INTRODUCTION
Among all cancer patients the 5-year relative survival rate is now almost 66%.
Because of the increased survival after cancer diagnosis it has become critical to identify and quantify the late effects of cancer and its treatment. One of the most serious events experienced by cancer survivors is the diagnosis of a new cancer. The number of patients with second cancers is growing rapidly. Travis et al. recently categorized second primary cancers into 3 major groups: treatment related, syndromic and those due to shared etiologic influences. In breast cancer survivors, second primary cancers reported so far are those of contra-lateral breast, ovary, lung, esophagus, colon, connective tissue, melanoma and leukemia. Although second primary cancer in urinary bladder has been detected in survivors of lymphomas, leukemias, testicular cancer and thyroid cancer but rarely such has been reported in breast cancer survivors.

Here, we report a case of second primary cancer in urinary bladder in a lady who was treated for breast cancer more than 10 years back.

CASE REPORT
A 70 years old normotensive, normoglycemic thin built female with no family history of cancer presented at Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad, with the complaints of painless hematuria for one year, increased urinary frequency and urinary incontinence for one and a half month.

In the past, she was treated for right sided infiltrating ductal carcinoma breast in 2001. For breast cancer, she had undergone right modified radical mastectomy followed by six cycles of adjuvant chemotherapy comprising of fluorouracil 500 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m². Chemotherapy continued from October 2001 to January 2002. She was also treated with locoregional radiotherapy 50 Gy in 25 fractions and hormonal treatment was also given. The hormone used was Tamoxifen 20 mg/day for 05 years. The patient was being followed regularly. She remained asymptomatic till February 2011 when she started having hematuria.

On examination, there were no signs of breast cancer recurrence. However, digital rectal examination showed thickening in anterior wall of rectum and impaired mobility of rectal mucosa. Ultrasound abdomen and pelvis done in December 2011 showed left sided hydronephrosis and irregular thickening of left anteroinferior wall of urinary bladder. CT scan revealed asymmetric soft tissue contrast enhancing thickening of left anteroinferior wall of urinary bladder, left distal ureteric involvement with mild proximal hydronephrosis (Figure 1). The patient underwent cystoscopy and transurethral resection of bladder tumour (TURBT) in December 2011. Histopathology turned out to be muscle invasive transitional cell carcinoma of urinary bladder (Figure 2 and 3). It was staged as T2bN0M0 (Stage II).

The patient was not willing for radical cystectomy, therefore, she was treated with concomitant chemoradiation which continued from 09/02/12 to 11/04/12. The regimen comprised of external beam radiotherapy (EBRT) 64 Gy in 32 fractions simultaneously with cisplatin 25 mg/m² on days 1 to 5 and 29 to 33 of radiotherapy. Post-treatment CT scan showed complete resolution of disease which was confirmed on cystoscopy and biopsy. Now the patient is on regular follow-up.
DISCUSSION
Breast cancer is the commonest cancer worldwide. With the use of highly effective and individualized treatment, the number of breast cancer survivors is increasing rapidly. Because of rise in survival, the risk of developing second cancers is also increasing proportionately. Second primary cancers have become an increasingly important concern in oncology during the last two decades. They now comprise the sixth most common group of malignancies. Numerous studies have demonstrated that women with breast cancer are at 2 to 3 fold increased risk of developing a new primary cancer in contralateral breast. Significant excesses relative to general population have also been observed for cancers of ovary, endometrium, lung, esophagus, colon, connective tissue, melanoma and leukemia. These may be due to common etiology, genetic factors or treatment related. But the case reported here is a breast cancer survivor who developed second malignancy in urinary bladder more than 10 years after treatment for breast cancer. Extensive literature survey has not shown any such association between breast cancer and urinary bladder cancer. These two cancers do not share any common etiological or genetic factor. Guo pei found risk ratios for cancer of urinary bladder comparing female breast cancer patients to the general population as 1.7 in 20 - 49 years age group, 0.8 in 50 - 64 years age group and 0.9 in ≥ 65 years age group. In Pakistan, neither such a case has been reported nor has any such study been done.

Worldwide cancer of urinary bladder is more common in males. In a study done in Pakistan, male female ratio was found to be 14:1. The occurrence of cancer urinary bladder in the case reported here can be explained by its association with treatment factors though it could have happened de Novo as well. The patient was treated with radiotherapy and hormonal treatment in addition to chemotherapy. Radiotherapy was given to chest wall and regional nodes; therefore, it could not play a role in causation of malignancy of urinary bladder although urinary bladder cancer can develop after pelvic radiotherapy. Tamoxifen has no effect on urinary bladder. However, causal link has been shown between chemotherapeutic agents particularly cyclophosphamide and carcinoma of urinary bladder. The case reported was given cyclophosphamide in a dose of 500 mg/m² in each cycle to a total dose of 4500 mg. Although trials have shown association of higher dose of cyclophosphamide in causing cancer of urinary bladder as in case of non-Hodgkin's lymphoma (750 mg/m² for 6 - 8 cycles). The drug has been found to increase the risk of cancer urinary bladder in a dose dependent fashion and the risk increases with radiotherapy. The commonest second malignancy caused by cyclophosphamide is acute leukemia. Several studies have observed that chemotherapy significantly increased the risk of solid malignancies particularly lung cancer.

Other possible risk factors for cancer of urinary bladder in the patient reported were excluded by detailed history. The patient was non-smoker and there was no history of exposure to aromatic amines, aniline dyes, nitrites and phenacetin. There was no history of chronic irritation of urinary bladder caused by catheter, schistosomiasis and pelvic irradiation. Moreover, cancer breast and cancer urinary bladder do not share common genetic factors except p53 tumour suppressor gene but literature survey has not proven such an association between bladder and breast cancers.

Thus the occurrence of cancer urinary bladder with relatively low dose of cyclophosphamide in breast cancer survivor is the first case of its kind. This shows that breast cancer survivors should be strictly followed not only for breast cancer recurrence and commonly occurring second malignancies but also for rare second cancers including cancer urinary bladder. Because of rarity of association of Ca urinary bladder with breast cancer screening tests cannot be recommended but patients should be inquired about common symptoms related to the disease. This will help in early detection and treatment. At the same time health care providers should be aware of the risk of bladder...
cancer among patients who had been treated with cyclophosphamide regimens. Fewer data exist with regard to underlying molecular mechanisms. It would seem logical to be able to prospectively identify patient subgroups that might be at heightened susceptibility of developing therapy associated second cancers.

REFERENCES