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Concurrent Challenges: Insights into Synchronous Dual Malignancies

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Abstract

Synchronous dual malignancies are increasingly encountered in clinical practice, posing significant challenges for diagnosis and management. This case series presents five cases of synchronous dual malignancies identified during patient evaluation. From cervical and breast cancers to lung and prostate malignancies, each case highlights the complexity of managing multiple dual primary tumors concurrently. Through detailed diagnostic work-ups and tailored treatment approaches, navigating the intricacies of these cases, emphasizing the importance of early detection and comprehensive patient care. Insights gained from these cases highlighted the need for vigilant evaluation and proactive management strategies to optimize outcomes in patients with synchronous dual malignancies.

1. Abbreviations

IACR/IARC: International Association of Cancer Registries and International Agency for Research on Cancer; MPMs: Multiple primary malignancies; PET CT: Positron emission tomography–computed tomography; SEER: Surveillance, Epidemiology, and End Results; ER: Estrogen Receptor; PI-RADS: Prostate Imaging–Reporting and Data System; TRUS: Transrectal Ultrasound; ICD: Intercostal Drainage; EBRT: External Beam Radiation Therapy; PR - Progesterone Receptor

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1. Introduction

The incidence of primary multiple malignancies is on the surge, attributed to various risk factors among cancer patients and advancements in diagnostic and therapeutic methodologies. Studies report the frequency of multiple primary malignancies within the same or different organ systems to range from 2% to 17% [1]. There is not enough information about a causal relationship between a risk factor and each of the two cancers. The relative risk for the association between the risk factor and each of the two cancers varies from 2 to 10 and the prevalence of the risk factor in the population varies from 5% to 50% [2]. The possibility that MPMs exist must always be considered during pretreatment evaluation. Screening procedures are especially useful for the early detection of associated tumors, preferably before clinical manifestations occur. There is some evidence that screening will improve outcomes among patients who may develop second malignancies, although the data are limited. The optimal screening modalities and strategies to reduce mortality from second malignancies remain to be defined for most tumor sites [3].

The International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) define synchronous multiple primary malignancies as the diagnosis of two or more primary malignancies within a 6-month period [4]. Furthermore, beyond this timeframe, the occurrence of more than two primary malignancies at different times is categorized as metachronous multiple primaries [1]. This case series presents five instances wherein synchronous dual primary malignancies were identified during patient evaluations.

By shedding light on these cases, we aim to underscore the significance of early detection, meticulous evaluation, and vigilant follow-up in the management of patients with synchronous dual primary malignancies. These insights are crucial for optimizing patient care and outcomes in the face of the increasing incidence of such complex clinical scenarios.

2. Incidence Data

Multiple primary malignancies (MPMs) in a single individual is considered a well-established phenomenon with a reported prevalence ranging between 0.73% and 11.7% [5]. However, synchronous category of MPMs that is found either simultaneously or within 6 months of the diagnosis of the first primary malignancy is considered less common [6,7].

Tanjak et al. retrospectively investigated 109,054 adult patients with a first solid cancer and followed them for the occurrence of a second primary cancer over a 25-year period [8]. They defined a 2-month period between the first and second primary cancers as synchronous multiple primary cancers, and cancers occurring after 2 months as metachronous multiple primary cancers. Their results showed that 1785 (1.63%) patients developed multiple primary cancers, and that most (70.87%) occurred after 2 months. The first cancers were breast, skin, colorectal, lung, head and neck, liver, prostate, thyroid, and female non-uterine genital cancers. Head and neck cancers had the highest metachronous association with second esophageal cancers [1]. The shortest median time to develop a second cancer was 55 days in the patients with uterine cancer [1].

During 1995-2008, the percentage of MP cancers (all sites, both sexes) increased 25.4% by using SEER rules (from 14.6% to 18.4%) and 20.1% by using IACR rules (from 13.2% to 15.8%). More MP cancers were registered among females than among

males, and SEER rules registered more MP cancers than IACR rules (15.8% vs. 14.4% among males; 17.2% vs. 14.5% among females). The top 3 cancer sites with the largest differences were melanoma (5.8%), urinary bladder (3.5%), and kidney and renal pelvis (2.9%) among males, and breast (5.9%), melanoma (3.9%), and urinary bladder (3.4%) among females [9]. Five cases with synchronous primary malignancies diagnosed from 2019 to 2024 are described.

3. Case No 1

A fifty-three-year-old female patient presented with post-menopausal bleeding and white vaginal discharge. Pelvic examination revealed an ulceroproliferative growth involving both lips of the cervix, predominantly involving the anterior and right lateral fornices, with the posterior and left lateral fornix remaining unaffected. The right parametrium felt indurated, while the anterior upper half of the vaginal mucosa was involved, with no rectal or rectovaginal septum involvement. Concurrently, a solitary, hard, non-tender, mobile swelling measuring 3 cm × 2 cm was found in the right breast during routine examination. No palpable axillary nodes were noted.

