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REVIEW

Staging of non-small cell lung cancer (NSCLC): A review

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Summary
Lung cancer remains the most common cause of cancer-related mortality in Scotland, accounting for 28.9% of all cancer deaths in 2007.[1] Current guidelines recommend assessment of patient fitness and operability by a multi-disciplinary team when selecting management options.[2–6] Two of the most important prognostic markers are the stage of disease and ECOG performance status.

The most commonly used cancer staging system is the tumour, node, metastasis (TNM) staging system, which is maintained by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). In 1998, the International Association for the Study of Lung Cancer (IASLC) established The Lung Cancer Staging Project, collecting data on over 100,000 patients diagnosed with lung cancer between 1990–2000 worldwide, in order to revise the 6th edition TNM staging system for non-small cell lung cancer (NSCLC).[7] The 7th edition was published in late 2009.

This review of staging in NSCLC, includes a summary of the different staging techniques currently available and the 7th edition TNM staging system for NSCLC.[8]

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Staging

Lung cancer staging is the process by which the extent of the primary tumour and the extent of tumour spread within the body are established. The TNM staging system guides patient management, provides information regarding prognosis and eligibility for clinical trials, and allows international comparisons. TNM staging is based on the characteristics of the primary tumour (T), the degree of lymph node involvement (N) and the presence or absence of metastasis (M).[9,10]

The combination of T, N and M descriptors are then used to give the tumour an overall stage (I—IV), with the aim of grouping patients into stages with similar prognoses. Treatment options also vary from stage to stage.

There are two predominant types of staging for NSCLC[11]:

1. Clinical staging, 'cTNM'
2. Pathological stage, 'pTNM'

Clinical staging

Clinical staging is based upon careful history-taking and physical examination, in conjunction with laboratory, radiological and bronchoscopic findings before recommending primary therapy.

History and clinical examination

Patient history and clinical examination are used to elucidate features suspicious of locally advanced or metastatic disease, as well as determining patient fitness and comorbid disease, which may impact upon treatment options. Patients often present with multiple symptoms, both respiratory and constitutional. The most common presenting symptom is cough, accounting for up to 75% of all presentations.[12] A meta-analysis by Toloza et al[13] assessing the accuracy of clinical detection of brain, abdominal and skeletal metastases using history, clinical examination and blood investigations revealed a 0.94, 0.95 and 0.90 negative predictive value (NPV) respectively.

Radiological investigations

Chest radiography (CXR)

All patients being evaluated for lung cancer should have a plain chest X-ray performed to provide a baseline for future comparison. It may also reveal features that indicate disease stage, including pulmonary nodules, pleural effusion, rib destruction (direct or metastatic) or an elevated hemidiaphragm indicating involvement of the phrenic nerve, and thus locally advanced disease.

Computed tomography (CT)

Contrast-enhanced CT scan visualising from the base of the neck to below the adrenal glands should be performed in all patients being investigated for lung cancer.[6] CT can determine tumour size, mediastinal and vascular invasion, and suggest lymph node involvement. It can also determine the presence of distant metastases and estimate the proximal extent of the tumour within the airways. CT can provide important anatomical information in patients being considered for surgical resection.

Limitations of CT scanning in the staging of NSCLC include its limited reliability in differentiating between benign and malignant mediastinal lymph node enlargement, and its inability to detect microscopic nodal and metastatic disease. Suspicion of lymph node metastasis on CT can be correlated with nodal size, tumour enhancement and tumour appearance. A short-axis diameter of $>$10 mm on CT assessment of mediastinal lymph nodes is considered suspicious of malignancy, with a resulting sensitivity of 57—70% and a specificity of 59—82%.[13—16] Malignant nodes typically show similar attenuation to surrounding mediastinal blood vessels and exhibit little or no evidence of calcification. In addition, appearances of a solid or spiculated primary mass in comparison to a ground glass opacity, or peak enhancement $>$110 Houndsfield Units (HU) and net enhancement

>60—70 HU on dynamic CT is considered to indicate a greater likelihood of lymph node metastasis.[17,18] Thus, CT remains a valuable tool for evaluating the T and M descriptors but is relatively poor at evaluating the N descriptor in NSCLC, and in the majority has been superseded by newer imaging techniques such as PET-CT and minimally invasive sampling techniques such as Endobronchial ultrasound guided FNA (EBUS).

