Pertanika J. Sci. & Technol. 26 (3): 953 - 964 (2018)

SCIENCE & TECHNOLOGY

Journal homepage: http://www.pertanika.upm.edu.my/

The Association of FDG-PET (Suvmax) and Inflammatory Marker in Predicting Tumour Aggressiveness

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ABSTRACT

Chronic inflammation is associated with processes that contribute to the onset or progression of cancer. This study examined the correlation between dichotomised patients with malignant tumours and inflammatory markers based on the altered glucose metabolism measured by the FDG SUVmax that underpins the degree of tumour aggressiveness. Thirty-one patients underwent ^{18}F-FDG PET/CT for various carcinoma along with blood inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL6), lipid profile and fasting blood glucose (FBG) levels were obtained in retrospective study. Patients were dichotomised by the cut-off SUVmax value of 6.0 dl/ml derived from curve analysis (P=-0.025). The mean age of the subjects were 53.16 ± 12.06 years and mean SUVmax of 8.80±6.27 g/ml. Significant correlation was noted between the SUVmax and CRP and IL6 ($r=0.361$; $P<0.05$) and IL-6 with BMI and FBG with $r=0.38$; $p<0.05$ and $r=0.34$; $p<0.05$ respectively. The odds ratio (95% confidence intervals) for patients with the SUVmax cut-off 6.0dl/ml was predicted by FBG (OR:0.385, $p<0.05$) and the SUVmax > 6.0 dl/ml was inversely related to IL-6 (OR: 0.049, with $p<0.005$). Serum inflammatory markers and endogenous glucose are associated with a potentially more aggressive malignant cancer. In particular, IL6 may be used as a useful surrogate marker for tumour aggressiveness with an important prognostic value.

Keywords: Inflammation, Computed tomography, positron emission tomography, [18F]-fluorodeoxyglucose, multimodality

ARTICLE INFO

Article history:
Received: 18 October 2016
Accepted: 06 April 2018

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INTRODUCTION

Development of cancer is significantly higher among patients with diabetes. In this regard, infection or chronic inflammation are associated with mutagenesis in 15-20% of all cancers among which are breast, colorectal and bronchus followed by cancer of liver, stomach and lung (Kuper, 2000; Balkwill, 2001; World Cancer Report, 2008).

ISSN: 0128-7680

Inflammatory factors, such as interleukin-6 (IL-6), plasminogen activator, inhibitor-1 (PAI-1), free fatty acids, monocyte chemo-attractant protein, leptin, fatty acids, adiponectin and tumour necrosis factor-α are produced by adipose tissue (Van Kruijsdijk et al., 2009). These factors are important in the progression of malignant cancer. In particular, the knowledge of IL-6 for immune homeostasis and how it induces profound activities in acute phase reaction has rapidly increased in chronic inflammation and carcinogenesis. The progression of cancer resulting from chronic inflammation is well known (Naugler et al., 2008). IL-6 is a commander marker in promoting inflammation to inflammation-associated cancer (Tangkijvanich et al., 2004). In most cases, the level of IL-6 is elevated which favours the development of carcinogenesis.

In recent decades, multimodality imaging was used to detect early progression of cancer, such as MRI, Single-Photon Emission Computed Tomography(SPECT) and Positron Emission Tomography PET-CT (Townsend et al., 2008). The PET-CT uses small amount of radiotracer to evaluate tissue functions, early onset of disease and lesion localisation via imaging sessions (Beyer et al., 2004; Nakamoto et al., 2003; An et al., 2007). The system complements each other to detect the lesion and hence help improve diagnostic yield by offering substantial advantages over anatomic and physiologic imaging techniques, unlike the standalone PET or CT system.

The study examined potential association of chronic inflammation and the molecular marker – 18 F FDG –PET-CT which contributes to the transformation and early onset of cancer.

MATERIALS AND METHODS

Patients

Thirty-one patients with lung carcinoma (11), oesophageal carcinoma (7), metastatic paraganglioma (3), colonic carcinoma (3), transitional cell carcinoma (3) and one each with lymphoma, hepatoma, nasopharyngeal carcinoma and breast carcinoma were investigated in a retrospective study. All patients underwent [18F] fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) for various indications of disease progression.

