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# Tumor heterogeneity measurement using [$^{18}$F] FDG PET/CT shows prognostic value in patients with non-small cell lung cancer

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## Abstract

**Background:** The aim of this study was to evaluate primary tumor heterogeneity in patients with FDG-avid non-small cell lung cancer on PET/CT, with a view to optimising prognostic information from the metabolic signature of the primary tumor.

**Methods:** A retrospective analysis of 94 [$^{18}$F] FDG PET/CTs (56 M:38F) in patients with a diagnosis of primary lung malignancy was performed. Data collected included patient demographics, tumor size, maximum standardized uptake value (SUVmax), clinical stage and tumor histology. Clinical follow up and survival data were obtained from the available medical records. Tumor FDG spatial uptake heterogeneity was evaluated by the lack of conformity of the FDG pattern within the tumor region of interest to a simple 3-dimensional ellipsoidal form. A multivariate Cox regression analysis was used to assess the added prognostic benefit of heterogeneity information beyond radiological staging and other factors.

**Results:** Ninety four patients (mean age 67 years, range 36–85; 59.6% male) were available for analysis. The clinical staging distribution had 25 Stage I, 14 Stage II, 38 Stage III and 17 Stage IV. Mean tumor FDG spatial uptake heterogeneity was 25.87% with a range 2.78%–83.52%. Multivariate analysis found that heterogeneity, clinical stage, SUVmax and gender were associated with survival. Greater FDG spatial uptake heterogeneity is associated with significantly shorter survival ($p = 0.0152$). An increase of 19.5% (1 standard deviation) in FDG spatial uptake heterogeneity, is associated with a 43% increase in the risk of death.

**Conclusion:** Quantification of the FDG spatial uptake heterogeneity of lung tumors has potential to add prognostic information to lung cancer staging beyond SUVmax and clinical stage information.

**Keywords:** [$^{18}$F] FDG PET/CT, NSCLC, Image analysis, Heterogeneity

## Background

Lung cancer is the leading cause of cancer deaths worldwide (World Health Organisation, 2017). Net survival rates are poor in comparison to many other cancers, even for early stage disease with technically successful surgical excision. National Institute for Healthcare and Excellence (NICE) guidelines recommend all patients with a primary lung cancer who are being treated with curative intent undergo [$^{18}$F] Fluoro-deoxy-glucose Positron Emission Tomography/ Computed Tomography (FDG

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PET/CT) as part of the staging process (National Institute for Health and Care Excellence (NICE), 2011). PET/CT is a non-invasive imaging test commonly used for diagnosis and staging of malignant diseases. The most commonly used radiotracer is [$^{18}$F] FDG. It is now generally accepted that there is a strong correlation between [$^{18}$F] FDG uptake assessed with Positron Emission Tomography (PET) and number of viable cancer cells in many solid tumors (Wahl et al., 2009). Combined [$^{18}$F] FDG-PET/ CT plays a unique role in the assessment of many solid tumors due to its dual assessment of metabolic function and tumor morphology rather than just morphology alone.

[$^{18}$F] FDG PET/CT is used to help make the diagnosis of lung cancer, to help define surgical versus non-surgical treatment candidates, and occasionally as part of follow-up to assess for treatment response or recurrence. [$^{18}$F] FDG-PET/CT has been shown to be more accurate than conventional imaging in the detection of both nodal and distant metastases in lung cancer, particularly in the more common non-small cell subtype (Vansteenkiste & Dooms, 2007). Several studies have demonstrated the ability of [$^{18}$F] FDG-PET/CT to accurately predict favourable pathologic response to neoadjuvant chemotherapy and radiotherapy (Hicks, 2009). Furthermore, there is accumulating data to suggest that response to treatment on [$^{18}$F] FDG-PET/CT is associated with improved overall survival (Hicks, 2009).

Prognosis and treatment response variability are likely manifestations of the underlying tumor biology and heterogeneity in specific tumor biology characteristics. Tumor heterogeneity refers to features at a cellular level (e.g. cellular proliferation and necrosis); to physiological changes (e.g. altered perfusion including haemorrhage and hypoxia and tumor metabolism) as well as to molecular changes (e.g. EGFR mutations). These factors can lead to different responses to therapy introducing significant challenges in designing effective treatment strategies. The purpose of this study was to evaluate primary tumor metabolism heterogeneity reported with [$^{18}$F] FDG PET/CT in the primary tumor of patients with non-small cell lung cancer with a view to optimising the prognostic information from the metabolic signature of the tumor.