Integrated positron emission tomography-computed tomography (PET-CT)

Occult disease can be detected by the use of integrated PET-CT using the tracer ^{18}Fluoro-Deoxy-Glucose (FDG). Lung cancer cells have high metabolic activity and therefore increased glycolysis, hexokinase activity and expression of glucose transporter-1 receptors compared with surrounding normal cells. This results in increased uptake of FDG in cancer cells. PET-CT is used to confirm staging, detecting metabolically active intrathoracic lymph nodes, including those of normal size (<8 mm on PET-CT) and any occult distant metastatic disease, thereby potentially avoiding futile thoracotomy.

The PLUS trial,[19] a multi-centre randomised controlled trial (RCT) comparing conventional work-up with conventional work-up plus PET found that the additional use of PET-CT reduced futile thoracotomy rates by 20%. Meta-analyses have shown that FDG-PET is more sensitive than CT scanning for the detection of mediastinal disease, with sensitivities of 85% using PET in comparison to 61% using CT scanning.[20] A further study found that integrated PET-CT provided a sensitive (98% sensitivity, in comparison with 86% with CT scanning alone and 94% with PET scanning alone) although not specific (44% specificity) means of detecting mediastinal lymph node involvement in NSCLC.[21]

PET scanning should not be used on its own as it provides inadequate information on the anatomic location of increased FDG uptake. The integrated use of PET-CT combines metabolic and morphologic data, allowing anatomical localisation of disease. False positives can arise from increased FDG uptake secondary to inflammation, infection or infarction. False negatives do occur and consequently current guidelines recommend the use of invasive staging to confirm radiographic stage in patients with discrete nodal enlargement (>10 mm on PET-CT) or a centrally located tumour, regardless of PET-CT result.[22] PET-CT has limited use in the detection of brain metastases as normal brain tissue relies on glucose metabolism and therefore has physiologically high levels of FDG uptake. Lesions with increased FDG uptake should be biopsied as use of PET-CT will result in an up-staging of 15—20% of patients in comparison to CT scanning alone; it is therefore important to exclude false positive PET-CT results given the impact that this would have on patient treatment.[23]

Radionuclide bone scintigraphy

Bone scintigraphy is used to detect bone metastases in the staging of patients with NSCLC. A retrospective study by Cheran et al.[24] in 2004 compared the accuracy of bone scintigraphy with PET scanning in the detection of bone metastases in lung cancer. The study included 257 patients with a new diagnosis of lung cancer undergoing PET and bone scan. It found that PET scanning had a higher sensitivity and specificity than bone scintigraphy for the detection of bone metastases (91% vs. 75% and 96% vs. 95% respectively), and a higher overall accuracy (95% vs. 90%), suggesting that PET-CT may in the future replace bone scintigraphy as the principal modality for detecting bone metastases in lung cancer. Significant problems with bone scintigraphy include false positives (e.g. in osteoporosis) and false negatives (when the metastatic deposits are highly lytic).

Magnetic resonance imaging (MRI)

MRI scanning may be used in conjunction with CT scanning to detect chest wall or mediastinal invasion or transdiaphragmatic spread of the tumour. Limitations in assessing lung lesions lie in its sensitivity to artefact created by respiration. However, a 2008 study of 165 patients[25] comparing efficacy of PET-CT and whole body MRI in the staging of NSCLC found similar rates for assessing T descriptor (82% vs. 86% accuracy respectively), N descriptor (70% vs. 68% respectively) and M descriptor (86% vs. 86% respectively). MRI is the most effective modality for detecting brain and hepatic metastases.[25]

Laboratory investigations

Laboratory investigations are used principally to identify abnormalities resulting from metastatic disease, although some tests are known to be useful as independent prognostic markers, including C-reactive protein (CRP), albumin and lactate dehydrogenase (LDH).[26—29]

Pathological staging

Some controversy exists about the definition of pathological staging. Some believe that pathological stage can only be established after complete surgical exploration of the hemithorax and mediastinum. Others accept that pathological stage is based upon histological findings that will establish highest stage of disease. Tissue sampling provides histopathologic data, allowing confirmation of the diagnosis. Some methods of obtaining tissue also allow for assessment of tumour extent within the airways and mediastinum.