Patient Preparation

All patients fasted for at least 6 hours prior to scanning session and only oral hydration with glucose-free water was allowed. Fasting blood glucose was recorded for all patients. Oral gastrografin solution (sodium meglumine diatrizoate; BerliMed S.A., Madrid, Spain) was given to patients in dilution in three parts before IV administration of radiopharmaceutical agent and immediately before scanning. Becquerel range from 290.5 – 415.5 mega (Mean 347.5 MBq) of 18F-FDG was injected intravenously. All patients were placed in a special room ranging from 23 – 190, for an average of mean 70.6 minutes before they were asked to empty their bladder prior to the PET/CT scan imaging study.

PET/CT Imaging Protocol

Studies were standardised using a dedicated integrated PET-CT system (Siemens Biograph–64, Germany). This device comprises a dedicated PET scanner with Optimum Performance in 3-D Imaging with Lutetium Oxyorthosilicate (LSO) scintillator crystal technology. The system is incorporated with a multislice CT scanner with capability for 64 slice CT and high spatial resolution. For the purpose for attenuation correction, a scout view was performed in cranio-caudal direction followed by low dose CT protocol in caudo-cranial. Contrast-enhanced CT (CECT) protocol, iohexol (Omnipaque 350 mgI/mL, GE Healthcare, Shanghai, China) ranging from 50 – 100 ml with mean 83.07 ml was injected intravenous by using dual head automatic pressure injector (Mallinckrodt, M.O, and USA) with flow rate at 2.5 ml per second and followed by 20 ml saline flush. At the start of the CT scan, CECT acquisition started in caudo-cranial direction with 80 seconds delay, ensuring optimised intravenous (IV) contrast in the circulation and tissue enhancement. Subsequently, in view of the higher sensitivity of the PET scan, the acquisition time for PET was 2 min per table position.

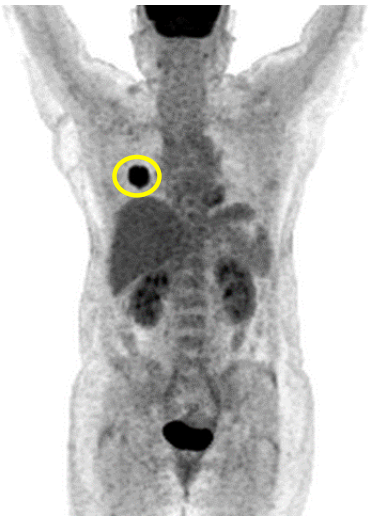


Figure 1. A circular region of interest (ROI) is drawn to evaluate the SUVmax value

Image Interpretation

PET/CT scans were read by an experienced radiologist with more than 5 years of clinical experience. The radiologist was blinded to the diagnosis and he/she was unaware of any biochemical findings or clinical information. The circular region of interest was drawn at the FDG-avid area (Figure 1) and the SUVmax value was automatically calculated.

Statistical Analysis

All patients with biopsy-proven cancer were dichotomised into groups based on the cut-off SUVmax value of 6.0 derived from the ROC statistical analysis (Figure 2-3). Paired t-test (two-tailed) and Wilcoxon signed rank test were used for parameters, which were normally

distributed and not normally distributed. Results were evaluated at a 95% confidence interval and the level of significance was set as $p<0.05$. Data was analysed using the Pearson correlation coefficient and binary logistic regression. All statistical tests were two-sided, and p values <0.05 were considered statistically significant. Data was analysed using Statistical Package for Social Sciences program (SPSS 21) (IBM Corp, Somers, New York).

RESULTS AND DISCUSSION

Patient Characteristics

The study investigated 31 retrospective patients (17 males) with mean age of 53.16±12.06 years. These patients who underwent FDG PET-CT l had biopsy-confirmed lung carcinoma (11), oesophageal carcinoma (7), metastatic paraganglioma (3), colonic carcinoma (3), transitional cell carcinoma (3) and one each with lymphoma, hepatoma, nasopharyngeal carcinoma and breast carcinoma (Table 1). Among them, there were subjects having NIDDM (10), Hypertension (16), Hypercholesterolemia (6) & history of smoking (8) with mean BMI of 23.56±5.31kg/m2 and FBS 5.30 ± 1.33 g/dl. The mean SUVmax values measured for the target lesions was 8.80±6.27 (Table 1).