## Methods

A retrospective analysis of [$^{18}$F] FDG PET/CTs in patients with a diagnosis of primary non-small cell lung cancer was performed over a three year period (18/05/2012–18/05/2015). Data collected included patient demographics, primary tumor PET/CT derived maximum standardized uptake value (SUVmax) and clinical stage. Stage was reported in standard categories as per International Association for the Study of Lung Cancer (IASCLC) 7th edition (Stage I; II; IIIA; IIIB, IV). Our analysis combines Stages IIIA and IIIB so that each patient falls into one of Stages I, II, III and IV. The study was designed with overall patient survival as the main clinical end point of interest. Clinical follow up and survival data were obtained from the available medical records. End points chosen were death, date of last clinic appointment and date lost to follow up.

### [$^{18}$F] FDG PET/CT

Prior to treatment all patients underwent standard [$^{18}$F] FDG PET/CT on a GE Discovery VCT system as per our institutional protocol. The same protocol was used for all patients, and all were performed on one machine in a single PET/CT centre. Patients

were fasting for 6 h and a capillary glucose sample was checked prior to intravenous injection of [$^{18}$F] FDG (340–400 Megabecquerels) one hour before PET acquisition and subsequent low dose non-contrast attenuation correction CT. Patients were positioned supine with arms up and the scan range was from the lower orbital margin to the upper third of the femora. CT was performed using free breathing and using standard filter back projection reconstruction. 30 cm bed positions were obtained with 2–3 min per bed position. PET/CT images were reconstructed and reviewed using a GE AW workstation by a fellowship-trained radiologist. The PET reconstructed FDG images are in units of activity (kBq/cc) are converted to standardized uptake units by scaling the activity of the injected dose per unit weight of the patient (kBq/g). The primary tumor for FDG spatial uptake was selected by a radiologist and a region of interest (ROI) mapped around the entire tumor volume demonstrated by the [$^{18}$F] FDG uptake on the axial images. SUVmax was recorded as the maximum voxel-level SUV within the ROI.

### Heterogeneity analysis

An image analysis algorithm, previously validated in patients with sarcoma (Eary et al., 2008), was used to quantify spatial heterogeneity of [$^{18}$F] FDG SUV distribution. This approach models the 3-D pattern of radiotracer uptake in a homogenous tumor mass by a general ellipsoidally contoured structure, whose voxel intensity is greatest at the centre and diminishes in a monotone fashion as one moves radially towards the periphery of the mass. All voxels within the ROI are used for assessment. Thresholding was not performed as voxels of lower intensity typically found at the tumor boundry would by construction have only a very limited statistical influence on this model-based heterogeneity quantitation. FDG spatial uptake heterogeneity is assessed by the lack of conformity of the observed uptake pattern to the best fitting ellipsoidally contoured model. Heterogeneity (HET) is evaluated as the percent variance unexplained in the ROI uptake values using the ellipsoidally contoured model. A comparative analysis presented by O'Sullivan et al. (2011), carried out on a sarcoma cohort including heterogeneous profiles, indicated that the nature of the nature of tumor delineation had only a limited impact on the model-based heterogeneity assessment used in this analysis. By construction, the latter is mainly driven by the uptake data located at the core of the ROI, rather than the information located at its boundry (Eary et al., 2008). HET is expressed as a percent (range 0–100), a low value indicating a more homogeneous volumetric uptake distribution. Our heterogeneity analysis was performed on a stand-alone workstation off-site using the R (R Core Team, 2016) statistical software. Open-source R code for this analysis is available in (Wolsztynski & O'Sullivan, 2018).

### Statistical analysis

Patient death was the primary endpoint; survival was defined as days from baseline FDG PET scan to death. Clinical records were used to determine patient disease status and prognostic factors. Univariate and multivariate analyses were performed using R (R Core Team, 2016).

