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QUADRUPLE PRIMARY MALIGNANCIES: A RARE CASE OF BREAST, BLADDER, LUNG, AND LARYNGEAL CANCER

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ABSTRACT

Background: Multiple primary cancer (MPC) is defined as two or more primary malignant tumours in the same or a different organ that are simultaneous or metachronous. The reported incidence of MPC varies between 2 to 17%. The vast majority are patients with two primary neoplasms, while quadruple cancers are extremely rare. We present the first documented case of quadruple primary malignant neoplasms, comprising breast ductal carcinoma, papillary urothelial carcinoma, laryngeal fibrosarcoma, and lung squamous cell carcinoma.

Case presentation: A 55-year-old female first presented in 2006 with a palpable lump in the right breast and was first diagnosed with breast cancer. In 2010, following haematuria, urothelial carcinoma in the bladder was identified, with more than 15 recurrences in a 13-year period. In 2014 urothelial carcinoma of the renal pelvis and proximal ureter was detected. She developed hoarseness and in 2019 a laryngeal fibrosarcoma was found. During follow-up in 2022, she was diagnosed with lung cancer. The patient received multiple rounds of chemotherapy, radiotherapy and surgical interventions. In June 2023 the patient died due to chemotherapy-related complications.

Conclusions: This case highlights the importance of adapting treatment to the individual patient, long-term monitoring and the necessity of genetic counseling.

KEYWORDS

Multiple primary cancer, breast carcinoma, urothelial carcinoma, laryngeal sarcoma, lung carcinoma

LEARNING POINTS

- Long-term multidisciplinary follow-up is essential for patients with multiple primary malignancies, as timely surveillance can enable early detection and management of new cancers.
- Individualized treatment decisions are crucial when standard surgical or chemoradiation options are limited by treatment intolerance or patient refusal.
- Delayed initiation of appropriate sepsis management can critically impact patient outcomes; despite optimal subsequent treatment, disease progression may become irreversible.

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INTRODUCTION

Multiple primary cancers (MPC) must originate either in separate organs or exhibit divergent histological or morphological features. Quadruple primary cancers are extremely rare; under 0.1% of all malignant tumours[1]. Survivors of a first primary malignancy face an increased risk of subsequent tumours as a result of genetic predisposition, environmental exposure, or treatment related effects[2].

To contribute to the limited literature, we present a case of a patient with four primary malignancies treated in the Oncology Centre of Latvia from 2006 until 2023. This patient was diagnosed with ductal carcinoma of the breast, urothelial carcinoma, laryngeal fibrosarcoma, and squamous cell carcinoma of the lung, the chronological order of initial diagnosis can be seen in *Figure 1*. Family history was notable for paternal gastric cancer diagnosed at the age 51. This case was further complicated by the patient's limited compliance with treatment and the absence of genetic testing despite the clinical presentation.

CASE DESCRIPTION

In January 2006 a 55-year-old woman felt a lump in her right breast. In February, a mammography was performed and a 2 cm round low-density mass with spiculated borders behind the nipple was found. Her gynaecological history was as follows: menarche at the age of 14, menopause at the age of 50, one delivery, 3 abortions.

Due to suspected malignancy, surgery was planned on April 20, 2006. However, the patient did not show up for the procedure. In January 2007, a radical mastectomy of the right breast was performed. Histology confirmed invasive ductal carcinoma stage IIA, pT2N0M0. Immunohistochemistry showed oestrogen receptor (ER) 10%, progesterone receptor (PR) 0%, and human epidermal growth factor receptor 2 (HER2) score 0/1+.

From February until July 2007, the patient received 6 cycles of CMF chemotherapy (cyclophosphamide 1000 mg, methotrexate 65 mg, 5-fluorouracil 1000 mg). Followed by radiotherapy to the mastectomy scar and supraclavicular nodes (50 Gy in 2.5 Gy/fraction). During therapy, no significant side effects were reported.

