and neoplasms, bee sting is a very rarely documented cause (3). Bee stings are a fairly uncommon cause of PFP, even though there is a broad range of etiologies, including diseases, trauma, and tumors (1, 2).

The relationship between the two disorders is supported by the fact that our patient's symptoms developed about 48 hours after the bee sting. The pathophysiology of this condition can be explained by several mechanisms.

Bee venom contains proteases and other bioactive compounds that may directly cause neurotoxic effects (2). Toxic neuropathy can develop because of the sting

site's anatomical proximity to the facial nerve's peripheral branches.

Local inflammatory edema and compression, however, are more likely causes. Neuropraxia may develop from compression of the facial nerve at the stylomastoid foramen exit or peripheral branches due to edema caused by inflammation triggered by IgE-mediated or non-IgE-mediated mediators. Furthermore, ischemia or vascular spasm at the vasa nervorum level may also be considered as a possible explanation.

Our patient's history of diabetes mellitus is also noteworthy. Diabetes mellitus may increase the risk of peripheral nerve damage because of microvascular changes and neuropathy susceptibility (11). This condition may have contributed to a more severe effect of the inflammatory or ischemic process triggered by the bee sting on the facial nerve.

Corticosteroid treatment was initiated in the preliminary period in accordance with Bell's palsy protocols. The three documented cases of bee sting-induced facial palsy differ significantly in terms of corticosteroid treatment. In order to address the systemic toxic and allergic response in the context of multiple organ dysfunction, Li et al. (9) gave intravenous dexamethasone at a fixed dose of 10 mg/day mixed with 5% dextrose in normal saline for 4-5 days, with a maximum duration of 7 days. In accordance with normal Bell's palsy protocols, Arun et al. (12) employed oral prednisolone at a fixed dose of 60 mg/day for the first week, followed by gradual tapering without stating the rate of dose reduction. In the present case, methylprednisolone was initiated at a weight-based dose of 1 mg/kg/day (80 mg/day) and tapered by 10 mg every two days over a total treatment period of three weeks. By using weight-based dosing and a systematic, predetermined tapering schedule, which may enable a more customized corticosteroid tapering strategy, our method was different from both previously reported cases. Methylprednisolone was selected due to its excellent pharmacokinetic profile and low mineralocorticoid activity, which may be especially beneficial for patients with metabolic comorbidities (13). Additionally, our patient's diabetes mellitus is significant since it is linked to chronic nerve ischemia and reduced nerve blood flow, which may have a detrimental impact on the healing and repair processes of the facial nerves (11, 14). All three patients recovered completely or almost completely despite variations in corticosteroid agents, dosage methods, and treatment lengths. This suggests that early corticosteroid therapy administration may be a significant predictor of outcome, independent of the particular regimen used. The rapid and complete recovery observed in the patient suggests that the pathology was at the level of neuropraxia rather than permanent axonal damage.

## CONCLUSION

Although rare, bee stings should be considered as a potential trigger associated with the development of PFP. This possibility should be considered especially in patients with microvascular risk factors such as diabetes mellitus. Complete clinical recovery can be achieved with early corticosteroid treatment.

### Ethics

*Informed Consent:* An informed oral consent was obtained from the patient.

### Footnotes

*Conflict of Interest:* The authors declared no conflict of interest

*Author Contributions:* Surgical and Medical Practices: A.K., Concept: İ.G.A., A.B., A.K., Design: İ.G.A., A.B., A.K., Data Collection or Processing: İ.G.A., A.B., A.K., Analysis and/or Interpretation: İ.G.A., A.B., A.K., Literature Search: İ.G.A., A.B., A.K., Writing: İ.G.A., A.B., A.K.

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# CASE REPORT: SYNCHRONOUS LUNG ADENOCARCINOMA AND PRESUMPTIVE ANAL/RECTAL CARCINOMA IN A 67-YEAR-OLD MALE

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## ABSTRACT

Multiple primary malignant neoplasms pose significant challenges in staging and treatment, particularly when they present synchronously with widespread metastatic burden. This report details the rare case of a 67-year-old male with a significant smoking history who was diagnosed with synchronous, advanced-stage malignancies: lung adenocarcinoma and a highly suspicious second primary tumor in the anal canal/rectum. Initial evaluation the lung cancer was Stage IVB with extensive metastases (liver, brain, adrenal, lymph nodes). Crucially, the <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography indicated a distinct, highly active lesion in the anorectal region, necessitating definitive pathological distinction from metastasis. The management plan initiated palliative radiotherapy for cerebral metastases, reflecting the complexity of treating two concurrent primary cancers.