The question of interest is whether heterogeneity significantly contributes to a multivariable model of patient survival in non-small cell lung cancer which includes all

known prognostic variables that were available in this dataset (age, gender, SUVmax, and clinical stage were included in the analysis along with heterogeneity). Hazard ratios were scaled so that they are shown as the hazard associated with a one standard deviation increase in the comparison covariate.

## Results

The PET/CT examinations of 98 patients with non-small cell lung cancer were evaluated. Four studies were excluded as two demonstrated no [$^{18}$F] FDG uptake, one study had no follow-up data and one study was performed post-treatment (final $n = 94$). There were 56 male and 38 female patients with a median age of 69 years (range: 36–85 years-of-age). Histological diagnoses included squamous cell carcinoma ($n = 49$), adenocarcinoma ($n = 32$), mixed non-small cell carcinoma and small cell carcinoma ($n = 3$), poorly differentiated non-small cell carcinoma ($n = 2$), non-small cell lung carcinoma with neuroendocrine morphology ($n = 1$), carcinoid ($n = 1$), pleomorphic carcinoma ($n = 1$), adenosquamous carcinoma ($n = 1$) and non-small cell carcinoma not otherwise specified ($n = 4$). There were 25 patients with clinical stage I disease, 14 patients with stage II disease, 38 patients with stage III disease and 17 patients with stage IV disease. There were 58 deaths during the study interval with a mean survival time of 332 days for those patients (range: 9–976 days).

Heterogeneity analysis was performed on 94 studies. The SUVmax range was from 0.91–26.2; the mean value was 9.95, median 8.91. The heterogeneity [HET] range was 2.78–83.53%; the mean value was 25.87%, median 20.19%.

### Univariate analysis

Cox proportional hazard models were used to evaluate age, gender, clinical stage, SUVmax and heterogeneity. Note clinical stage is partially based on radiological interpretation of the PET information. Figure 1 presents Kaplan-Meier curves for the patient cohort separated by clinical stage. Clinical stage and SUVmax were the strongest predictors of patient survival (see Table 1). Heterogeneity factor was not statistically significant predictor of survival in univariate analysis ($p = 0.082$).

### Multivariate analysis

Multivariate Cox proportional hazard models were also used to evaluate the relationship between prognostic factors and time to death. Prognostic factors assessed included gender, SUVmax, PET stage and heterogeneity. Clinical stage is the strongest predictor of patient survival but all variables assessed, with the exception of age, showed significance for survival prediction (Table 2, Figs. 2 and 3). Incorporation of FDG tumor spatial uptake heterogeneity into the analysis significantly ($p = 0.0152$) improves a model which included age, gender, clinical stage and SUVmax. This study finds that an increase of 19.5% (1 SD) in heterogeneity is associated with 43% increase in the risk of death, when all other variables remain fixed. A standalone increase of SUVmax of 6.11 (1 SD) is associated with a 36% increase in the risk of death.

## Discussion

Accurate staging of non-small cell lung cancer is essential to plan appropriate management and treatment strategies. NICE guidelines recommend that all patients with a