Table 1
Patient characteristics

Patient	Age	Sex	BMI	Histology	Types	FBG	CRP	IL_6	Cholst	Trigl	HDL	LDL	SUVmax
P1	57	F	22	Left lung adenoca	Malignant	5.0	122.22	5.39	3.06	1.03	0.49	1.65	7.90
P2	59	F	19	Carcinoma esophagus	Malignant	5.0	0.98	6.08	4.27	0.78	1.06	2.56	13.51
P3	33	F	20	Carinoma of esophagus	Malignant	5.3	0.63	6.06	4.79	1.31	1.05	3.01	4.08
P4	59	F	21	Adenoca esophagus	Malignant	3.5	2.04	6.22	3.81	1.17	1.08	1.79	12.60
P5	50	M	22	Adenoca esophagus	Malignant	5.8	0.46	5.94	4.10	0.66	2.07	1.73	5.00
P6	68	F	21	Adenoca esophagus	Malignant	3.8	14.59	4.52	5.57	1.52	1.01	3.38	22.64
P7	45	M	29	Melanoma	Malignant	5.0	2.22	6.00	6.34	1.10	1.18	4.49	17.66
P8	47	F	23	Adenoca esophagus	Malignant	4.3	21.31	5.91	4.04	1.27	0.68	2.60	24.32
P9	56	F	22	Left adrenal phaeo	Benign	7.1	0.90	6.12	4.61	2.13	0.93	2.83	4.68
P10	59	F	19	Left lung adeno	Malignant	4.3	1.69	6.09	2.74	0.58	0.82	1.76	4.11
P11	60	M	19	Clear cell adenoca	Malignant	3.6	2.52	6.18	5.15	1.12	1.88	3.01	6.71
P12	42	F	29	Hepatocellular Ca	Malignant	5.3	10.05	5.87	3.50	0.97	0.68	2.63	4.16
P13	64	F	27	Rt chest wall tumour	Malignant	6.4	14.94	5.52	2.68	0.94	1.04	1.51	6.15
P14	38	M	33	Lt infraclavicular tumour	Malignant	6.7	0.32	6.13	3.86	1.11	0.79	2.85	3.02
P15	70	M	27	Rectal ca with	Malignant	6.0	5.65	6.26	3.28	0.97	1.12	2.42	4.50

Table 1 *(continue)*

Patient	Age	Sex	BMI	Histology	Types	FBG	CRP	IL_6	Cholst	Trigl	HDL	LDL	SUVmax
P16	57	F	26	Adrenal tumour	Benign	6.6	1.30	6.13	2.55	1.80	0.54	2.07	5.83
P17	61	F	16	Lung cancer	Malignant	4.7	184.41	5.36	3.01	0.74	0.62	2.54	10.40
P18	62	M	24	Primary clear cell Ca	Malignant	8.0	217.37	6.21	1.26	0.89	0.34	0.57	5.00
P19	63	M	20	Ca pancreas	Malignant	5.6	0.73	6.13	3.07	1.06	0.86	2.49	4.40
P20	67	M	22	Ca caecum with	Malignant	5.3	13.03	5.77	4.02	1`.48	0.96	3.22	11.40
P21	47	F	20	Adenoca esophagus	Malignant	4.4	0.52	6.25	3.15	0.99	0.79	2.57	3.64
P22	59	F	21	Adenoca esophagus	Malignant	4.3	1.45	5.26	3.94	1.68	0.86	3.33	3.04
P23	33	M	14	Stage iv NPC	Malignant	3.7	11.26	5.82	3.09	1.74	0.67	2.42	9.05
P24	32	F	29	Ca lung	Malignant	5.0	2.25	6.05	3.11	2.22	0.85	2.25	2.81
P25	58	M	26	Stage IV ca colon	Malignant	5.3	6.90	6.15	3.94	0.63	1.02	3.30	4.70
P26	18	M	23	Adrenal tumour	Benign	5.0	186.44	4.78	2.91	0.97	0.56	2.38	20.30
P27	44	M	22	Ca breast	Malignant	5.0	15.85	6.17	6.05	0.97	0.90	2.50	13.00
P28	62	M	13	Recurrent gastroc Ca	Malignant	2.8	0.51	4.94	3.19	1.91	0.92	2.23	6.12
P29	61	M	34	Recurrent ca cecum	Malignant	5.6	17.39	5.88	3.10	1.80	0.55	2.47	20.12
P30	35	F	27	Ca esophagus	Malignant	3.8	3.70	6.00	2.95	0.93	0.59	2.37	4.08
P31	61	F	34	Ca lung	Malignant	5.0	1.40	5.99	3.47	1.32	0.77	3.01	9.86