**Keywords:** Adenocarcinoma, anal, cancer, lung, multiple, synchronous, tumor

## INTRODUCTION

The diagnosis of multiple primary malignant neoplasms (MPMN), particularly those presenting synchronously, represents a significant and complex clinical challenge (1). These conditions, defined by two or more histologically distinct cancers in one patient, are broadly classified as synchronous (diagnosed within six months) or metachronous (diagnosed after six months). Clinical analyses of large patient cohorts, some numbering over 15,000 individuals, have highlighted a clear increase in the incidence of MPMN (2, 3). This trend poses diagnostic and therapeutic dilemmas, as the detection of a second, or even a third, unexpected primary malignancy profoundly impacts staging, prognosis, and therapeutic selection (4). This rising incidence is often attributed to a combination of longer patient survival, the effects of carcinogens, genetic predispositions, and the increased sensitivity of modern diagnostic imaging (5).

The simultaneous presentation of a primary lung malignancy and a secondary lesion in the gastrointestinal tract, particularly the anorectum, represents a clinically significant subset of synchronous MPMN (SMPMN). A new lesion discovered in the colorectum or anal canal of a patient with established primary lung cancer is conventionally presumed to be an aggressive pulmonary metastasis until proven otherwise.

This presumption, however, carries a significant risk of misdiagnosis, which can lead to inappropriate clinical staging and suboptimal patient care. This is because the treatment for a single widely metastatic cancer differs drastically from that for two concurrent, independent primary malignancies. This diagnostic challenge is bidirectional; for example, cases of primary colorectal adenocarcinoma metastasizing to the lung can mimic a new primary lung adenocarcinoma, further underscoring the need for definitive pathology (6). The specific pairing of synchronous lung adenocarcinoma and colorectal cancer presents its own set of clinicopathological



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characteristics and prognostic challenges, which must be carefully analyzed to guide appropriate care (7).

To resolve this critical diagnostic dilemma, advanced imaging and pathology are indispensable. <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT) has emerged as a crucial tool, specifically validated for the evaluation of synchronous or metachronous colorectal cancers in patients who already have a known lung cancer. By quantifying metabolic activity (SUV<sub>max</sub>) and delineating anatomical spread, PET/CT findings that demonstrate a distinct, highly-avid lesion, as opposed to a typical metastatic pattern, can strongly suggest an independent primary tumor (8). Ultimately, however, immunohistochemistry (IHC) remains the gold standard for definitive diagnosis.

Immunohistochemistry profiling, which confirms distinct cellular origins (e.g., lung adenocarcinoma typically staining thyroid transcription factor-1 (TTF-1); anal/rectal adenocarcinoma typically staining

Cytokeratin20 (CK20) and caudal homeobox2 (CDX2), is essential to confirm the diagnosis of SMPMNs.

This pathological confirmation is non-negotiable, as it is the only method to rule out metastatic spread and is critical in complex cases, such as the rectum presenting with mixed histologies like squamous cell carcinoma and adenocarcinoma components (9).

This case report details the rare and clinically demanding presentation of a 67-year-old male with a heavy smoking history who was diagnosed with Stage IVB lung adenocarcinoma and a highly suspicious second primary tumor in the anal canal/rectum. The case specifically highlights the decisive role of <sup>18</sup>F-FDG PET/CT in suggesting the SMPMN diagnosis in the face of extensive metastatic burden, underscoring the necessity of

a rigorous, multidisciplinary approach to avoid misstaging and ensure that highly individualized treatment plans are established for patients with this complex synchronous disease.

## CASE REPORT

The case is characterized by an extensive metastatic burden confirmed at the time of initial diagnosis in late 2025. The 67-year-old male patient first presented to the clinic in October 2025 with the primary complaint of a persistent, debilitating cough that had been worsening over time. The patient's epidemiological risk profile was significant: he was an ex-smoker with a substantial history totaling 35 pack-years, having ceased smoking approximately fifteen years prior to presentation. This heavy smoking history provided a strong index of suspicion for the pulmonary malignancy that was subsequently diagnosed. Furthermore, a family history of malignancy was noted, specifically lung cancer (brother) and stomach cancer (mother).