Biopsies confirmed well-differentiated squamous cell carcinoma of the cervix and invasive ductal carcinoma, grade 2, of the left breast. Hormonal receptor status was positive for estrogen and progesterone and negative for Her-2 neu receptors, with a Ki-67 index of 5%.

PET CT scan demonstrated heterogeneous enhancement with ill-defined hypermetabolism in the outer lower quadrant of the left breast and a metabolically active soft tissue mass arising from the cervix, alongside lymph node involvement.

Staging revealed Carcinoma Cervix stage IIIC1 and Carcinoma Left Breast cT2N1M0, anatomical stage IIB, prognostic stage IB. The patient received treatment with 50 Gy in 25 fractions of External Beam Radiation Therapy to the pelvis, concurrent with weekly Paclitaxel and Carboplatin. Post-EBRT, the cervical lesion showed partial response and was subsequently treated with intracavitary brachytherapy.

Following treatment for cervix, patient underwent Breast Conservation Surgery and Axillary Clearance. Histopathological examination revealed invasive carcinoma ductal with a lobular component, grade I, with free margins, positive lymphovascular stromal invasion, and perineural invasion, staged as ypT2N0. Adjuvant chemotherapy with FAC regimen and radiation therapy to the left breast and regional lymph nodes were administered.

On follow-up, PET CT scan showed complete response in both breast and cervical lesions. The patient is currently on hormonal therapy and scheduled for regular review every three months.

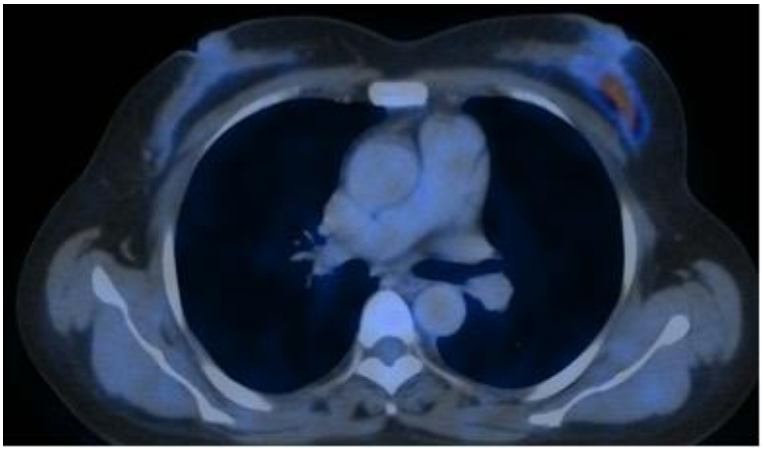


Fig 1(a)

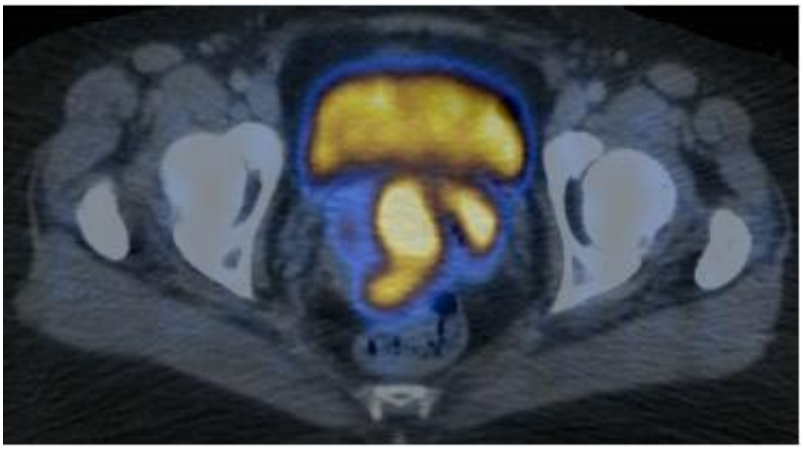


Fig 1(b)

FIG. 1. **(a,b) PET/CT scan images showing left breast and cervical lesions.**

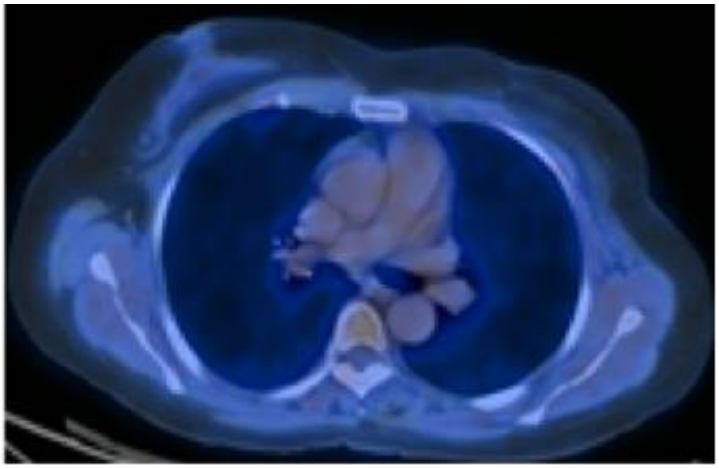


Fig 1 (c)