Approximately 3 years after the breast cancer treatment, in November 2010, the patient presented with a 2-week history of haematuria. Ultrasonography revealed a 2.7 × 2.3 cm exophytic tumour in the bladder. Cystoscopy and transurethral resection of a bladder tumour (TURB) confirmed a pT1NxM0G2 papillary urothelial carcinoma on histology. Between 2011 and 2022, multiple non-muscle-invasive bladder cancer (NMIBC) recurrences were documented. After the second recurrence, cystectomy was recommended, but the patient refused. During this time, the patient underwent a total of 14 TURB procedures, 7 courses of doxorubicin therapy and 2 courses of Bacillus Calmette-Guérin immunotherapy (50 mg each once weekly for 6 weeks per course). *Table 1* summarizes the treatment the patient received for bladder cancer.

At the end of 2014, ultrasonography revealed right sided hydronephrosis with suspicion of a tumour in the renal pelvis and proximal ureter. Renal scintigraphy demonstrated markedly reduced function on the right side. In December 2014 nephroureterectomy was performed. Histological examination confirmed multilocular tumour growth with invasion into the renal pelvis and urethral muscular layer, grade 3 invasive papillary urothelial carcinoma (pT2N0M0). Despite more than a decade of treatment, the bladder cancer did not progress to a muscle-invasive or metastatic disease.

The patient complained about progressing hoarseness since 2018. In July 2019, at the age of 69, she underwent surgical ablation, and histology revealed a low-grade fibrosarcoma. In September of the same year, a computed tomography (CT) scan of the head and neck soft tissues showed a tumour in the posterior larynx 1.13 × 1.16 cm, involving nearly all levels, extending from the arytenoid cartilages to the upper margin of the cricoid cartilage, with a partial subglottic component and narrowing of the glottic airway. The disease was staged as cT3N0M0, stage III. The multidisciplinary tumours board (MTB) recommended total laryngectomy, but the patient declined further treatment.

A year later, in November 2020 she was acutely hospitalized with dyspnoea after mild physical exertion. An emergency tracheostomy and micro laryngeal ablation of the lesion on the left vocal cord were performed. A CT scan of the neck revealed a pathological mass measuring approximately 2 × 1 cm, with glottic narrowing of more than 50%. The MTB once again recommended total laryngectomy as the most appropriate further treatment; however, the patient categorically refused. Radical stereotactic radiotherapy was given to the larynx (66 Gy, 2.2 Gy/fraction) and the cervical nodes (51 Gy, 1.7 Gy/fraction). The therapy was well tolerated.

Repeated CT scans of the head and neck revealed post-radiation mucosal changes, but no evidence of tumour progression or metastasis. The patient had a permanent tracheostomy, maintained stable respiration, and no

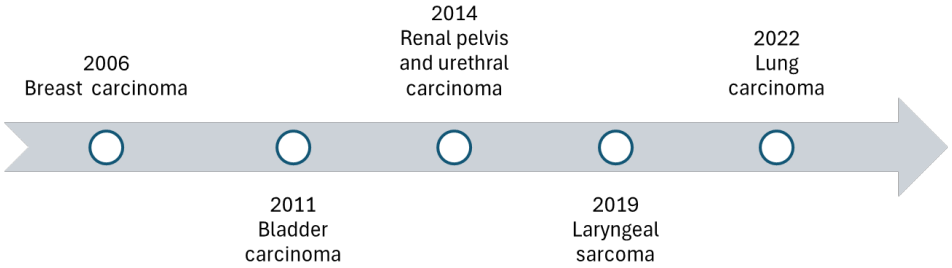


Figure 1. Timeline of initial oncologic diagnoses.