Notes: FBG: fasting blood glucose, CRP- C-reactive protein, Cholst: cholesterol, Trigl: triglyceride, HDL-high density lipoprotein, LDL: low density lipoprotein, SUVmax: PET-Ct marker (standardised uptake values)

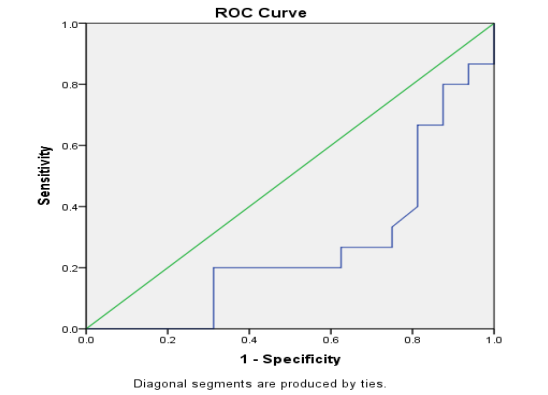
Biochemical analysis for inflammatory markers revealed mean CRP of 25.59±53.25U/I, IL-6 5.87± 0.47U/I with Triglyceride 1.22± 0.52 U/I, HDL.89 ± 0.32 mg/dl and LDL 2.59 ±0.89 mg/dl (Table 2).

Table 2
Mean biochemical results

Characteristic	Mean ± SD
BMI (kg/m^2)	23.56±5.31
FBS (g/dl)	5.30 ± 1.33
CRP (U/l)	25.59±53.25
IL-6 (U/l)	5.87± 0.47
Tg (U/l)	1.22± 0.52
HDL(mg/dl)	0.89 ± 0.32
LDL(mg/dl)	2.59 ±0.89

Stratification of Patient by the Index of Tumour Aggressiveness (SUVmax) on FDG PET

The patients were divided into two groups based on the SUVmax cut-off. Using the Receiver operating curve (Figure 2), the cut-off SUVmax of 6.0 was found significant for which (P< 0.005).

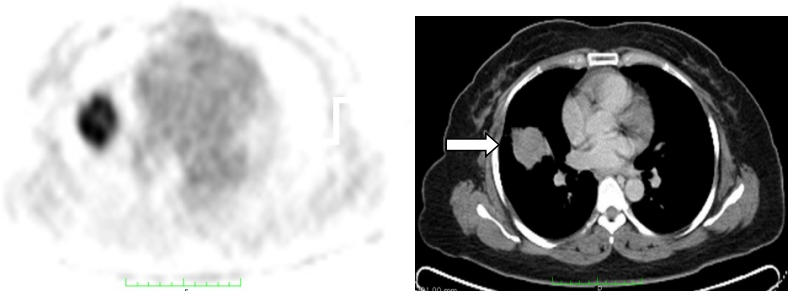


Area Under the Curve (AUC)

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.265	.092	.026	.084	.445

[a]Under the nonparametric assumption
[b]Null hypothesis: true area = 0.5

Figure 2. ROC curve with cut-off value of 6.0



(a) (b)

Figure 3. P31: (a) Axial FDG-PET and (b) CT images of a 61 years –old-male ex-smoker with high CRP diagnosed with lung carcinoma showing an FDG-avid mass in the right lung (arrowed) – SUVmax of 10.40