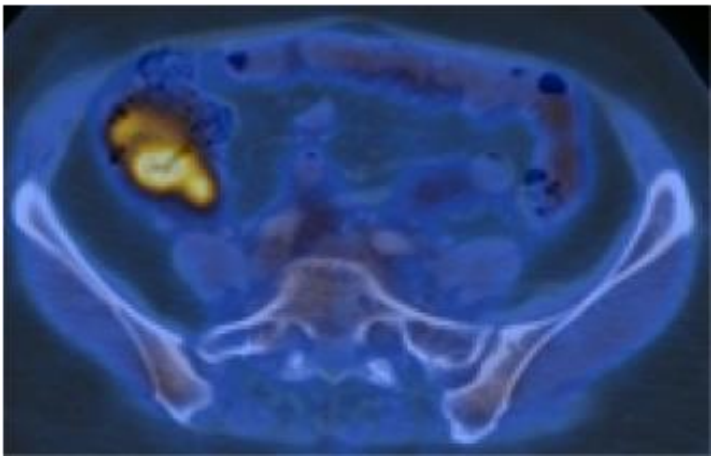


Fig 1(d)

FIG. 1. **(c,d) PET/CT scan images showing left breast and cervical lesions.**

4. Case No 2

A forty-eight-year-old nulliparous female presented with a palpable lump in her left breast associated with pain. Physical examination revealed a solitary, non-tender, mobile lump measuring 3 cm × 3cm in the upper outer quadrant of the left breast, with no lymphadenopathy. Biopsy results indicated an invasive ductal carcinoma lesion, grade 2, negative for estrogen and progesterone receptors, and confirmed negative for Her-2/neu by FISH. The Ki-67 index was elevated at 70%. PET/CT scan revealed an enhancing mass lesion in the upper outer quadrant of the left breast measuring 3.2 cm × 2.7 cm, with similar lesions in the upper central and upper outer quadrants, along with left axillary lymphadenopathy. Additionally, a 4.5 cm × 2.7 cm mass was identified in the right lobe of the lung-FIG. 2(a,b)

CT-guided biopsy of the left lung lesion showed poorly differentiated adenocarcinoma with ALK positivity on immunohistochemistry. The patient was diagnosed with synchronous dual malignancy: Multicentric Carcinoma Left Breast,cT2N1, stage IIB(anatomical), stage IIIB(prognostic) and Carcinoma Right Lung cT4N0, stage IIIC. The patient received neoadjuvant chemotherapy with 5 cycles of Nab-Paclitaxel and Carboplatin, resulting in marginal interval regression of the left breast lesion, left axillary lymph nodes, and right lung lesion. Subsequently, she underwent a left modified radical mastectomy and axillary clearance, revealing residual multifocal invasive ductal carcinoma of no special type, grade 2, with lymphovascular invasion and lymph node involvement (pathological stage mypT2N1a).

Post-surgery, the patient was treated with Ceritinib, an ALK inhibitor, in addition to hormonal therapy with Anastrozole. Follow-up PET/CT scan after three months revealed interval soft tissue changes in the left anterior chest wall and axilla - suggestive of post treatment changes. Interval regression of irregular heterogeneously enhancing mass in the right middle lobe medial segment abutting the pleura and additional lobulated soft tissue nodule in the anteromedial right upper lobe-FIG. 2(c) Adjuvant radiation therapy was delivered - 50 Gy in 25 fractions to the left chest wall. The patient is scheduled for Stereotactic body radiation therapy to the right lung lesion.

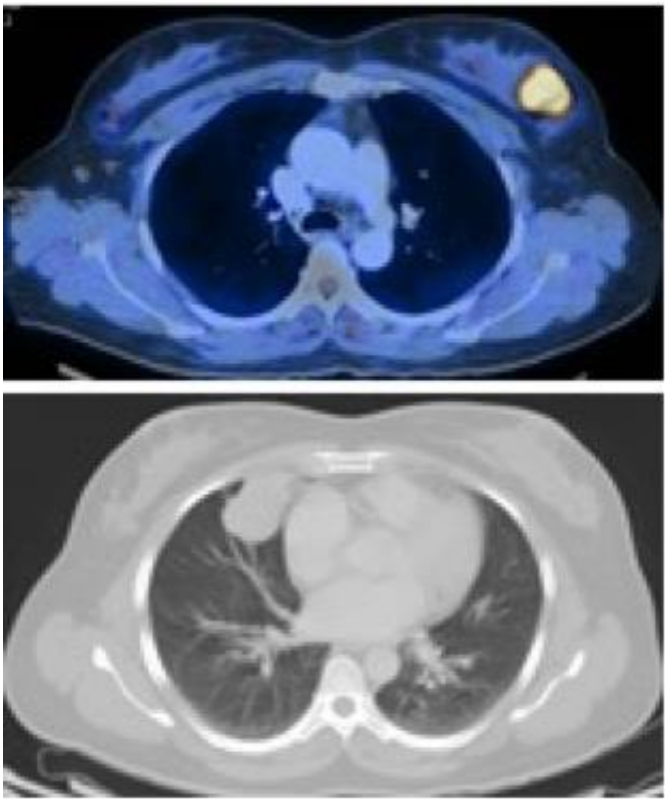


Fig 2(a)