A crucial element of the presentation, which later complicated the differential diagnosis, was the patient's secondary complaints of dysuria and persistent anal pain. The anal discomfort, a highly relevant symptom, was initially investigated and clinically attributed to internal thrombosed hemorrhoids by a general surgeon, temporarily diverting attention away from an underlying anorectal malignancy. Despite the advanced stage of the disease discovered shortly thereafter, the initial physical examination was largely unremarkable for generalized lymphadenopathy or organomegaly.

The advanced-stage diagnosis was rapidly confirmed following a comprehensive staging workup initiated in October 2025 (Table 1). The clinical data and serology findings, documented in the electronic medical record, characterized an aggressive, systemic disease process.

**Table 1: Staging workup.**

Category	Date	Test/location	Key finding/dimension	Clinical significance
Anatomical correlate	Post-PET MRI	Rectal wall	70 mm mass (left lateral wall)	Supports suspicion of independent anorectal carcinoma
Tumor marker 1	10.06.2025	Serology	CEA:776 ng/mL	Markedly elevated; common in GI and lung primaries
Tumor marker 2	10.06.2025	Serology	PSA:6 ng/mL	Mildly elevated; contributes to benign prostate hyperplasia
Inflammatory marker	10.06.2025	Serology	CRP:100 mg/L	Reflects significant systemic inflammation/stress
Primary lung mass	10.10.2025	CT/PET (RUL)	46x46x50 mm mass	Histology: lung adenocarcinoma
Metastasis (widespread)	10.16.2025	MRI/PET/CT	Involvement of brain, liver, left adrenal gland	Establishes Stage IVB status
Lymphadenopathy	10.16.2025	PET/CT	Extensive nodal burden (3-4 cm nodes)	Includes mediastinal, paraaortic, celiac, hilar
Primary diagnosis	10.24.2025	Biopsy/staging	Stage IVB lung disease confirmed	Initial definitive classification (EMR)
Pulmonary histology	10.24.2025	IHC (lung biopsy)	TTF-1 positive	Confirms pulmonary origin
Suspicion of SMPMN	10.24.2025	PET/CT (anal canal)	Highly FDG-avid focus	Explicitly indicative of a second primary

EMR: Electronic medical record, CT: Computed tomography, PET: Positron emission tomography, RUL: Right upper lobe, IHC: Immunohistochemistry, MRI: Magnetic resonance imaging, FDG: Fluorodeoxyglucose, CEA: Carcinoembryonic antigen, GI: Gastrointestinal, PSA: Prostate-specific antigen, CRP: C-reactive protein, TTF-1: Thyroid transcription factor-1, SMPMN: Synchronous multiple primary malignant neoplasms, GI: Gastrointestinal.

The initial focus on the large pulmonary mass (SUV<sub>max</sub>:17.6) in the right upper lung led to a biopsy confirming lung adenocarcinoma. The tumor's aggressive nature was evident in the rapid staging to Stage IVB disease confirmed on October 24, 2025. The metastatic survey detailed a substantial nodal and distant burden. Lymphadenopathy was extensive, with large 3-4 cm nodes observed in the mediastinal and para-aortic chains, confirming high-volume lymphatic involvement. Distant visceral spread included confirmed lesions in the liver (specifically noted in segments 2 and 7) and a metastasis to the left adrenal gland. Crucially, the presence of symptomatic cranial metastases was a key factor in determining the immediate palliative strategy.

Pathological analysis of the lung primary confirmed the adenocarcinoma phenotype, exhibiting characteristic positive staining for the transcription factor TTF-1. This IHC profile established the cell of origin and became the essential reference marker for differentiating this tumor from the second suspicious lesion (6).

The most significant diagnostic challenge presented by the case was the presence of a second, highly metabolically active lesion in the lower GI tract (6). The whole-body <sup>18</sup>F-FDG PET/CT identified a distinct, highly FDG-avid focus in the anal canal (Figure 1) (8).

This finding was not casually dismissed as a potential metastasis; instead, the interpreting radiologist highlighted its atypical nature by explicitly labeling it as indicative of a second primary tumor (1, 8). This was supported by subsequent abdomen/pelvic magnetic resonance imaging, which provided the anatomical correlate: a large 70 mm mass fixed to the left lateral wall of the rectum.