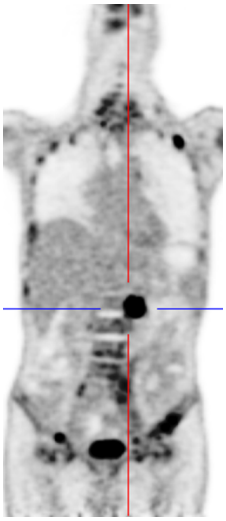


Figure 4. (P17); 18-year-old-male with NIDDM and abdominal paraganglioma (hairline marker) (SUVmax: 15.79)

Correlation Between Inflammatory Markers and SUVmax

Based on spearmen correlation (Table 3), there was strong correlation noted between the CRP and SUVmax (P<0.005); r: 0.527). The CRP was also strongly correlated with IL-6 (r=0.361; P<0.05). IL-6 was strongly correlated with the BMI (r: 0.38) and FBG (r: 0.34) with (P<0.05) respectively.

Table 3
Spearman Rhos to assess correlation between baseline inflammatory biomarkers and clinical marker and the SUVmax

Interleukin-6		P value
	Rho	
Age	0.23	0.88
BMI	0.38	*0.01
FBG	0.34	*0.03
CRP		p-value
	Rho	
SUVmax	0.527	*0.005
IL-6	0.361	*0.05

*statistical significant P<0.05

Predictor for the Carcinogenesis (FBS & IL-6)

The Figure 5 shows there is a one-unit increase in the FBS for patients with SUVmax of more than 6.0 are 0.38 times the odds of default for patients with SUVmax < 6.0. Conversely a 1-unit decrease in IL6 for patients with SUVmax more than 6 is associated with 0.049 times the odd of default for patient with lower SUVmax in this category.

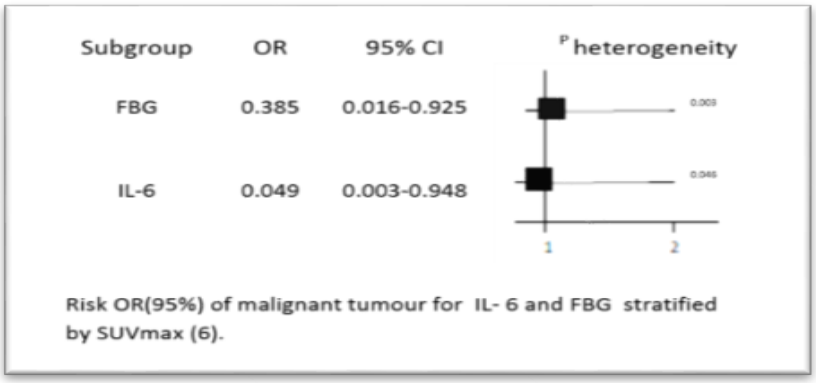


Figure 5. The odd ratios (95% confidence intervals) for patients with SUVmax cut-off of 6

The primary interest of this study was to evaluate the potential association of the inflammatory markers and the altered glucose metabolism in carcinogenic environment. The basis of inflammation in carcinogenesis has been well recognised especially in several known cancer i.e. endometrial cancer (Key et al.,1988). This study evaluated the imaging marker exploiting glucose analog (FDG) as a signal for altered glucose metabolism in different types of cancer and potential association with common inflammatory markers. The degree of altered glucose metabolism was measured using the standardised uptake value (SUVmax) of the PET image evaluated using PET-CT.

The higher value of SUVmax is correlated with the cellular proliferation and poor prognosis (Fathinul et al., 2015). Traditionally, the cut off value for SUVmax 2.5 was used to distinguished malignancy from benignity (Fathinul et al., 2015; Fathinul et al., 2014). Given all subjects were harbouring malignant cellular entity, the SUVmax of 6.0 was utilised to dichotomise groups of cancer patients for which rationale of higher SUVmax value raises the potential of cellular stress that underpins the carcinogenic reprogramming. Diabetes mellitus (with fasting blood sugar > 7.0 mmol/L) for instance is associated with increased tumour burden (Kaaks et al., 2002). The study found an association between patient with high glucose level and the altered glucose metabolism (SUVmax) which form the basis of strong signalling of the cancer-prone environment. The basis of this can be explained by the fact that isoform of the insulin receptor expression will induce cancer cells to produce insulin and IGF-I. The A receptor isoform can stimulate insulin-mediated mitogenesis and hence, the development of carcinogenic cellularity (Denley et al., 2007). There is also a strong correlation between SUVmax and the serum C-reactive protein among the cancers subjects. This is in line with other reports which found inflammatory process a potential precursor for cancer development (Love et al., 2005).

