Original Article

Serum tumor markers and positron emission tomography-computed tomography scan as post-breast cancer treatment surveillance

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Background: Post-operative surveillance is an important aspect in managing breast cancers. The primary aim is to allow early detection of metachronous breast cancers. However, post-operative breast cancer surveillance has not been standardized. Mammography has been the only evidence-based imaging modality for detecting metachronous breast cancers. The value of regular monitoring with serum carcinoembryonic antigen (CEA) and CA 15-3 has been controversial. The aim of this study is to evaluate the efficacy of using tumor markers as a surveillance tool in post-operative patients.

Methods: This is a retrospective review of all post-breast cancer surgery patients monitored with tumor markers from 2005–2010. Correlation between tumor markers and subsequent detection of metachronous breast cancer was evaluated. Long-term survival data was analyzed.

Results: Six hundred and forty-nine patients underwent positron emission tomography-computed tomography (PET-CT) scan, 250 patients had regular tumor markers monitoring. By using 5 ng/mL as cutoff for CEA, and 23 U/mL for CA 15.3, elevated levels are associated with development of metachronous breast cancer (P=0.004 and P<0.001). The positive predictive values of CEA and CA 15.3 were 61.8% and 64.1% respectively. After median follow-up interval of 8 years after primary operation (range, 2–13 years). There were 93 breast-cancer related mortalities, 47 had elevated tumor marker, 142 patients remained disease free, 27 patients had elevated tumor marker levels. Elevated tumor marker during surveillance is associated with breast-cancer mortality in the current study (P<0.001).

Conclusions: Elevated serum CEA and CA 15-3 is associated with metachronous breast cancer and is associated with adverse long-term survival outcome.

Keywords: Breast neoplasm; tumor marker; recurrence

Introduction

Breast cancer is one of the commonest causes of cancer death in women worldwide (1,2). In Hong Kong, it is the commonest cancer in female population with more than 4,000 new breast cancers diagnosed annually (3). Long-term survival rate of breast cancer has significantly improved over the last 10 years especially when early breast cancers are more frequently detected by screening mammogram and widespread use of adjuvant systemic therapies (4). Surveillance of these long-term survivors is becoming an important aspect in breast cancer management.

It is known that patients with personal history of breast cancer are at risk for metachronous breast cancers, these
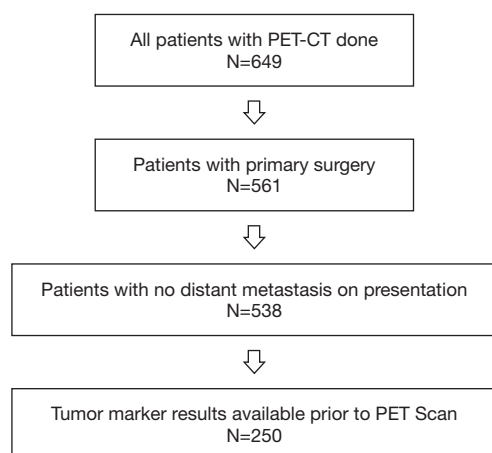
Figure 1 Inclusion criteria of the study.

include recurrence in the ipsilateral breast or a newly developed cancer in the opposite side (2,5,6). Locoregional tumor recurrence rate was reported to range from 5–27%, whereas the risk for development of contralateral breast cancer was reported to be 5–10%, with a two to six-fold increased risk (5,7-11). In fact, recent studies have demonstrated that local recurrence is an independent predictor of survival (11).

As a result, it is important to have a standardized, evidence-based post-treatment surveillance protocol to allow early detection of tumor recurrence. Up till now, mammography has been the only evidence-based imaging modality with demonstrated efficiency for detecting asymptomatic tumor recurrence or a second breast cancer in women who have been treated for primary breast cancer (2,12-18). Ultrasonography (US), magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT) have been utilized in many institutions to increase detection of second cancers at an early stage.

This study is to evaluate the accuracy of detecting metachronous breast cancers (including local or metastatic recurrence) by regular monitoring with carcinoembryonic antigen (CEA) and CA 15-3.

Methods

Institutional board approval and patient consent were obtained for patient data collection. Clinicopathological data collected in a prospective database, of patients undergoing regular postoperative surveillance by tumor markers and PET-CT scan between January 2005 and December 2010 were reviewed. Patients who did not receive surgery, had metastatic disease on presentation and patients with final histopathology other than invasive ductal carcinoma or ductal carcinoma *in situ* (DCIS) were excluded (*Figure 1*).