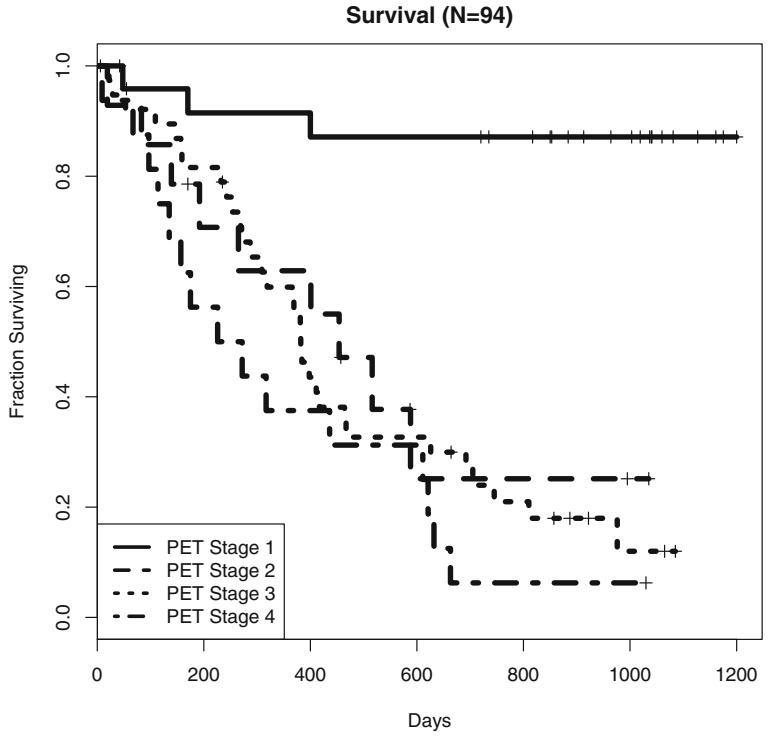



**Fig. 1** The Kaplan-Meier Survival curves for stage I-IV patients

primary lung cancer who are being treated with curative intent undergo [$^{18}$F] FDG PET/CT as part of the staging process (National Institute for Health and Care Excellence (NICE), 2011). Studies have shown that [$^{18}$F] FDG PET/CT improves sensitivity in pre-operative staging of non-small cell lung cancer (Fischer et al., 2009) and our results have verified that stage is a strong predictor in multivariate prognostic models. With the unique ability of PET/CT to provide both functional and anatomic information we propose to add increased prognostic capability to clinical lung cancer staging obtained from metabolic imaging of the primary tumor by evaluating FDG spatial uptake heterogeneity in the tumor volume.

At present the metabolic assessment of the tumor is generally performed using the measurement SUVmax. SUVmax has been confirmed to be a significant indicator of tumor aggressiveness and prognosis in non small cell lung cancers (Berghmans et al.,

**Table 1** Univariate analysis

| | Hazard Ratio | *p*-value | R-sq | C |
|---|---|---|---|---|
| Age | 0.9710 | 0.8221 | 0.0005 | 0.5013 |
| Sex | 1.5306 | 0.1214 | 0.026 | 0.5544 |
| SUVmax | 1.7746 | < 0.0001 | 0.163 | 0.6339 |
| StageII[a] | 9.943 | 0.0006 | 0.3387 | 0.6783 |
| StageIII[a] | 11.6324 | 0.0001 | 0.3387 | 0.6783 |
| StageIV[a] | 17.6745 | < 0.0001 | 0.3387 | 0.6783 |
| HET | 1.2363 | 0.082 | 0.0293 | 0.6023 |

[a]Clinical Stage for each of stages II-IV is relative to stage I

**Table 2** Multivariate analysis

| | Hazard Ratio | *p*-value | R-sq | C |
|---|---|---|---|---|
| Age | 1.0333 | 0.8303 | 0.4503 | 0.7531 |
| Sex | 1.9773 | 0.0281 | | |
| SUVmax | 1.3563 | 0.0329 | | |
| Stage II | 8.7036 | 0.0018 | | |
| Stage III | 10.3671 | 0.0002 | | |
| Stage IV | 20.2719 | < 0.0001 | | |
| HET | 1.4287 | 0.0152 | | |

2008). While the single measurement provided by the SUVmax is useful, any one value is unlikely to capture all of the information that the 3-D PET scan may convey about the tumor. Thus there is on-going interest to evaluate further measures which may contribute to the prognostic value of the PET study. Texture-based radiomic measures are being explored in various NSCLC settings where PET is used (Cook et al., 2013; Tixier et al., 2014; Soussan et al., 2014; Orlhac et al., 2015).

Our approach adapts a technique developed and validated in the context of PET sarcoma (Eary et al., 2008) to the NSCLC setting. Unlike texture-based radiomic approaches, our technique is based on a model of radiotracer uptake pattern. Heterogeneity (HET) is assessed in terms of deviation from that model. The present study shows that HET in a primary lung cancer tumor has the ability to add new