Date	Received treatment
December 2010	TURB
April 2011	TURB
July 2011	DOX
September 2011	TURB
January 2012	BCG
April 2012	TURB
June 2012	BCG
December 2012	TURB
April 2013	TURB
June 2013	DOX
September 2013	TURB
December 2013	TURB
January 2014	DOX
June 2014	TURB
December 2014	Right nephroureterectomy + TURB
December 2015	TURB
January 2016	DOX
April 2016	DOX
January 2019	DOX
September 2019	DOX
December 2019	TURB
May 2021	TURB
October 2021	TURB

Abbreviations: TURB, transurethral resection of the bladder; DOX, doxorubicin; BCG, Bacillus Calmette–Guérin.

Table 1. Timeline of bladder cancer treatment (2010–2021).

recurrence or metastases were detected up to the last follow-up.

In December 2022, during follow-up of bladder cancer, CT scans of the chest and abdomen revealed pathological changes in the left lung. Bronchoscopy with biopsy revealed invasive squamous cell carcinoma in the distal left main bronchus with invasion into the left lower lobe bronchus — stage IIIB, cT3N2M0, grade 2, with programmed cell death-ligand 1 (PD-L1) 10%. If surgery were considered, the only technically feasible procedure would be a pneumonectomy. However, pulmonary function tests were insufficient for surgery, with forced vital capacity (FVC) 56% and forced expiratory volume in 1 second (FEV1) 58%.

In February 2023, chemotherapy with gemcitabine and cisplatin was initiated. The first cycle was completed in full. The second cycle included gemcitabine only, and the patient did not attend the next planned cycle for unknown reasons. A subsequent cycle began in May 2023 with gemcitabine and cisplatin, but therapy was discontinued in June due to severe toxicity.

In May, repeat CT scan of the chest and abdomen showed disease progression: enlargement of the primary tumour in the left lung, and a new lesion in the right upper lobe suggestive of metastasis. No abdominal metastases were detected.

Following the last chemotherapy cycle on June 6, 2023, the patient reported severe weakness. Emergency medical services were initially called, but she was not hospitalized. On a subsequent call, the patient was in critical condition and urgently transferred to the intensive care unit at the Oncology Center of Latvia.

On admission, she had severe pancytopenia, hypotension, respiratory distress, tachycardia, and hepatorenal syndrome. Polymicrobial sepsis was confirmed by positive blood cultures.

Despite intensive treatment - including intravenous platelet transfusions, colony-stimulating factors, broad-spectrum antibiotics, glucocorticoids, vasopressors, and diuretics-her condition progressively deteriorated. On June 17, 2023, the patient died. The cause of death was attributed to a combination of chemotherapy complications, pancytopenia, sepsis, and multi-organ failure.

DISCUSSION

For breast cancer surgery, chemotherapy, radiotherapy, and endocrine therapy was administered. Due to failure to attend initially scheduled surgery, the mastectomy was delayed by 9 months, and it is possible that during this time the tumour progressed from stage T1 to T2. According to the guidelines, instead of CMF chemotherapy regimens containing anthracyclines were preferred. Radiotherapy was not mandatory for patients with stage IIA disease after radical mastectomy. In this case, the MTB decision was more aggressive than recommended, but justified because of the ER-low status, PR-negative tumour, HER2-negative phenotype, and the delay in surgery[3].

Over a 13-year period, more than 15 bladder cancer recurrences were documented. Despite the doctor's recommendations, the patient refused a cystectomy. Benefits of radical surgery for this patient would have included long-term local disease control. In stage T1 patients undergoing radical cystectomy, 10-year disease-free survival rates reach up to 92%[4]. However, according to the pan-urothelial field defect theory, cystectomy would not have prevented the development of upper urinary tract tumours[5]. In 2014, the patient was diagnosed with a metachronous tumour of the right renal pelvis and ureter. The occurrence of the upper tract urothelial carcinoma following NMIBC is relatively uncommon, reported in only 2.6-5.8% of cases[6].