Invasive staging

There are a number of different tissue sampling modalities available. The choice of invasive test depends on the reliability of the test, size and location of the primary tumour and suspicious lymph nodes, extent of distant disease, test availability and patient comorbid disease. Current guidelines[21] recommend that invasive confirmation of clinical stage is required for patients with discrete mediastinal lymph node enlargement, patients with a central tumour or N1 lymph node enlargement on imaging and those with a left upper lobe primary tumour.

Currently available tissue sampling modalities include:

1. Flexible bronchoscopy.

   Flexible bronchoscopy has a different yield for obtaining a diagnostic specimen depending on the sampling technique used and the location of the primary tumour. Sampling techniques utilised include

endobronchial biopsy, bronchial brushing and bronchial washing, which have a sensitivity of 74%, 59% and 48% respectively in endobronchial disease. For peripheral lesions, brushing has a sensitivity of 52%, transbronchial biopsy has a sensitivity of 46% and bronchoalveolar lavage (BAL) has a sensitivity of 43%.[30] Flexible bronchoscopy has a better yield for obtaining a diagnostic specimen in patients with a central tumour in comparison to patients with peripheral tumours

2. Blind transbronchial fine needle aspiration (TBNA).

   TBNA is used most frequently to biopsy subcarinal nodes (station 7). It has an overall sensitivity of 78% and a false negative rate of approximately 28%.[22] This relatively high false negative rate means that additional confirmatory staging procedures are recommended following a negative TBNA result
3. Endobronchial ultrasound (EBUS) − guided biopsy.

   High mediastinal, upper and lower paratracheal, subcarinal and hilar lymph nodes (stations 1−4, 7, 10 and 11) are accessible using EBUS. It has an overall sensitivity of 90% and a false negative rate of 24%[22] EBUS-guided biopsy is being utilised with increasing frequency in mediastinal staging. When compared to blind TBNA, EBUS-guided biopsy has a high sensitivity and negative predictive value in diagnosing mediastinal metastasis (76−78% sensitivity, 71−72% NPV versus 90% sensitivity, 76% NPV). It also has a relatively good performance in comparison to cervical mediastinoscopy, which has 78−81% sensitivity, 91% NPV. EBUS has the advantage over mediastinoscopy in that it is a less invasive procedure, does not require a general anaesthetic and as a result has a lower morbidity and mortality rate associated. However, there remains limited access to EBUS in the UK.
4. CT/US-guided percutaneous needle biopsy

   Transthoracic needle biopsy has an overall sensitivity of approximately 90%.[22]
5. Mediastinoscopy

   Mediastinoscopy has long been regarded the gold standard for assessing disease in enlarged mediastinal lymph nodes.[22] It is performed under general anaesthetic, usually as a day case. Mediastinal lymph nodes are accessed via an incision just superior to the suprasternal notch, using a mediastinoscope. This technique has an average sensitivity of 80% and a false negative rate of approximately 10%. Approximately half of these false negatives resulted from disease in nodal stations inaccessible to mediastinoscopy: posterior subcarinal (station 7), inferior mediastinal (stations 8 and 9), aortopulmonary window (station 5) and anterior mediastinal nodes (station 6).
6. Video-assisted thoracic surgery (VATS) or thoracoscopy

   VATS is usually done under general anaesthetic and assessment is generally limited to one side of the mediastinum, with easier access to right-sided lymph nodes. It is predominantly used to assess pleural effusions but can also be used to assess aortopulmonary (AP) window nodes and its use has resulted in a reduction in the use of left anterior mediastinotomies. VATS has a sensitivity of 50−100% in patients with enlargement of discrete mediastinal nodes, and a false negative rate of 15%.[22] There are a growing number of units in the UK where thoracoscopy is performed by Respiratory Physicians. It is performed under conscious sedation and has the advantage in that biopsies are done with direct visualisation, and as a result has a higher diagnostic yield in staging of the mediastinum and pleural space than more traditional sampling techniques of blind needle biopsy and fluid cytology (sensitivities of 95%, 44% and 62% respectively).[31,32]
7. Thoracocentesis in pleural effusions