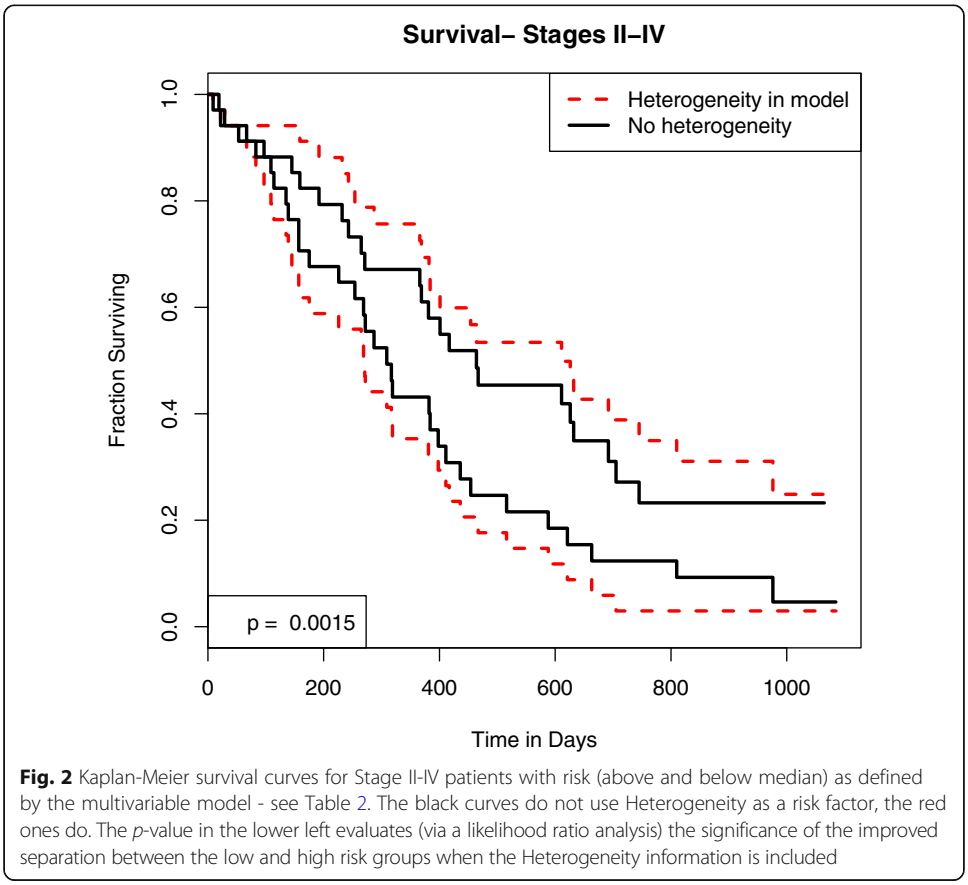



**Fig. 2** Kaplan-Meier survival curves for Stage II-IV patients with risk (above and below median) as defined by the multivariable model - see Table 2. The black curves do not use Heterogeneity as a risk factor, the red ones do. The *p*-value in the lower left evaluates (via a likelihood ratio analysis) the significance of the improved separation between the low and high risk groups when the Heterogeneity information is included

