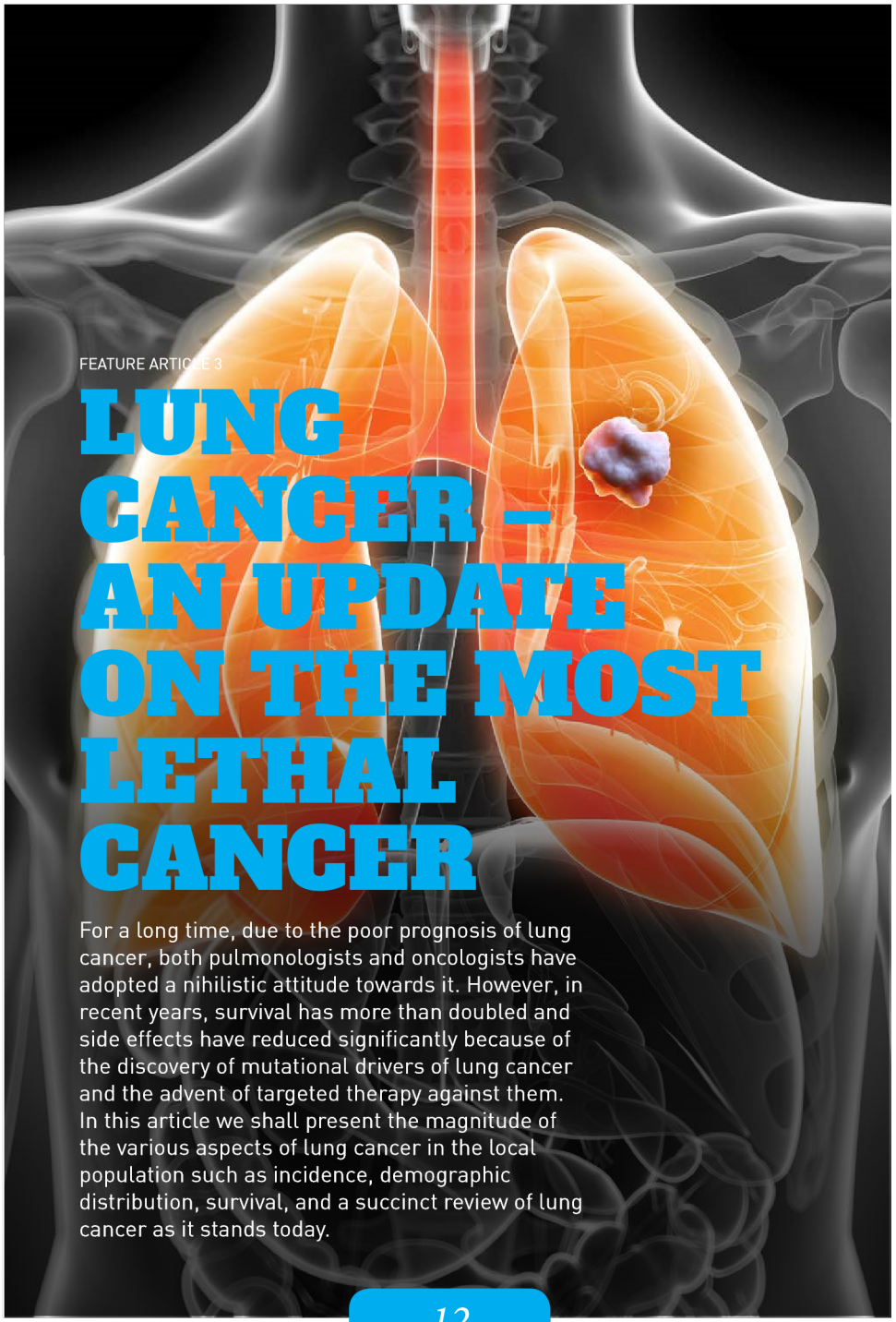

FEATURE ARTICLE 3

LUNG CANCER – AN UPDATE ON THE MOST LETHAL CANCER

For a long time, due to the poor prognosis of lung cancer, both pulmonologists and oncologists have adopted a nihilistic attitude towards it. However, in recent years, survival has more than doubled and side effects have reduced significantly because of the discovery of mutational drivers of lung cancer and the advent of targeted therapy against them. In this article we shall present the magnitude of the various aspects of lung cancer in the local population such as incidence, demographic distribution, survival, and a succinct review of lung cancer as it stands today.