Post-breast cancer surgery follow-up

Department of Surgery, The University of Hong Kong is currently the largest academic based breast cancer center in Hong Kong. We have developed a standardized protocol to monitor the disease status after breast cancer surgery. This includes yearly mammogram and ultrasound of the breasts and monitoring of CEA and CA 15-3 (MUC-1 mucin glycoproteins) tumor markers on every outpatient visit. PET-CT scan will be arranged for patients with elevated tumor markers (tumor marker levels above normal range). All patients have regular follow up—once every 3 months within 2 years of primary treatment, half-yearly during 3rd to 5th year post-treatment and yearly follow-up subsequently after 5 years.

Definition of abnormal tumour marker levels

CEA and CA 15-3 levels were reported by American College of Pathology accredited laboratory (CAP Accreditation Number 71755-25), CEA <5 ng/mL and CA 15-3 <23 U/mL were used as cut-off values.

PET- CT acquisition protocol

PET-CT scan was performed 60 min after injection of 18F-FDG. Patients were instructed to fast for at least 6 h before injection, except for glucose-free oral hydration. Blood glucose was measured before injection of the tracer to ensure a level lower than 9 mmol/L. The standard injected dose of 18F-FDG was 4–5 MBq/kg. Acquisition was performed after injection in 2-D mode, from skull to upper thigh, with 5–7 bed positions of 4–5 min each. Images were captured with patients in the supine position. Non-contrast-enhanced CT images were acquired with the following parameters: 40 mAs, 140 kV, 5 mm section thickness, 0.8 s per CT rotation, 22.5 mm/s table speed. This acquisition was used for attenuation correction and fusion and also for diagnosis. Immediately after the CT, PET data were collected in a caudocranial direction. The

Table 1 CEA level and PET positivity

	PET positivity (local/systemic recurrence)		Total
	Positive	Negative	
CEA <5 ng/mL	24 (40.7%)	35 (59.3%)	59
CEA ≥5 ng/mL	118 (61.8%)	73 (38.2%)	191
Total	142	108	250

P=0.004. CEA, carcinoembryonic antigen; PET, positron emission tomography.

Table 2 CA 15-3 level and PET positivity

	PET positivity (local/systemic recurrence)		Total
	Positive	Negative	
CA 15-3 <23 U/mL	30 (36.1%)	53 (63.9%)	83
CA 15-3 ≥23 U/mL	107 (64.1%)	60 (35.9%)	167
Total	137	113	250

P<0.001. PET, positron emission tomography.

CT data were resized from a 512 × 512 matrix to a 128 × 128 one to match the PET data and to fuse the images. PET-CT will be considered positive if increased focal FDG update is detected (using liver tissue as normal reference for tissue metabolism).

Correlation between tumor markers and PET-CT findings, as well as long term survival outcomes were analysed by Chi-square test or Fisher-exact test where appropriate.

Results

Six hundred and forty-nine patients underwent PET-CT scan from 2005 to 2010, 561 of them had primary surgery performed for breast cancers, in which 538 were for curative intent (no distant metastasis at the time of diagnosis). One hundred and forty-eight PET-CT scans were done as pre-operative work-up and the remaining 390 patients had PET-CT done after surgery. Two hundred and fifty of them had regular tumor markers monitoring and surveillance in our department (*Figure 1*) and were included in the final analysis.

Median CEA and CA 15-3 levels were 2.2 ng/mL (range, 0.2–1,763 ng/mL) and 16 U/mL (3.9–558 U/mL) respectively. Considering the pre-operative tumor status, the mean clinical tumor size was 30 mm (range, 0–150 mm), 3 (1.2%) patients had DCIS; the others had invasive ductal carcinoma, 55 (22%) patients were node-positive. 164 (65.6%) patients were hormone receptor positive, 65 (26%) patients were hormone receptor negative, and 25 (10%) had unknown hormone receptor status, 70 (28%) patients were HER-2 receptor positive, 158 (63.2%) patients were HER-2 receptor negative and 26 (10.4%) patients had unknown HER-2 receptor status. All patients were treated with standardized breast cancer management protocol using multidisciplinary approach based on the current National Comprehensive Cancer Network (NCCN) Guidelines.

When CEA was ≥5 ng/mL, recurrence (local or systemic) was detected in 61.8% patients on PET-CT scan (P=0.004) and when CA 15-3 was ≥23 U/mL, 64.1% patients had positive PET-CT (P<0.001). The positive predictive values of CEA and CA 15-3 were 61.8% and 64.1% respectively (*Tables 1,2*).

After median follow-up interval of 8 years after primary operation (range, 2–13 years). There were 93 breast-cancer related mortalities, 47 (50.5%) had elevated tumor markers upon follow-up. One hundred and forty-two patients remained disease free, and 27 (19.0%) patients had elevated tumor marker levels. Elevated tumor marker during surveillance is associated with breast-cancer mortality in the current study (P<0.001).