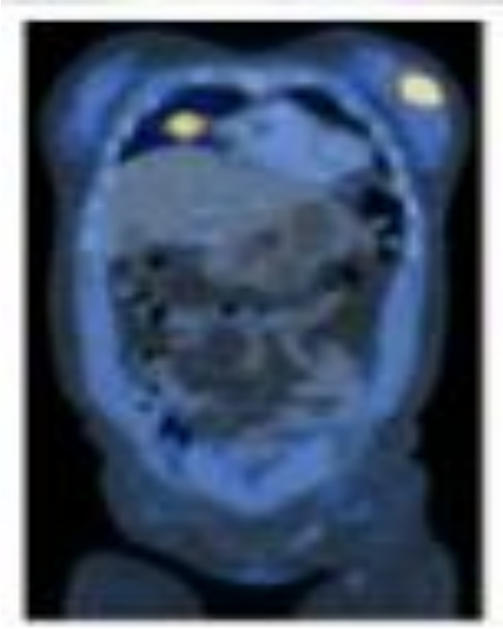


Fig 2(b)

FIG. 2. **(a,b) PET/CT scan images showing left breast and right lung lesions.**

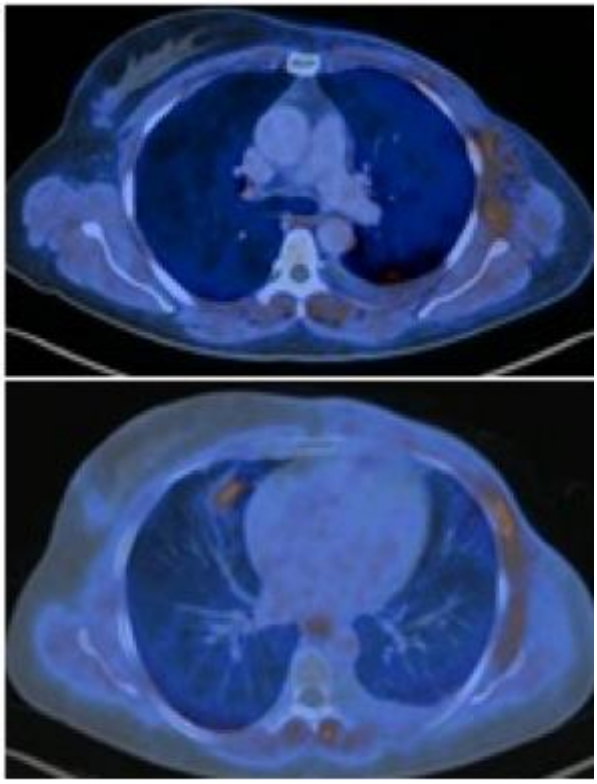


Fig2(c)

FIG. 2. **(c) PET/CT scan images showing left breast and right lung lesions.**

5. Case No 3

A seventy-year-old gentleman presented with symptoms of difficulty in breathing, urinary incontinence, and generalized weakness. PET CT evaluation revealed metabolically active mass lesions in the superior and posterior basal segments of the right lower lobe of the lung, along with a focal area of metabolic activity in the left transitional and peripheral zones at the apex and mid prostate gland-FIG. 3 (a,b). Biopsy from the right lung lesion confirmed invasive adenocarcinoma. Further evaluation indicated a lesion in the prostate gland, classified as PI-RADS IV, with biopsy results showing Acinar Adenocarcinoma, Gleason score 6 (3+3), Grade Group 1.

A diagnosis of dual synchronous malignancy was confirmed: Carcinoma Right Lung, cT1cN3M0, STAGE IIIB, and Carcinoma Prostate, categorized as cT2aN0M0 (Low risk group). Treatment entailed external beam radiation therapy 60 Gy in 30 fractions to the lung lesion and involved lymph nodes, along with concurrent weekly Inj Carboplatin for 6 cycles. Following radiation therapy, the patient was started on Tab Afatinib 30 mg for lung carcinoma, while active surveillance was advised for the prostate carcinoma.

After a year of treatment, the patient experienced breathlessness and low saturation. PET CT scan revealed interval increase of right pleural effusion with the development of pneumothorax-associated subpleural atelectasis in the right lower lobe, alongside interval progression of the prostate lesion-FIG. 3 (c,d). Thoracoscopy with pleural biopsy and ICD insertion was performed.

Pleural fluid cytology showed lymphocytes and neutrophils, with no evidence of malignancy in the parietal pleura biopsy, revealing radiation-induced pleural effusion.