Statistics of Lung Cancer

Lung cancer kills more people than the other four most common cancers (breast, colon, pancreas and prostate) combined.[1] It is the second most common cancer after prostate cancer in men, and breast cancer in women. Approximately 1500 people are diagnosed with lung cancer every year in Singapore.[2] Adenocarcinoma is the most common sub-type, affecting 43.5% of patients with lung cancer.[3] Women affected are more frequently diagnosed with adenocarcinoma (43% of all lung cancer subtypes) than men (21%), and the age of onset of adenocarcinoma can be as early as 31 years.[3] Approximately 32% of all lung cancer patients and 55% of patients with adenocarcinoma sub-type are non-smokers, dispelling the notion that only smokers are at risk.[3] The right and left upper lobes are the most affected sites, leading to the frequent misdiagnosis of tuberculosis. Eighty-two percent of patients present with central lesion adjacent to the large airways either in the form of parenchymal lesion located next to the airways, mediastinal lymph node, or mediastinal infiltration.[3] Thirty-two percent of patients with adenocarcinoma carry activating epidermal growth factor receptor (EGFR) mutation. Most patients (68%) present in advanced stage, and median survival among all cancer sub-types locally in advanced lung cancer is 122 days.[3]

Diagnosis

Chest radiographs can only pick up early-stage cancer if the lesion is more than 1 cm in size; anything smaller is missed. Chest radiography is limited in that it fails to diagnose early cancer when there is potential cure with resection (figure 1). Computed tomography (CT) is needed in each and every patient to guide the choice of modality for tissue diagnosis. On CT, lung cancer manifests in five radiological patterns: peripheral nodule or mass, discreet mediastinal lymph node, mediastinal infiltration, endobronchial lesion with distal lung atelectasis, and pleural effusion (figure 2).[4] In order to confirm the diagnosis, a tissue sample is needed. This is best obtained by transthoracic needle aspiration (TTNA) or navigation bronchoscopy for peripheral lesions, convex probe endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS-TBNA) for discreet mediastinal lymph node or mediastinal infiltration, bronchial biopsy for endobronchial lesion, and pleural tap followed by thoracoscopic biopsy for pleural effusion (figure 3). TTNA entails passing the biopsy needle percutaneously through the chest wall, into the lesion in the lung under CT guidance. Although TTNA is associated with a 24-40% risk of pneumothorax, the detection rate is close to 90%.[4] EBUS-TBNA is a technique that uses a bronchoscope fitted with an ultrasound probe at its tip to visualise structures outside the trachea and bronchi. When the ultrasonic bronchoscope is connected to the processor, it is possible to view the sonographic images of the structures outside the airways or inside the mediastinum. This enables biopsy of mediastinal or hilar lesions under real-time ultrasonographic image guidance. The diagnosis detection rate of EBUS-TBNA for such

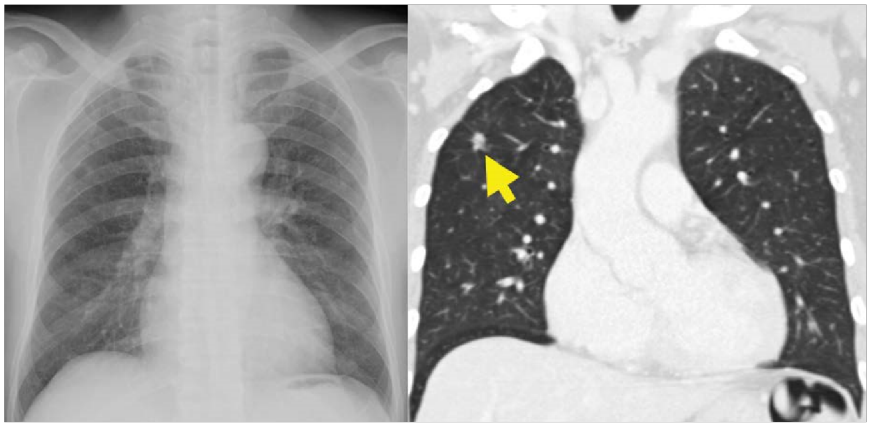

Figure 1. The right upper lobe pulmonary nodule (1 cm in size) is not visible on the radiograph (left) and only seen in the CT scan (right).