Discussion

Surveillance and monitoring of disease status is an

important part in breast cancer management after primary treatment. The aim of regular cancer surveillance is to identify recurrence at an earlier stage, with the assumption that early management of recurrence will result in better patient outcome. However, there is yet no consensus on the optimal surveillance protocol. Two large prospective randomised trials performed in the early 1990s concluded the use of intensive follow up of asymptomatic patients after primary breast cancer treatment is not associated with improvement in overall survival (19,20). After that, guidelines have been published by the expert panels (1,12,21,22), which recommend the use of clinical follow up with detailed history taking, physical examination and annual mammography only. The use of routine blood tests or tumor markers is discouraged for monitoring patients for recurrence after primary breast cancer therapy due to lack of evidence to support its association with survival and prognosis. Today, monitoring of CA 15-3 and CEA is suggested only by the European Group on Tumor Markers (EGTM) for post-operative surveillance of breast cancer patients. (23,24).

CA 15-3 assay testing MUC-1 mucin (a membrane glycoprotein in epithelium of breast duct) and CEA (a glycoprotein found normally in embryonic entodermal epithelium) are the commonly used serum tumor markers in breast cancer. Their sensitivities have been reported to be highly variable, depending on the cut-off values in different studies. The reported sensitivity of single tumor marker was between 7% and 70% for CEA and between 32% and 90% for CA 15-3 (25-28), while their combination can increase the sensitivity (25,28). The addition of other tumor markers such as tissue polypeptide antigen (TPA) and the mucin-like carcinoma-associated antigens can further increase the sensitivity in detecting cancer recurrence to around 90% (25,27). In our center, we routinely monitor CEA and CA 15-3 during the first 5 years after primary breast cancer therapy. When the trend of one or both tumor markers show a persistent rise (two readings higher than normal range, 1 month apart), metastatic workup such as PET-CT scan will be performed and patient will be managed accordingly.

However, as the cutoff value of tumor markers influences the sensitivity of the test, some researchers introduce the concept of individual reference limit in the interpretation of tumor markers (27,29). To our knowledge, there is no standardized method in the calculation of individual baseline so far. Di Gioia *et al.* (29) defined it as the mean value of the first three tumor marker measurements, measured at least

4 weeks after the end of adjuvant therapy and 6 weeks apart. Nicolini *et al.* (27), on the other hand, took into account the mean and standard deviation of the first five consecutive monthly measurements. This should be an area which will require further evaluation in large-scale study.

The use of serial tumor marker measurement in the early detection of recurrent or metastatic disease is based on the finding that increasing levels of serum tumor markers often precede clinical or radiological signs of disease recurrence (29-31). Incoronato *et al.* (30) studied the correlation between serial tumor markers measurements and findings of PET-CT. An increase in tumor markers 3–6 months before PET-CT could already identify patients at risk of cancer relapse. This lead-time was reported to be between 2 and 18 months in the literature (30,31). However whether earlier detection of recurrence could be extrapolated into survival benefit is still controversial. On the contrary to the two large randomised trial published in the 1990s (19,20), Nicolini *et al.* (32) compared the survival between tumor marker guided salvage treatment and those treated after radiological confirmation of disease recurrence. Tumor marker guided salvage treatment significantly prolonged the disease-free and overall survival. With the increasing use of PET-CT scan, and newer imaging modalities such as whole body MRI, PET-MRI which is more sensitive compared to conventional imaging such as CT Scans and ultrasound, further study will be needed to re-evaluate their use in conjunction with serial tumor marker monitoring in surveillance after primary breast cancer treatment.

Our study demonstrated statistically significant association between raised tumor markers and subsequent development of metachronous breast cancer. And this has in turn found to be associated with adverse long-term survival outcome. Monitoring of serum tumor markers is non-invasive and is relatively inexpensive. Based on the findings from this cohort, adding tumor markers onto routine post-operative surveillance will improve early detection of metachronous tumor. PET-CT scan can be reserved to patients with clinical suspicion or with elevated tumor markers. Nevertheless, whether earlier detection of asymptomatic recurrent disease is associated with improved breast cancer survival will require further investigations.

Conclusions

Elevated serum CEA and CA 15-3 is associated with metachronous breast cancer and is associated with adverse long-term survival outcome. As such, we recommend

regular tumour marker monitoring (with clinical examination and breast imagings) in patients operated for breast cancers until newer biomarkers with higher sensitivity are available.

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional board approval and patient consent were obtained for patient data collection.

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