Continued treatment with Tab Afatinib was recommended, while evaluation for prostate carcinoma was conducted. MRI Pelvis showed interval development of a lesion at the junction of the left peripheral and transition zone, classified as PIRADS-V. Serum Prostate-specific antigen levels had elevated compared to the previous year. The patient underwent TRUS-guided core biopsy of the prostate, confirming Acinar adenocarcinoma, Gleason score 6(3+3), Grade group 1.

In light of progression from low risk to intermediate risk, the patient received Stereotactic body radiation therapy to the prostate gland, to a total dose of 36.25 Gy in 5 fractions. He continues to be under regular follow-up at present.

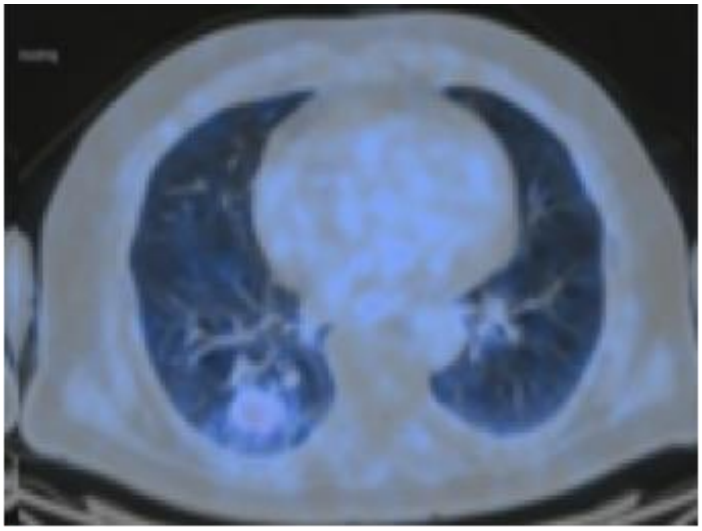


Fig 3(a)

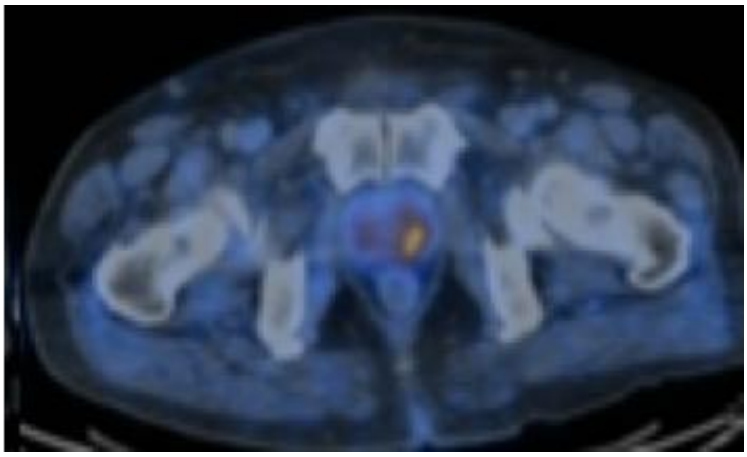


Fig 3(b)

FIG. 3. **(a,b) PET/CT scan images showing right lung and prostate lesions.**

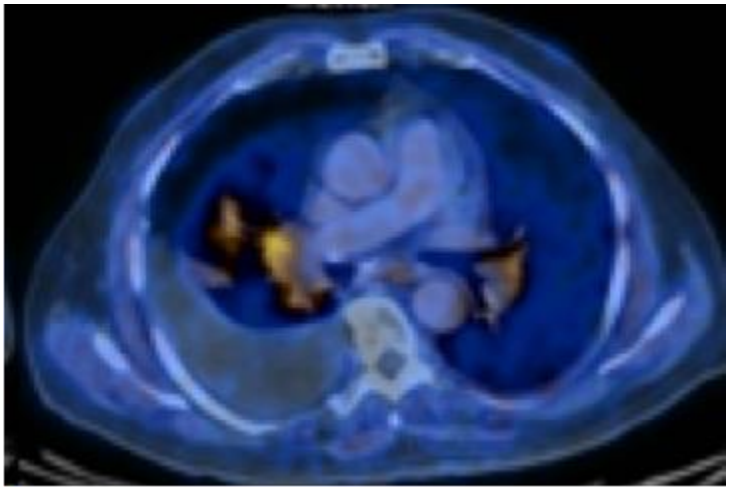


Fig 3(c)

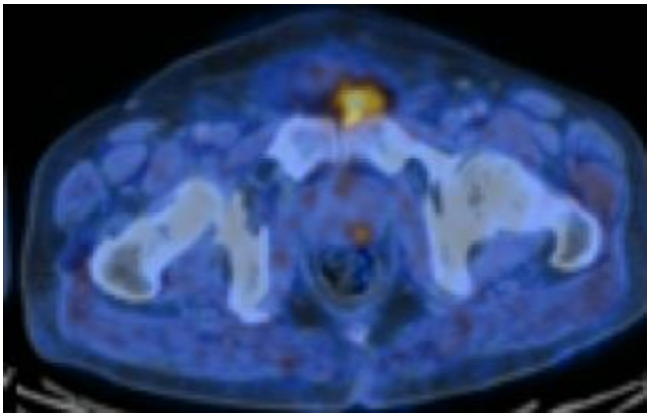


Fig 3(d)