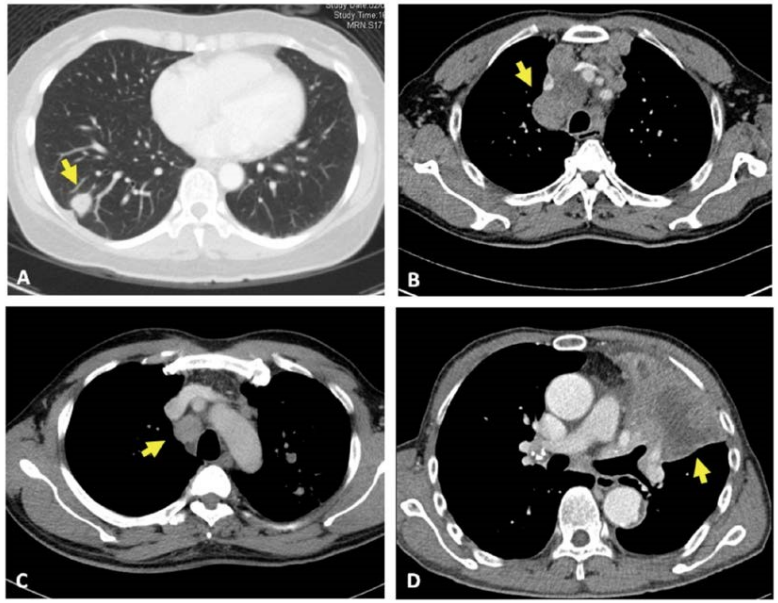

Figure 2. Common radiological patterns of lung cancer on CT scan. A: peripheral nodule or mass; B: discreet mediastinal lymph node; C: mediastinal infiltration; and D: endobronchial lesion with distal lung atelectasis.

lesions is close to 80%.[3] The historical alternative to EBUS-TBNA had been mediastinoscopy, but it is more invasive, requires an incision in the neck, and requires general anaesthesia. However, EBUS-TBNA can be performed via the trans-oral route under moderate sedation. The detection rate of bronchoscopic biopsy for endobronchially visible lesions is close to 70%, and for pleural tap, and thoracoscopic biopsy in cases of pleural effusion is 50% and 98% respectively.[5]

Surgical resection

Since surgical resection carries the highest chance of survival, this is the most important form of therapy. Lung cancer in stages I and II, and in some cases stage III (IIIA) are resectable, whereas stages IIIB and IV are not. Staging is determined in two ways. Some physicians prefer to perform a CT scan of the brain, abdomen and pelvis, and a bone scan, whereas others prefer a brain MRI and a PET scan (figure 4). Brain MRI and PET scan are more accurate and is the preferred strategy, but a PET scan is more expensive (~SGD1600) than a bone scan.[6] Any deposit outside the chest, in the contralateral lung, or pleural effusion renders the cancer stage IV.

Feasibility of surgical resection

Some patients, despite early stage lung cancer, are not physically fit to endure removal of a part of or the whole lung, especially if they have COPD and poor lung function from smoking. FEV1 and DLCO below 60% of predicted carry an increased risk from surgery. In addition, patients with poor heart function or advanced age are also contraindicated for surgical resection. Patients unfit for surgery are treated with radiation therapy, specifically stereotactic body radiation therapy. However, best supportive care or palliative care is not the only option left for the advanced stage cancer patients.