Primary laryngeal sarcoma is a rare malignancy, accounting

for approximately 1% of all laryngeal cancers. Surgery, either partial or total laryngectomy, remains the mainstay of treatment for laryngeal sarcoma. Radiotherapy alone is almost never used; while adjuvant radiotherapy may improve local control, its survival benefit remains uncertain. Chemotherapy is rarely administered, being considered mainly in high-grade sarcomas or in inoperable, recurrent, and metastatic disease[7]. This reveals an unusual outcome in which radiotherapy-only management achieved local disease control in T3N0M0 laryngeal sarcoma after the patient refused surgical treatment.

This case illustrates the therapeutic challenges in patients with centrally located squamous cell lung cancer who have insufficient pulmonary function to undergo pneumonectomy. According to guidelines, the optimal approach in such cases is concurrent chemoradiotherapy[8]. Due to concerns of treatment intolerance, the patient received chemotherapy alone with gemcitabine and cisplatin. The chemotherapy regimen was not completed as planned, which may have reduced the overall effectiveness of therapy.

The patient developed severe pancytopenia, likely secondary to chemotherapy-induced myelosuppression, which predisposed her to sepsis and ultimately multi-organ failure. This report highlights the importance of early recognition and aggressive management of sepsis in cancer patients with immunodeficiency.

This patient developed four primary malignancies over a 17-year period. The presence of MPC and occurrence of rare tumours are indicators of a possible hereditary cancer syndrome. However, she was never referred for genetic counselling.

This patient presents with a tumour pattern that is most compatible with Li-Fraumeni syndrome (LFS), caused by germline mutations in the TP53 tumour suppressor gene. The most frequent tumours observed in LFS are breast carcinomas, soft tissue sarcomas, osteosarcomas, central nervous system tumours and adrenocortical carcinomas. Other malignancies seen in this syndrome include lung, gastrointestinal, skin, and genitourinary cancers[9]. Early recognition could have influenced treatment choices, guided surveillance strategies, and clarified the genetic status of at-risk family members.

REFERENCES

1. Jiao F, Hu H, Wang LW. Quadruple primary malignancy patient with survival time more than 20 years. *World J Gastroenterol* 2013;**19**:1498-1501. doi: 10.3748/wjg.v19.i9.1498
2. Okeke F, Nriagu VC, Nwaneki CM, Magacha HM, Omenuko NJ, Anazor S. Factors That Determine Multiple Primary Cancers in the Adult Population in the United States. *Cureus* 2023;**15**:e44993. doi: 10.7759/cureus.44993
3. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thürlimann B, Senn HJ, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. *Ann Oncol* 2005;**16**:1569-1583. doi: 10.1093/annonc/mdi326
4. Bianco FJ Jr, Justa D, Grignon DJ, Sakr WA, Pontes JE, Wood DP Jr. Management of clinical T1 bladder transitional cell carcinoma by radical cystectomy. *Urol Oncol* 2004;**22**:290-294. doi: 10.1016/S1078-1439(03)00144-3
5. Picozzi S, Ricci C, Gaeta M, Ratti D, Macchi A, Casellato S, et al. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol* 2012;**188**:2046-2054. doi: 10.1016/j.juro.2012.08.017
6. Nishimura N, Miyake M, Miyamoto T, Shimizu T, Fujii T, Morizawa Y, et al. Routine Surveillance of Upper Urinary Tract Imaging for Diagnosing Upper Urinary Tract Urothelial Cancer Recurrence in Patients with Nonmuscle Invasive Bladder Cancer. *Adv Urol* 2024;**2024**:5894288. doi: 10.1155/2024/5894288
7. Astl J, Holy R, Tuckova I, Belsan T, Pala M, Rotnagl J. Sarcomas of the Larynx: One Institution's Experience and Treatment Protocol Analyses. *Medicina (Kaunas)* 2021;**57**:192. doi: 10.3390/medicina57030192
8. Zer A, Ahn MJ, Barlesi F, Bubendorf L, De Ruysscher D, Garrido P, et al. Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2025;**S0923-7534**:00923-009288. doi: 10.1016/j.annonc.2025.08.003
9. Schneider K, Zelley K, Nichols KE, et al. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2025 May 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1311/