The potential correlation of clinical parameter of patients with evidence of chronic inflammation as evidenced by high glycaemic index evaluated by biomarkers i.e. FBS, level of total cholesterol and high BMI was investigated. The results showed obesity (high BMI) and NIDDM (FBG >7.0 mmol/L) was well correlated with the IL-6. These supported other reports which suggested elevated serum level of IL-6 in patient with insulin resistance and obesity and correlated with BMI (Kern et al., 2001). This shows cell stress and the alteration in cellular reprogramming for the progression of carcinogenesis.

Lower level of IL-6 in malignant cells of this study was an independent predictor for the altered glucose metabolism in malignancy. The basis of low level of IL-6 in association with cancer is poorly explained. One of the potential lower IL-6 levels has been described in younger age group but will rise with aging (Sarkar et al., 2006). Nevertheless, there was no association between low IL-6 with age in this study. In mouse model of colitis-associated cancer (CAC), trans-signalling was inhibited by tumour growth factor (TGF-B) to suppress the early onset or formation of cancer, which leads to low level of IL-6 in human sample of colon cancer (Atreya et al., 2000). The high level of IL-6 explains the carcinogenesis via classical IL-6 signalling. This phenomenon is well described in multiple myeloma patients (Lattanzio et al., 1997), which show that the high level of IL-6 is associated with vice-versa. Another study found high levels of IL-6 expression was correlated with high rates of myeloma protein secretion, low proliferative compartment, and low tumour mass. IL-6 induces an undifferentiated tumour cell compartment into terminal differentiation (high rate of immunoglobulin production, low proliferative fraction) and eventual tumour cell death (low tumour mass (Kishimoto,1989). Therefore, the lower IL-6 level in an altered glucose metabolism of mitogenesis can be explained by the probable the predominant expression of TGF-B which could have suppressed the trans-signalling cancer reprogramming pathway in carcinogenesis.

Data was obtained from outpatients and inpatients (a large nationally representative sample). The diagnoses were caught blindly and confirmed by the biopsy findings. Limitations included a relatively small number of subjects and a lack of other parameters, such as genetics, hormones, biochemical, lifestyle and diet. Additionally, the duration for follow-up the onset of clinical parameter and biological changes leading to cancer is probably too short.

CONCLUSION

Serum inflammatory markers and endogenous glucose are associated with a potentially more aggressive malignant cancer. In particular, IL-6 may be used as a useful surrogate marker for tumour aggressiveness with an important prognostic value. The low-level IL-6 indicates the cellular reprograming of cancer development has been signalled via different pathway of the IL-6 transduction in inflammation-associated cancers and hence, requires further understanding of various cancers types on the potential mechanism that regulates the cellular reprogramming. The understating of varied levels of IL-6 associated carcinogenesis is important and can be used as a marker for treatment efficacy.

REFERENCES

An, Y. S., Sheen, S. S., Oh, Y. J., Hwang, S. C., & Yoon, J. K. (2007). Nonionic intravenous contrast agent does not cause clinically significant artifacts to 18F-FDG PET/CT in patients with lung cancer. *Annual Nuclear Medicine, 21*(10), 585-92.

Atreya, R., Mudter, J., Finotto, S., Müllberg, J., Jostock, T., Wirtz, S., ... & Strand, D. (2000). Blockade of interleukin -6 trans signalling supresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn disease and experimental colitis in vivo. *Nature Medicine, 6*(5), 583-588.

Balkwill, F., & Mantovani, A. (2001). Inflammation and cancer: Back to Virchow? *The Lancet, 357*(9255), 539-545.