   Aspiration and cytological examination of pleural fluid in patients presenting with suspected malignant pleural effusion provides a diagnostic yield of approximately 60%.[30] One study demonstrated a diagnostic rate of 44% with blind (Abrams) biopsy, rising to 74% when combined with pleural fluid cytology, however, in this study the diagnostic rate from medical thoracoscopy was 95%[32] and it is because of this increased diagnostic difference that many clinicians favour a thoracoscopic approach.
8. Anterior mediastinotomy (Chamberlain procedure)

   Left upper lobe primary tumours have a predilection for metastasising to AP window nodes (station 5). Anterior mediastinotomy can be used to assess these nodes via an incision in the second or third intercostal space. When used in conjunction with cervical mediastinoscopy, it has an overall sensitivity of 87% and a false negative rate of approximately 10% for assessing mediastinal lymph node disease.[22]
9. Oesophageal endoscopic ultrasound with needle aspiration (EUS)

   This technique is limited by its poor access to high and low paratracheal nodes (nodal stations 2R, 2L, 4R and 4L), which are the nodes most commonly involved in NSCLC. However it is useful in assessing the nodal stations inaccessible to EBUS (nodal stations 8 and 9). It has an overall sensitivity of 84% with a false negative rate of 19%.[22]
10. Resection with systematic nodal dissection

    Goldstraw et al.[33] conducted a study evaluating 227 patients who underwent pulmonary resection with systematic nodal dissection. All patients had a clinical stage of cT1-3, cN0-1 following CT, bone scan and, if lymph nodes were found to be $>$1.5 cm on CT, cervical mediastinoscopy. N2 disease was found in 18% of patients who subsequently underwent resection with systematic nodal dissection, highlighting the importance of systematic nodal dissection, at time of resection, for accurate staging of NSCLC. At present, all cases of NSCLC undergoing surgical management should undergo systematic nodal dissection.

TNM staging: the 7th edition

The 7th edition TNM classification of NSCLC has recently been published.[34] It follows findings from The Lung Cancer Staging Project established in 1998 by the IASLC.[8,35,36] The new edition aims to provide a more accurate correlation between TNM stage and statistical survival data for all patients with lung cancer than the 6th edition.

A retrospective analysis of a database of 100,869 patients with primary lung cancer, treated by all modalities, ranging

from surgical resection to supportive care alone, from 46 institutions in over 19 countries, between 1990 and 2000 was conducted. Of the 100,869 cases collected in the database, 81,015 were included in the study. A number were excluded due to unknown histology, not being a new diagnosis at point of registration or because there was inadequate information on the stage, treatment modality or follow-up of the patient. Of the cases included in the study, 67,725 were NSCLC and 13,290 were small cell lung cancers (SCLC). Patients were followed up for five-years and survival was measured from the date of diagnosis. Following analysis of the survival data, a number of changes were recommended to the TNM staging of lung cancer.

Changes to T descriptor

The study found significant differences in the five-year survival of patients with a tumour diameter of 2 cm (53%), 3 cm (47%), 5 cm (43%), 7 cm (36%) and >7 cm (26%) and recommended the addition of these tumour size cut-offs to the T descriptor, further delineating the T stage into T1a/T1b and T2a/T2b depending on the size of the primary tumour. Tumours >7 cm in diameter were found to have a comparable five-year survival to patients with invasion to the chest wall or mediastinal tumour and were thus up-staged to T3. It was also recommended that patients with satellite nodules in the same lobe as the primary tumour were down-staged from T4 to T3 due to comparable survival rates with T3 tumours (28% 5-year survival). Patients with metastatic nodules in a different lobe of the ipsilateral lung were down-staged from M1 to T4, given their relatively better survival rate than those with M1 disease but worse survival than those with T3 disease.[37]

The N descriptor

No recommendations were made for changes to the N descriptor following this study. The IASLC has however, since proposed the incorporation of the fourteen regional lymph node stations[38] into six nodal zones to resolve differences between the Naruke map,[39] used largely in Asia, and the 'Mountain-Dresler' modification of the American Thoracic Society map (MD-ATS)[40] used largely in Northern America and to a lesser extent Europe. Creating a universally accepted lymph node map will allow easier comparison of survival data between institutions and easier design and analysis of future clinical trials in the future.