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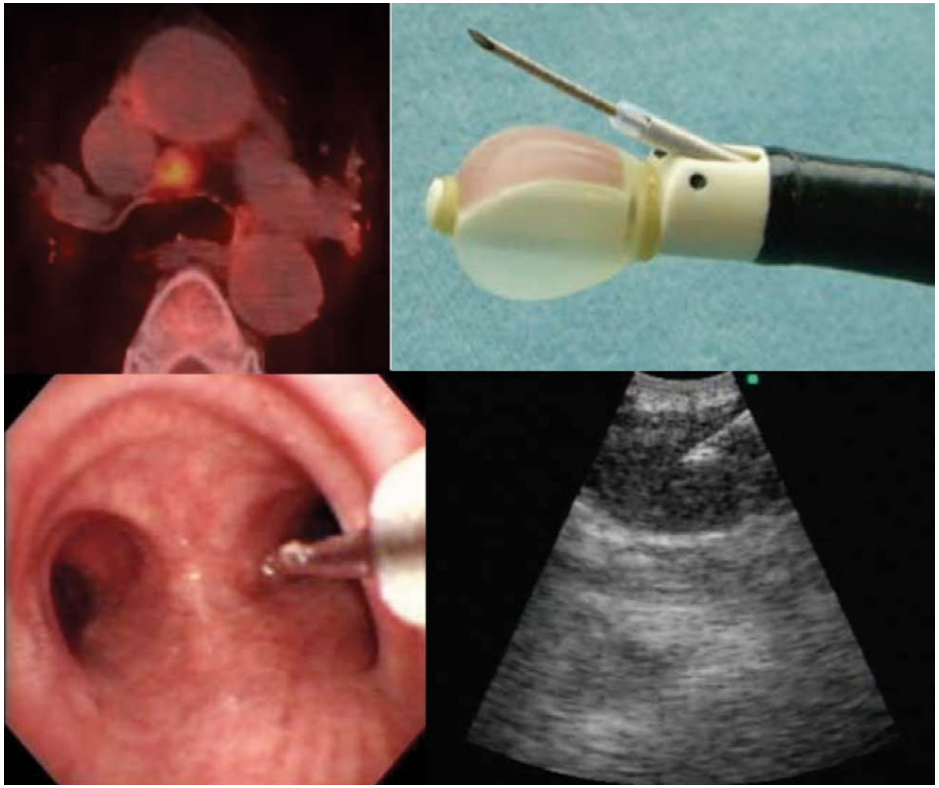

Figure 3. Convex Probe EBUS-TBNA, showing, clockwise from upper left, the lesion on CT scan, the tip of the probe, the passage of the probe into the bronchus and the ultrasound image.

Targeted Therapy

Median survival in "untreated" advanced lung cancer is 4-5 months, and 10% survive more than a year.[7] Platinum-based doublet chemotherapy has been the mainstay of treatment of advanced lung cancer in the last four decades but response rates and survival have remained dismal and largely unchanged from 13% in 1975 to 16% thirty years later in 2003.[7] Median survival in advanced lung cancer treated with platinum-based doublet chemotherapy is 8-12 months, and 33% survive more than a year.

However, over the last decade, there are new insights into the molecular pathogenesis of lung cancer. Lung cancer is more diverse at a molecular level than is apparent on histological appearance. The histological description of adenocarcinoma, for example, may encompass close to 10 different types of lung cancer from the genomic aberration point of view, each requiring a potentially different therapeutic agent (figure 5). This is in complete contrast with the historical practice of treating all adenocarcinoma patients with the same platinum-based doublet chemotherapy indiscriminately.

The identification of several activating mutations driving lung cancer, such as EGFR, ALK and ROS1, has significantly changed the outcome of lung cancer. The resulting emergence of therapy targeted at blocking the carcinogenic pathways activated by these mutations has proven to be twice as effective as standard chemotherapy.[8,9] Median survival in advanced lung cancer treated with EGFR-TKIs is 22 months and about 53% survive more than a year.[10] Targeted therapy carries minimal side effects (such as acne and diarrhoea) and can be administered orally, in contrast to conventional chemotherapy which is relatively more toxic and requires in-

hospital drug administration. Most therapeutic benefit has so far been seen in patients with "adenocarcinoma", which, anyway, affects the majority of patients. The striking success in treating adenocarcinoma has provided the impetus to harness similar benefits in squamous cell and small-cell carcinoma sub-types of lung cancer as well. In addition to targeted therapy, immunotherapy, which makes use of the patient's immune system to inhibit proliferation of lung cancer cells, is emerging as another option. Although limited to clinical trials currently, it carries significant promise.

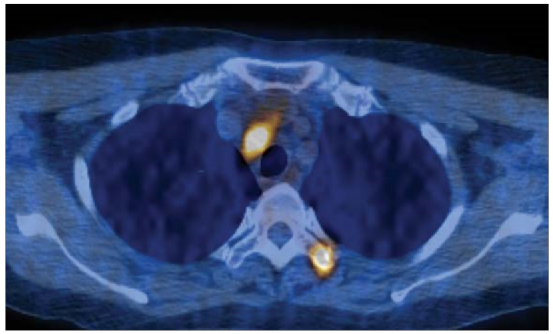

Figure 4. An example of a PET scan showing two lesions.