FIG. 3. **(c,d) PET/CT scan images showing right lung and prostate lesions.**

6. Case No 4

An eighty-six-year-old male patient presented with urinary retention and an elevated serum prostate-specific antigen level (36.84 ng/mL). Subsequent evaluation involved cystoscopy with Transurethral Resection of the Prostate (TURP) and bladder neck excision, revealing adenocarcinoma of the prostate with a grade group of 5 (Gleason score - 5+4 = 9/10). PSMA PET-CT imaging depicted heterogeneously enhancing metabolically active prostatic parenchyma post-TURP, suggesting carcinoma of the prostate with potential extension into the bladder base and bilateral seminal vesicles. Additionally, imaging also revealed irregular enhancing soft tissue lesions involving the left aryepiglottic fold and left pyriform fossa, alongside an enlarged left level II lymph node-FIG. 4 (a,b)

MRI of the prostate indicated lesions involving bilateral posterior peripheral zones, predominantly on the right side, with a PI-RADS Category V. Extra prostatic extension was noted, with infiltration of the base of bilateral seminal vesicles, bladder neck and base, right neurovascular bundle, and abutment of the right puborectalis sling. The biopsy from the left pyriform fossa lesions confirmed papillary squamous cell carcinoma.

The patient was diagnosed with synchronous dual malignancy: Carcinoma Prostate cT3bN1M0, very high risk, and Carcinoma Hypopharynx, cT2N1M0, stage III. After consultation within a multidisciplinary team, a treatment plan was devised, commencing with hormonal therapy followed by concurrent chemoradiation to address the head and neck malignancy. The patient received Inj Pamorelin 11.25 mg injections every three months for hormonal therapy and received external beam radiation therapy to a dose of 70 Gy in 35 fractions targeting the gross primary tumor and regional cervical lymph nodes. Considering the patient's advanced age, concurrent chemotherapy was deemed unsuitable.

Post chemoradiation, the patient continued hormonal therapy for the prostate carcinoma and remains under regular follow-up care.

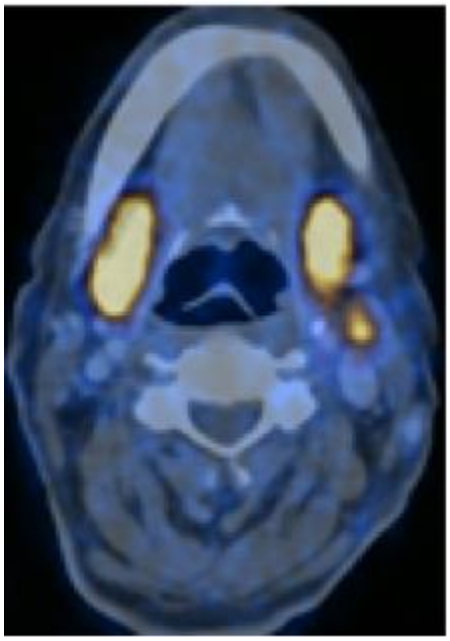
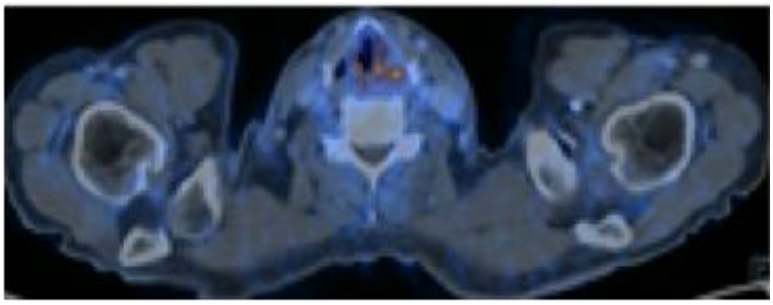


Fig 4(a)



Fig(b)

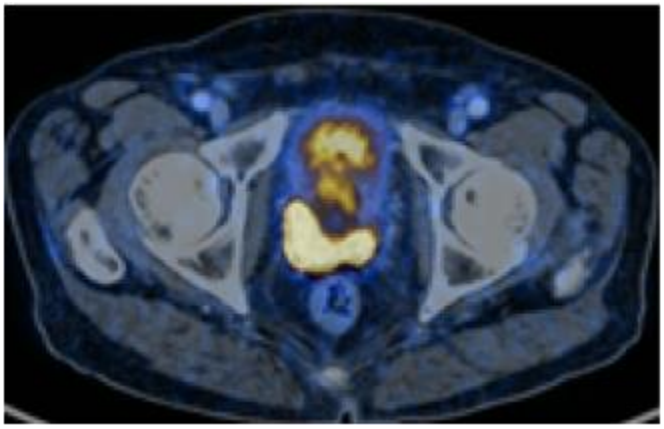


Fig 4(c)