The proposed nodal zones are:

1. Upper-nodal stations 1–4
2. Aortopulmonary-nodal stations 5 and 6
3. Subcarinal-nodal station 7
4. Lower-nodal stations 8 and 9
5. Hilar-nodal stations 10 and 11
6. Peripheral-nodal stations 12–14

The IASLC Lung Cancer Staging Project found differences in survival based upon the number of nodal zones involved within each N descriptor.[36,41] For example, patients with any T and M0 disease had a reduced median survival time if they had multiple N1 nodal zone involvement (31 months) versus single N1 nodal zone involvement (52 months).[36,42] Similar differences are seen for N2 nodal zones, however, the number of cases studied were too low to reach statistical significance. Although no changes were made to the N descriptor in the 7th edition, it is important to bear in mind the significance of the number of nodal stations involved when considering patient prognosis.

The M descriptor

Patients with malignant pleural effusions were up-staged from T4 to M1 following the finding of a comparably worse median survival time for patients with a malignant effusion (8 months) in comparison to patients with other aspects of a T4 tumour (13 months). The M descriptor has been further divided into M1a and M1b for intrathoracic and distant spread respectively, following the finding of a significant difference in the survival rates of patients with distant metastasis to patients with pleural involvement or metastasis to the contralateral lung, 1%, 6% and 3% 5-year survival respectively.[43]

Stage groupings

Following the alterations to the TNM descriptors, changes to the stage groupings were also recommended, based on comparative survival rates for each TNM subset (Fig. 1 and Tables 1 and 2).

Limitations of the 7th edition include the non-representation of Africa, South America and the Indian Subcontinent and the under-representation of Russia, China and Indonesia. In addition, the time period that was studied largely predated the widespread use of PET-CT scanning and the current widespread use of PET-CT for staging is likely to make a significant impact on staging results for future revisions.

Staging of small cell lung cancer (SCLC)

Approximately 15% of all lung cancers are small cell. Previously SCLC has been classified as limited disease or extensive disease, with tumour burden, including nodal metastases, confined to one hemithorax constituting limited disease. All other patients were classified as having extensive disease.[23,44] However, the IASLC group analysed 349 cases of SCLC, which had been surgically resected, and therefore had

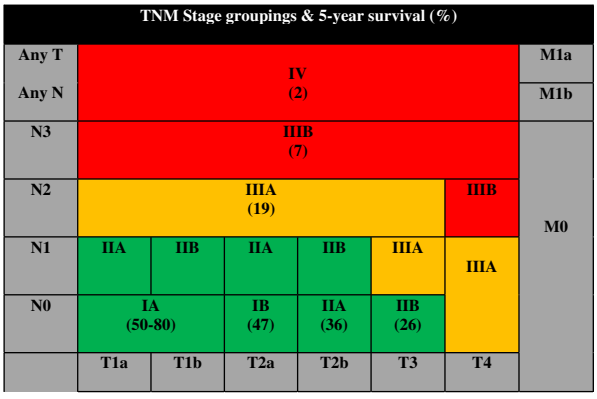

Figure 1 TNM and stage grouping – 7th edition.

Table 1 TNM staging of NSCLC 7th edition.[35]

Primary tumour (T)

- T1 — Tumour ≤3 cm in diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus.
- T1a — Tumour ≤2 cm in diameter.
- T1b — Tumour >2 cm but ≤3 cm in diameter.
- T2 — Tumour >3 cm but ≤7 cm in diameter, or tumour with any of the following features:
  - Involvement of the main bronchus ≥2 cm distal to the carina.
  - Invasion of visceral pleura.
  - Associated atelectasis or obstructive pneumonitis that does not involve the entire lung.
- T2a — Tumour ≤5 cm in diameter.
- T2b — Tumour >5 cm but ≤7 cm in diameter.
- T3 — Tumour >7 cm in diameter, or tumour with any of the following features:
  - Direct invasion of the chest wall, diaphragm, phrenic nerve.
  - Direct invasion of mediastinal pleura or parietal pericardium.
  - Associated atelectasis or obstructive pneumonitis of the entire lung.
  - Tumour within the main bronchus <2 cm to the carina, without involvement of the carina.
  - Satellite tumour nodules in the same lobe.
- T4 — Tumour of any size that has any of the following features:
  - Invasion of the mediastinum.
  - Invasion the heart or great vessels.
  - Invasion of the trachea, oesophagus or recurrent laryngeal nerve.
  - Invasion of a vertebral body or carina.
  - Separate tumour nodules in a different ipsilateral lobe.