In conclusion, the long-standing nihilism surrounding lung cancer is fading. Better understanding of the molecular profile of lung cancer and of the role of the immune system is making novel therapies available. It is hence necessary for doctors treating lung cancer to stay abreast of new developments to provide updated treatment strategies to patients.

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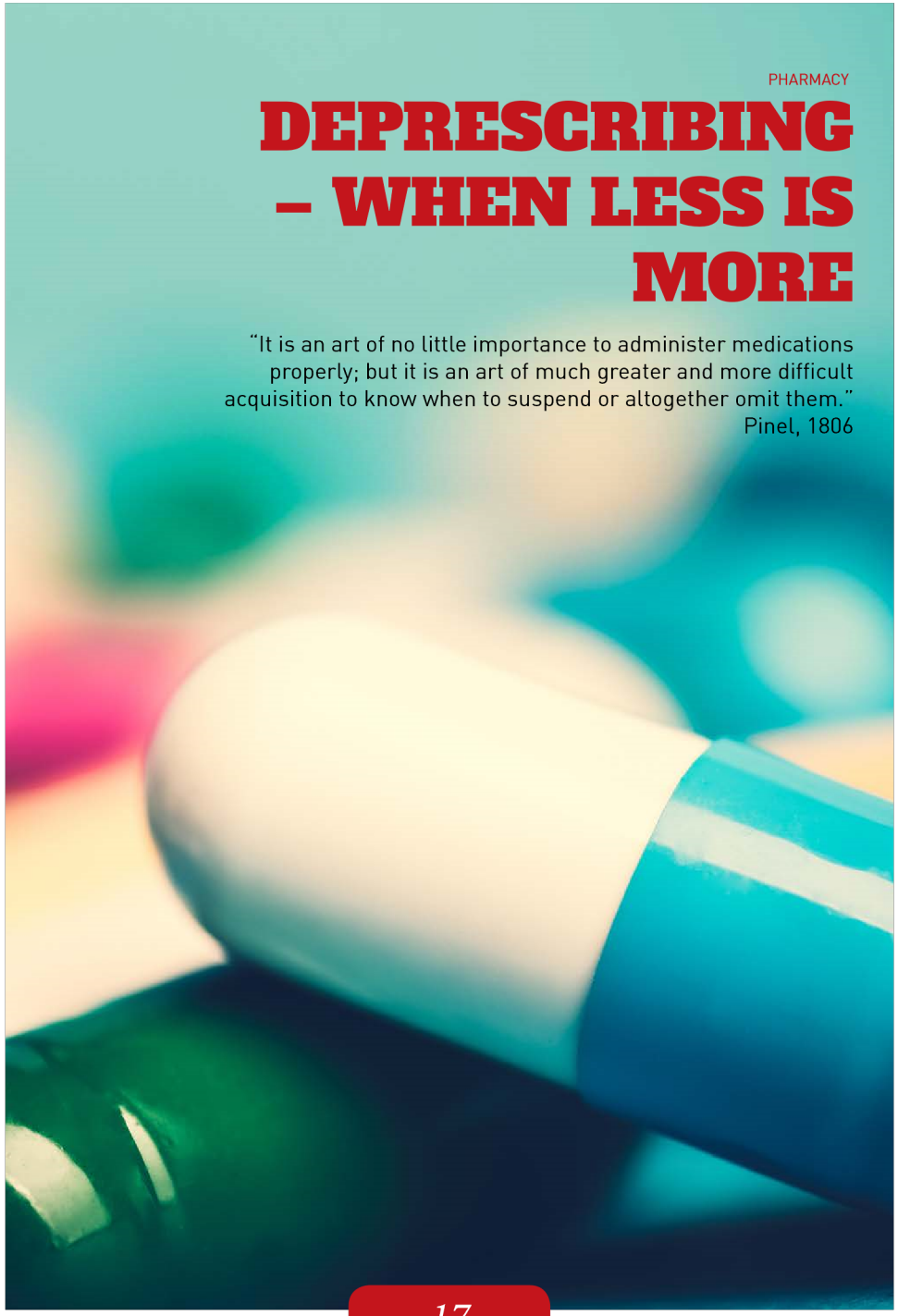

PHARMACY

DEPRESCRIBING – WHEN LESS IS MORE

"It is an art of no little importance to administer medications properly; but it is an art of much greater and more difficult acquisition to know when to suspend or altogether omit them."
Pinel, 1806