FIG. 4. **(a,b,c) PET/CT scan images showing left aryepiglottic fold and left pyriform fossa and prostate lesions.**

7. Case No 5

A sixty-year-old woman presented with complaints of nipple thickening and postmenopausal bleeding, coupled with a family history of malignancy. She sought medical attention following a Laparoscopic Total Hysterectomy with Bilateral Salpingo-Oophorectomy and Adhesiolysis performed at another facility. Postoperative histopathology revealed a diagnosis of moderately differentiated endometrial adenocarcinoma infiltrating myometrium by more than 50%. Additionally, a biopsy from the right breast indicated invasive ductal carcinoma grade I, positive for estrogen receptor (ER) and progesterone receptor (PR), while negative for Her2/Neu, with a Ki-67 index of 10%.

Subsequent PET-CT imaging identified a 1.8 cm x 1.2 cm ill-defined soft tissue density, heterogeneously enhancing metabolic active lesion in the distal area of the right breast, raising concerns for malignant neoplastic etiology. Furthermore, a soft tissue density mildly metabolically active nodule involving the cutaneous and subcutaneous planes of the lower anterior abdominal wall and hypogastrium prompted consideration for metastatic and inflammatory or infective etiology- FIG. 5 (a)

Upon review, the endometrial adenocarcinoma was reclassified as moderately differentiated endometrioid carcinoma with squamous differentiation, FIGO Grade II. A second opinion on the biopsy from the right breast confirmed invasive ductal carcinoma, NST, Grade 1, with a Nottingham Breast Cancer score of 5 (2+2+1). The patient underwent Right Radical Mastectomy, Axillary Dissection, and Bilateral Pelvic Lymph Node Dissection. Postoperative histopathology revealed a mixed diagnosis of Invasive Micropapillary Carcinoma (90%) and Invasive Ductal Carcinoma (10%), Grade 1, of the right breast with free margins and metastasis to 2 out of 17 lymph nodes, resulting in a pathologic stage of pT1cN1a.

Following surgery, the patient received 4 cycles of adjuvant chemotherapy with Paclitaxel and Carboplatin. External beam radiation therapy was administered to a total dose of 40Gy in 15 fractions to the right chest wall and right supraclavicular fossa, followed by Intravaginal brachytherapy to the vaginal vault at a dose of 8.5Gy × 3 fractions. The patient tolerated the treatment well, experiencing no significant side effects. Regular follow-up assessments revealed a complete response on PET-CT imaging, with no evidence of recurrent lesions.

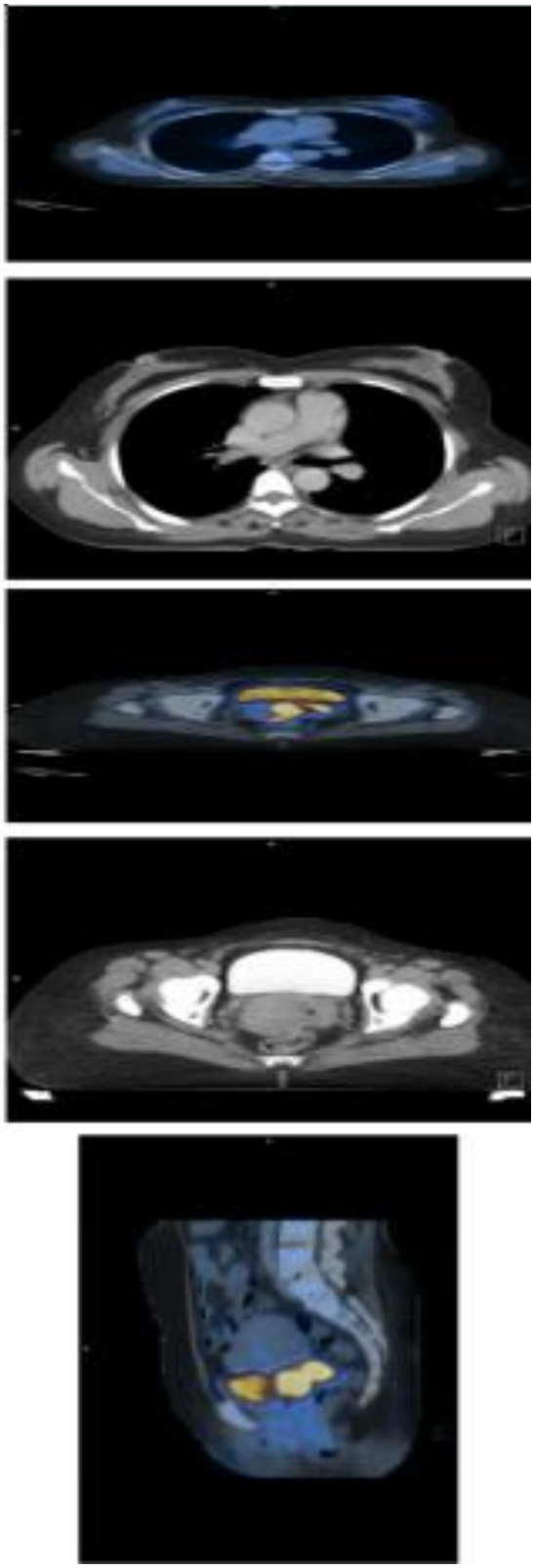
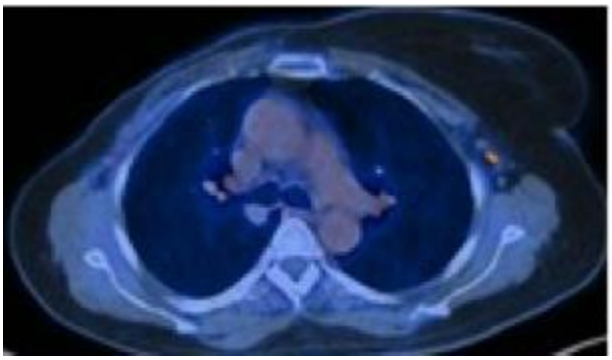