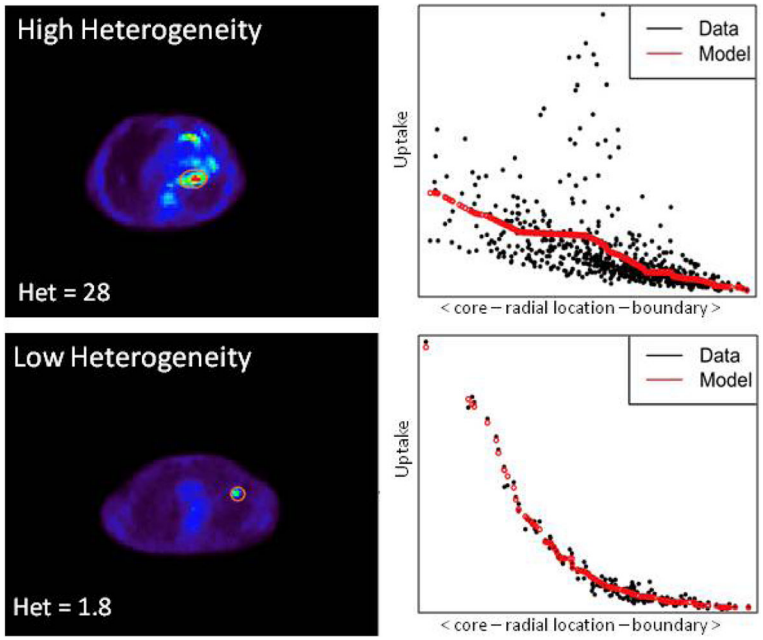



**Fig. 3** Illustration of the HET quantitation on two NSCLC studies, with high (top) and low (bottom) heterogeneity. The corresponding scatterplots (right) illustrate the representation of the volumetric tracer uptake (black dots) as a function of radial position within the ideal ellipsoid pattern, from core (left hand side of the x-axis) to the volume boundary (right hand side of the x-axis). The HET variable quantifies the lack of goodness-of-fit of the data-adaptive regression model (red) derived from this representation, thus assessing how well the idealized ellipsoidal pattern describes the observed uptake data

additional prognostic information to the tumor staging process. Incorporation of HET into a multivariate predictive model including gender, SUVmax and radiological stage significantly enhances the understanding of survival characteristics for all patients. Thus tumor heterogeneity measurements may provide further staging information that could potentially influence how patients with NSCLC might be better managed. This could be the focus for a further research study.

We hypothesize that the [$^{18}$F] FDG heterogeneity reflects underlying biological heterogeneity. Biological heterogeneity may be a reflection of cell populations with differing growth rates, vascularity, necrosis and cavitation which, when seen histologically, are features that may imply aggressive behavior. No single mechanism has been identified as a direct link between biologic heterogeneity and radiotracer heterogeneity (Gallivanone et al., 2017; Van Gomez Lopez et al., 2014) and it is likely a multifactorial association. The morphological appearance of lung tumors on CT can often be heterogenous, for example showing regions of contrast enhancement, necrosis, cavitation or ground-glass opacification. Thus application of the above spatially focused heterogeneity measure may merit evaluation in the context of diagnostic CT information obtained for NSCLC patients. In this context it could also be interesting to explore the added benefit of [$^{18}$F] FDG uptake heterogeneity, in relation to CT.

One of the limitations of our study is the small sample size which has not allowed for assessment of heterogeneity as an independent prognostic factor however we would propose that intratumoral heterogeneity assessment for tumor characterization would complement tumor staging or grading, and its inclusion in a multivariate model that

includes staging information serves to evaluate the additional prognostic potential it may provide. Further research is required to evaluate the influence of HET as a prognostic factor in different stages of lung cancers, with a larger sample size.

## Conclusion

FDG spatial uptake heterogeneity within a primary non-small cell lung cancer tumor may be associated with a poorer prognosis and incorporation of this tumor characteristic adds prognostic significance to a model including clinical stage, gender and tumor SUVmax. Further studies are required to demonstrate if lung tumor FDG heterogeneity measurement could provide valuable prognostic information which could be used as part of the decision making process for treatment planning. In conclusion, the use of PET/CT in this way has potential to add prognostic information beyond that of traditional imaging evaluation, by quantification of the spatial heterogeneity of [$^{18}$F] FDG uptake in the primary tumor.

### Abbreviations

3-D: three-dimensional; EGFR: Epidermal growth factor receptor; FDG: Fluorodeoxyglucose; HET: Heterogeneity; IASCLC: International Association for the Study of Lung Cancer; NICE: National Institute for Healthcare and Excellence; NSCLC: Non-small cell lung cancer; PET/CT: Positron emission tomography/Computed tomography; ROI: Region of interest; SUVmax: Maximum standardised uptake value

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### Availability of data and materials

Institutional restrictions on patient confidentiality, prior consent and privacy, mean that data cannot be made available.

### Authors' contributions

NMH - data collection, analysis, original manuscript author. TM - data collection, analysis. KNOR - data collection, analysis, study design, manuscript revision. PM - data collection. JNOS - data analysis, manuscript revision. EW - data collection, analysis, study design, manuscript revision. JH - data collection, analysis. MPK - manuscript revision. JFE conceptual ideas, study design, manuscript revision. FOS - conceptual ideas, study design, data collection, analysis, manuscript revision. All authors read and approved the final mansucript.

### Ethics approval

Ethical approval was obtained from the Clinical Research Ethics Committee (CREC) of the Cork Teaching Hospitals, University College Cork. A waiver of informed consent was also granted by the CREC given the retrospective nature of the study and the anonymisation of data.

### Competing interests

The authors declare that they have no competing interests.

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