Beyer, T., Antoch, G., Muller, S., Egelhof, T., & Freudenberg, L. S. (2004). Acquisition protocol considerations for combined PET/CT imaging. *Nuclear Medicine, 45*, 25-35.

Denley, A., Carroll, J. M., Brierley, G. V., Cosgrove, L., & Wallace, J. (2007). Differential activation of insulin receptor substrates 1 and 2 by insulin-like growth factor-activated insulin receptors. *Molecular Cell Biology, 27*(10), 3569–3577.

Fathinul, F. A. S., Nordin, A. J., & Immeran, M. Z. (2015). Application of PET-CT in oncology. *Pertanika Journal of Science and Technology, 23*(1), 1–12.

Fikri, A. S. F., Nordin, A. J., & Lau, W. F. E. (2014). 18(F) FDG-PET/CT is a useful molecular marker in evaluating tumour aggressiveness; A revised understanding of an in-vivo FDGPET imaging that alludes the alteration of cancer biology. *Cell Biochemistry and Biophysic, 55*(5), 631-640.

Kaaks, R., Lukanova, A., & Kurer, M. S. (2002). Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiology, Biomarkers and Prevention, 11*(12), 1531-1534.

Kern, P. A., Ranganathan, S., Li, C., Wood, L., & Ranganathan, G. (2001). Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *American Journal of Physiology-Endocrinology and Metabolism, 280*(5), E745-E751.

Key, T. J., & Pike, M. C. (1988). The dose-effect relationship "unopposed" oestrogens and endometrial mitotic rate: Its central role in explaining and predicting endometrial cancer risk. *British Journal of Cancer, 57*(2), 205-212.

Kinahan, P. E., Townsend, D. W., Beyer, T., & Sashin, D. (1998). Attenuation correction for a combined 3D PET/CT scanner. *Medical Physics, 25*(10), 2046-53.

Kishimoto, T. (1989). The biology of Interleukin-6. *The Journal of The American Society of Hematology, 74*(1), 1-10.

Kuper, H. (2000). Infection as a major preventable cause of human cancer. *Internal Medicine, 248*(3), 171-183.

Lattanzio, G., Libert, C., Aquilina, M., Cappelletti, M., Ciliberto, G., Musiani, P., & Poli, V. (1997). Defective development of pristane-oil-induced plasmacytomas in interleukin-6-deficient BALB/c mice. *The American Journal of Pathology, 151*(3), 689-696.

Love, C., Tomas, M. B., Tronco, G. G., & Palestro, C. J. (2005). FDG PET of infection and inflammation. *Radiographics, 25*(5), 1357–1368.

Nakamoto, Y., Chin, B. B., Kraitchman, D. L., Lawler, L. P., & Marshall, L. T. (2003). Effects of nonionic intravenous contrast agents at PET/CT imaging: Phantom and canine studies. *Radiology, 227*(3), 817-824.

Naugler, W. E., & Karin, M. (2008). The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. *Trends Molecular Medicine, 14*(3), 109-119.

Sarkar, D., & Fisher, P. B. (2006). Molecular mechanism of aging associated inflammation. *Cancer Lett, 236*(1), 13-23.

Tangkijvanich, P., Thong-ngam, D., Theamboonlers, A., Hanvivatvong, O., Kullavanijaya, P., & Poovorawan, Y. (2004). Diagnostic role of serum interleukin 6 and CA 19-9 in patients with cholangiocarcinoma. *Hepato-gastroenterology, 51*(55), 15-19.

Townsend, D. W. (2008). Positron emission tomography/computed tomography. *Seminars Nuclear Medicine, 38*(3), 152-66.

Van Kruijsdijk, R. C., van der Wall, E., & Visseren, F. (2009). Obesity and cancer: The role of dysfunctional adipose tissue. *Cancer Epidemiology Biomarkers Prevention, 18*, 2569–2578

World Cancer Report. (2008). *Boyle P, Bernard L Eds. Cedex, France, World Health Organization, International Agency for Research on Cancer.* Retrieved April 1, 2010, from http://www.iarc.fr/en/publications/pdfs-online/wcr/index.php.