Fig 5 (a)

FIG. 5. **(a) PET/CT scan images showing right breast and abdominal lesions.**



Fig(5b)

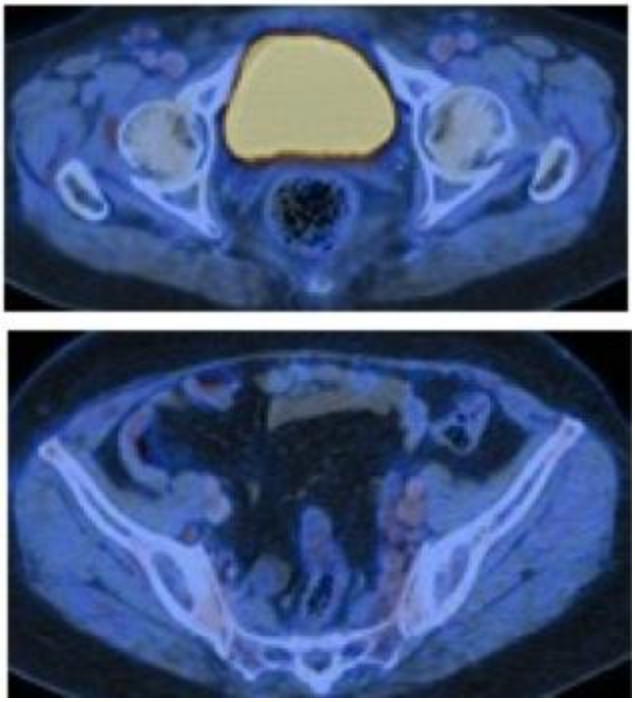


Fig 5(c)

FIG. 5. **(b,c) PET/CT scan images showing right chest wall and pelvis.**

8. Discussion

Synchronous double malignancies pose a significant challenge to clinicians and require careful consideration to avoid misdiagnosis. Early detection is paramount for achieving favorable treatment responses and disease-free survival. Tailoring treatment modalities to each individual patient with synchronous malignancies is crucial for optimal outcomes.

Several risk factors contribute to the development of synchronous primary malignancies, including smoking, alcohol intake, viral infections, chemotherapy, radiation therapy, genetic predisposition, betel quid chewing, and environmental factors.

Proposed diagnostic criteria for synchronous double primary malignancies necessitate that each tumor exhibits a definitive malignant profile, is distinct, pathologically proven, and excludes the possibility of one being a metastasis of the other [10].

While histopathologic examination remains the gold standard for confirmation, clinical acumen, detailed history-taking, thorough physical examination, and various radiological modalities (such as Ultrasound Scan, Computed Tomography, and positron emission tomography [PET]) aid in diagnosis [11]. Advanced diagnostic techniques, including immunohistochemical markers, may provide further clarity and refine treatment strategies [12].

In the evaluation of one primary malignancy, clinicians must always consider the possibility of encountering another primary tumor [11]. Treatment strategies are determined based on the stage of each tumor, the pathological type, and the patient's overall physical condition [13].

Effective counseling of patients regarding treatment options and follow-up is essential in managing synchronous malignancies, given the potentially prolonged duration of treatment compared to a single malignancy. Detailed financial planning is necessary to address the expenses associated with comprehensive treatment plans.

By emphasizing early detection, tailored treatment approaches, and comprehensive patient counseling, clinicians can optimize outcomes for individuals with synchronous malignancies.

9. Conclusion

In conclusion, the cases discussed in this series underscore the importance of early detection in the management of synchronous primary malignancies. Patients undergoing treatment for a primary malignancy should not overlook the possibility of developing additional tumors, emphasizing the need for vigilant evaluation during initial assessment and follow-up care. By recognizing and promptly addressing synchronous primaries, clinicians can implement appropriate interventions to maximize therapeutic efficacy and improve patient outcomes. Continued vigilance and thorough monitoring are essential to ensure comprehensive management and long-term success in the oncologic care of patients with synchronous malignancies.

10. Acknowledgements

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