The clinical and therapeutic ramifications are profound (2). If the rectal lesion is confirmed as a distinct primary (e.g., anal/rectal squamous cell carcinoma or adenocarcinoma), the patient would require two independent, potentially curative treatment protocols (7). Conversely, if it represents a metastasis from the lung, management must adhere to a palliative strategy for the single, widespread disease. The final distinction hinges entirely on obtaining pathological confirmation via IHC (colonoscopy images are shown in the Figure 2), seeking to contrast the TTF-1-positive lung primary with potential CK20/CDX2 positivity in the rectal lesion. The inability of non-invasive imaging techniques to reliably differentiate between metastasis and a synchronous primary necessitates this biopsy-based confirmation, which represents the gold standard in oncology (6). The pathology report confirms the diagnosis of multiple adenomatous polyps with different degrees of dysplasia (p53

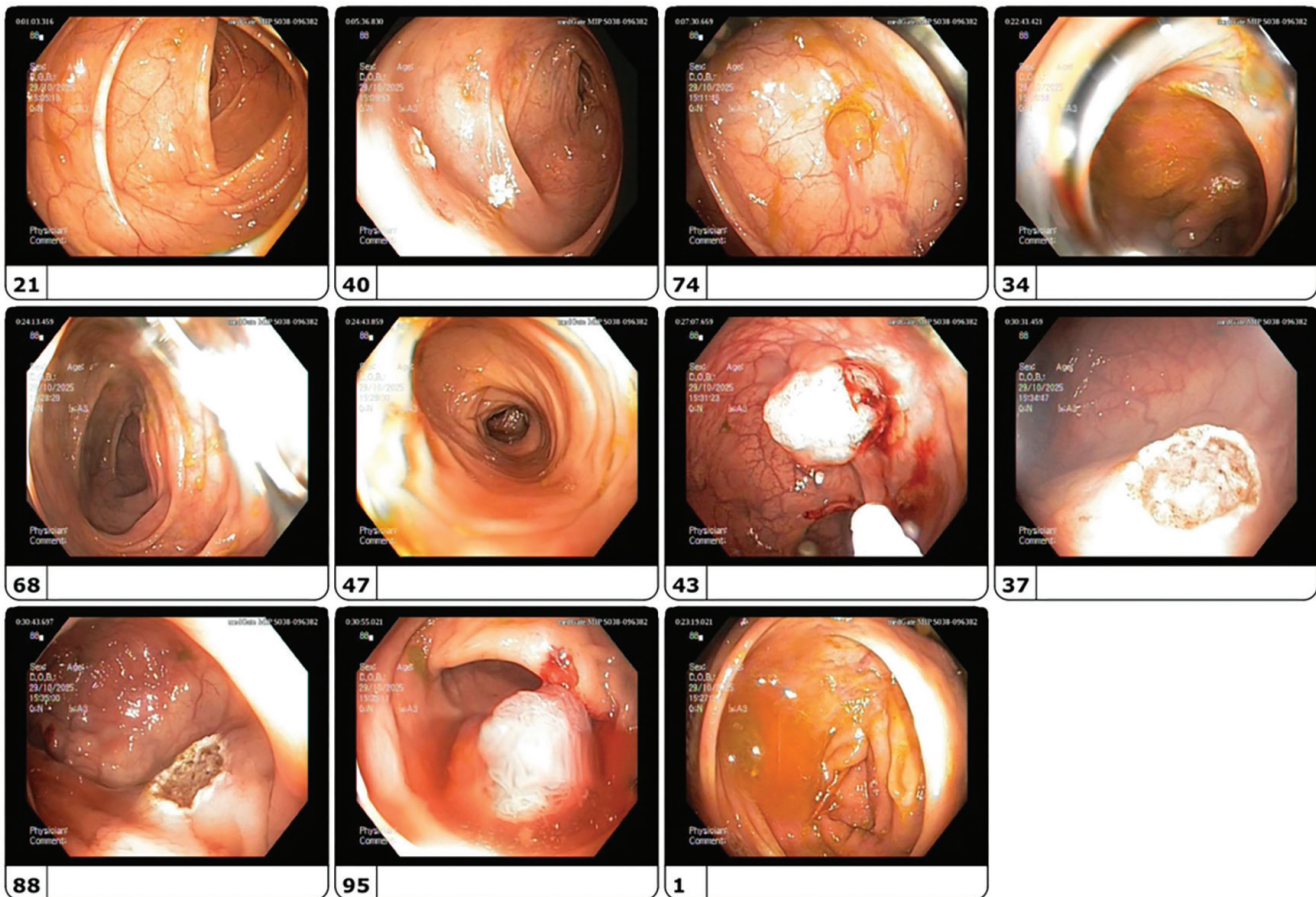


Figure 1: Colonoscopy images.

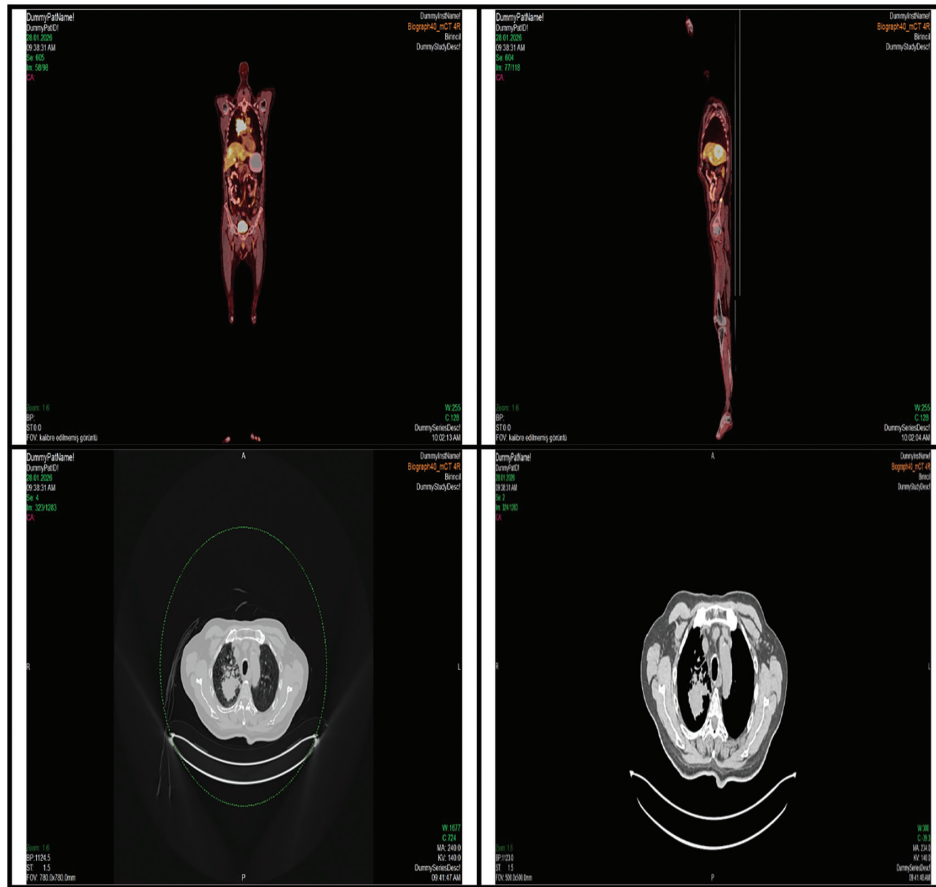


Figure 2: PET/CT images.

PET/CT: Positron emission tomography/computed tomography.

negative, increased Ki-67 proliferation index) removed from the colon and rectum. The final assessment confirms the removal of multiple polyps showing high-grade dysplasia. The patient will require close follow-up and monitoring due to the presence of high-grade dysplasia, which is a significant precursor to colorectal carcinoma.

The most time-sensitive intervention was dictated by the symptomatic cranial metastasis. Given the high-risk of neurological morbidity (including seizures, focal deficits, and rapid deterioration), the immediate clinical priority was the initiation of palliative radiotherapy for the cerebral metastases.