Regional lymph nodes (N)

- N0 — No regional lymph node metastasis.
- N1 — Involvement of ipsilateral hilar or peri-bronchial nodes.
- N2 — Involvement of ipsilateral mediastinal or subcarinal nodes.
- N3 — Involvement of contralateral mediastinal or hilar nodes, OR involvement of ipsilateral/contralateral scalene or supraclavicular nodes.

Distant Metastasis (M)

- M0 — No distant metastasis.
- M1 — Distant metastasis present.
- M1a — Separate tumour nodule(s) in a contralateral lobe or tumour with pleural nodules or malignant pleural/pericardial effusion.
- M1b — Distant metastases.

a pathological TNM staging information.[45] They found a correlation between TNM stage and survival rates, in particular, nodal status appeared to have the strongest correlation with disease survival. As a result, they have proposed the usage of the revised TNM system in the staging of SCLC in place of the historical limited or extensive disease stage. Despite this recommendation, the TNM system is still not being as widely adopted for the staging of SCLC compared to NSCLC.

Table 2 Stage Grouping — cTNM subsets 7th edition.[8]

Stage	cTNM Subset	Five-year Survival
0	Carcinoma in situ	
IA	T1a/T1b, N0M0	50—80%
IB	T2aN0M0	47%
IIA	T1a/T1b, N1M0	36%
	T2aN1M0	
	T2bN0M0	
IIB	T2bN1M0	26%
	T3N0M0	
IIIA	T1/T2, N2M0	19%
	T3, N1/N2, M0	
	T4, N0/N1, M0	
IIIB	T4N2M0	7%
	Any T, N3, M0	
IV	Any T, Any N, M1a/M1b	2%

Conclusion

Accurate staging of non-small cell lung cancer and assessment of a patient's performance status is vital as it provides the framework for patient management. The 7th edition TNM staging system, illustrates the prognostic importance in staging accurately the mediastinum and pleural space.[46] The pleural space has often been poorly evaluated and this must change and as a consequence medical thoracoscopy will become an increasingly valuable method of evaluating malignant pleural effusions and should be incorporated early into the diagnostic and staging pathways.

Similarly it is essential that the mediastinum is staged as accurately as possible with the combination of PET-CT, EBUS and/or mediastinscopy. It is essential that centres continue

to work towards providing access to EBUS to all patients with Lung Cancer in order to accurately stage the mediastinum where appropriate.

Recent publications have highlighted the importance of not only accurate staging but also accurate histological subclassification of Non-Small Cell Lung Cancers as this will further determine specific treatment modalities. Recent NICE guidelines[47] have recommended pemetrexed and cisplatin in combination for the first-line treatment of NSCLC confirmed to be adenocarcinoma or large-cell carcinoma. This was following a non-inferiority randomised control trial comparing the combination of pemetrexed and cisplatin versus the combination of gemcitabine and cisplatin in the treatment of patients with both squamous and non-squamous NSCLC. This trial demonstrated improved survival in patients with non-squamous NSCLC treated with pemetrexed/cisplatin chemotherapy.[48]

The future of NSCLC management will involve the analysis and revision of existing treatment protocols according to the new staging system and the continued expansion and analysis of the central database for future revisions. It is imperative that wherever possible, multi-disciplinary teams strive to obtain accurate pathological staging for all cases of NSCLC and to build all available staging techniques into their diagnostic pathways to direct patient management and clinical trials, and to allow effective communication between centres.

Competing interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that Dr. S. Tsim, Dr C. O'dowd, Dr. R. Milroy or Dr. S. Davidson have no financial relationships that may be relevant to the submitted work; and no non-financial interests that may be relevant to the submitted work.

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