Further definitive therapeutic decisions for the lesions were critically dependent on the histological confirmation of the anal/rectal mass. Systemic therapy for the lung adenocarcinoma (e.g., targeted therapy based on molecular profiling or chemotherapy) and local surgical treatment for the anorectal lesions are planned along two separate, individualized oncological pathways (7). This case highlights the paradigm shift required in managing SMPMN, where the indispensable role of IHC transforms the patient's clinical course from a single palliative journey into a complex, dual-treatment strategy (1, 7). The distinction between metastasis and a second primary must be established, as it fundamentally dictates the selection of two

parallel, individualized oncological treatment pathways rather than a single palliative approach for one widespread cancer (6). An informed oral consent was obtained from the patient.

## DISCUSSION

This case highlights the complexities in the diagnosis and management of synchronous primary malignancies, especially lung adenocarcinoma and anorectal cancer, in a patient with extensive metastatic disease.

While  $^{18}\text{F}$ -FDG PET/CT confirmed the extent of the Stage IVB lung adenocarcinoma and its metastases, the FDG-positive region in the anal canal is the crucial finding that shifts the diagnosis from a solitary primary with metastasis to SMPMN. In published cases of synchronous lung and colorectal adenocarcinomas,

PET/CT has been shown to assist in differentiation, particularly when the two lesions exhibit distinct  $\text{SUV}_{\text{max}}$  values or unique anatomical patterns not typical of hematogenous spread (4). A definitive diagnosis requires IHC analysis of the anal mass to prove distinct cellular origins. For example, lung adenocarcinoma is typically TTF-1, while anal adenocarcinoma is typically CK20 and CDX2.

The patient possesses multiple risk factors for cancer, including heavy smoking and a strong family history of cancer. The simultaneous presence of two primary tumors, coupled with adverse prognostic factors like male gender, symptomatic disease (cough, anal pain), elevated carcinoembryonic antigen, and extensive nodal and distant metastasis (brain, liver, adrenal), dictates a guarded prognosis. Management must simultaneously address two distinct cancers. The immediate priority was palliative radiotherapy for symptomatic cranial metastasis. Subsequent systemic therapy should be selected based on the molecular profile of the lung adenocarcinoma, while the anal/rectal primary requires specific local treatment (e.g., chemoradiation for anal squamous cell carcinoma, or surgery/chemotherapy for anal/rectal adenocarcinoma) once its independent histology is confirmed.

## CONCLUSION

This case of a 67-year-old male presenting with synchronous, highly aggressive lung adenocarcinoma and a highly suspicious anal/rectal primary tumor underscores the necessity of a rigorous diagnostic protocol in patients with multiple lesions.

<sup>18</sup>F- FDG PET/CT served as a vital tool in suggesting the possibility of a second primary. This modality is often crucial for identifying synchronous lesions, such as colorectal cancers in patients with lung cancer, where metabolic differences can aid in differentiation (4). Final pathology and IHC results are indispensable for confirming SMPMN.

Specifically, IHC is the only way to prove distinct cellular origins (e.g., TTF-1 vs. CK20) and distinguish a second primary from a metastasis, which is critical, particularly given the known clinicopathological challenges when lung and colorectal cancers co-exist (7). The diagnosis of SMPMN is essential for accurate prognostication and highly individualized, multimodal oncological management.

Large-scale clinical analyses of MPMNs demonstrate the high level of complexity involved, noting that these patients often present with advanced disease and require highly tailored management strategies, as highlighted by reports on diverse synchronous presentations including breast, kidney, and thyroid primaries (4, 9). The presence of SMPMN dictate a guarded prognosis, reflecting the substantial therapeutic challenge

of addressing two concurrent malignancies that impact multiple organ systems, requiring close consideration of the overall survival benefits versus the cumulative toxicity of dual treatments. Ultimately, this case contributes to the understanding of rare presentations in oncology, reaffirming that multiple lesions must always be approached with a low threshold for pursuing definitive pathological evidence of distinct primary origins before initiating therapy.

## Ethics

*Informed Consent:* An informed oral consent was obtained from the patient.

## Footnotes

*Conflict of Interest:* The authors declared no conflict of interest

*Author Contributions:* Surgical and Medical Practices: Y.A.Ç., A.T., Concept: Y.A.Ç., A.T., Design: Y.A.Ç., A.T., Data Collection or Processing: Y.A.Ç., A.T., Analysis and/or Interpretation: Y.A.Ç., A.T., Literature Search: Y.A.Ç., A.T., Writing: Y.A.Ç., A.T.

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