Original Article

The rate of incidental secondary tumours in 18-fluorodeoxyglucose positron-emission tomography in current literature—a systematic review and meta-analysis

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Background: 18-Fluorodeoxyglucose (18-FDG) Positron emission tomography (PET) is a commonly used nuclear medical imaging modality utilised in the primary staging of cancer, treatment planning, and treatment response. It is often used for these indications in head and neck squamous cell carcinoma where incidental secondary areas of uptake are rarely discovered. The significance of these often remains controversial and sometimes attributed to normal metabolic activity. The authors sought to determine the incidence of true secondary tumours published in the literature.

Methods: The authors performed a systematic review and meta-analysis of the literature looking at incidental findings on 18FDG-PET scanning in 8 studies comprising 10,068 total scans.

Results: Eight studies were identified which looked at the number of incidental findings on ^{18}FDG-PET scans. A total of 10,068 scans were performed. Of these 487 (4.8%) incidental positive results were identified. One hundred and sixty-six patients were not investigated further due to prognosis, patient wishes, unavailability of results, or loss to follow-up. Of the 321 remaining positive findings, 210 (2.1% overall) were found on biopsy to be true positives of either malignant or benign nature. One hundred and eleven (1.1% overall) false positive results were identified. Meta-analysis demonstrated a 2.29% effect rate (95% CI: 1.07–3.96).

Discussion: The above study demonstrates that a number of patients (210 patients, or 2.1% of all patients studied) with one neoplastic process may indeed have a second primary disease elsewhere. This puts the ^{18}FDG-PET at an advantage in identifying potentially treatment altering disease. The study also demonstrates that ^{18}FDG uptake often felt to be metabolic may indeed represent a second primary and these should be investigated fully by appropriate teams.

Keywords: Second primary disease (SPC); PET/CT; incidental

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Introduction

18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET) scanning is a nuclear medical imaging modality which provides a way to assess the biochemical and metabolic activity of tissues. Tissues which are metabolically active, such as cancer cells, have an increased utilisation of the radiolabelled glucose analogue 18-FDG. The metabolic activity is detected by localisation of annihilation photons (1). There is good evidence that this metabolic activity decreases with appropriate treatment, which may not be congruent with size decreases seen on other modalities such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) alone (2). PET can detect cancers when they reach a size of 4–10 mm, and studies have demonstrated a strong correlation between PET estimated and histopathological tumour volumes. This is in contrast to CT which showed significant overestimation of tumour size compared with pathology (3).

Furthermore, previous large database studies including Dong (633,964 patients) which looked at the Swedish Family-Cancer Database, and Ueno (24,498 patients) who analysed the Cancer Institute Hospital database demonstrated that a significant proportion of patients with one primary had a second primary diagnosed during their treatment (4,5). Dong and colleagues found a 8.4% incidence of a second primary cancer in males, and 8.7% in females. The rate was lower in the Ueno group where a 5.2% incidence was demonstrated. The differences are likely explained by the fact that Ueno and colleagues were looking primarily from the point of colorectal cancer whereas the Dong study looked at a more extensive database of patients encompassing all cancers. Nevertheless, there is at least a 1:20 rate of second primary if we are to take the lower number and identifying these at the time of the diagnosis of the first primary with FDG-PET may be a possibility.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/ajo-21-17).

Objectives

The authors were interested in what the published rate of unknown synchronous cancers found on PET scanning was in adults who underwent imaging for cancer staging. The goals of this systematic review were to assess: the rate of unknown synchronous disease found on PET, and whether various PET protocols changed the rates of these findings.

Methods

A systematic review and meta-analysis were performed in multiple databases (CENTRAL, MEDLINE, EMBASE, PsychINFO, and CINAHL) between January and March of 2021. The literature search was performed by the two authors independently and blinded to one another. Where there was discrepancy in the inclusion or exclusion of an article, the full article was accessed to allow a final decision to be made. The primary author extracted the data and this was reviewed by the second author for veracity.

The dataset extracted from the selected papers included fasting time, FDG dose, post-dose waiting time, bed positions, acquisition time per bed position, resolution, field of view (FOV), pixel size, and scanner type used. Where data was lacking or not specifically provided, the authors were contacted for clarification.

The authors adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. A grey literature search was performed in Google. Non-English papers were included and authors were contacted for clarification and further information where required. The details of the search criteria are given in the flowchart below (*Figure 1*). Studies were excluded when they included single case reports, or small case series less than 10 patients, as well as when the study did not show relevance to the search terms or the study. Duplicates were removed during the process of screening abstracts. Of 58 identified relevant papers, 8 studies were included in the study which looked at the criteria set out by the authors.

Statistical analysis

All descriptive statistics were performed using Microsoft's Excel (Microsoft Co., USA). The data is provided as Incidence Rate, False Positive Rate, and True Positive Rate. Meta-analysis of the dataset was performed using a commercially available version of MedCalc (MedCalc Software Ltd., Belgium).

A meta-analysis for proportions was performed using the MedCalc statistical software package. The results of this are given in *Tables 1* and *2*, and graphically demonstrated in the Forest plot in *Figure 2*. The results of a Q-test indicate the presence of heterogeneity between the studies. The I2 index supports this proposition with a finding of significant heterogeneity between the studies which required a random effects model to be used for the meta-analysis.

Subgroup analysis was performed on the proportions of patients who were lost to follow-up. Analysis of the scan

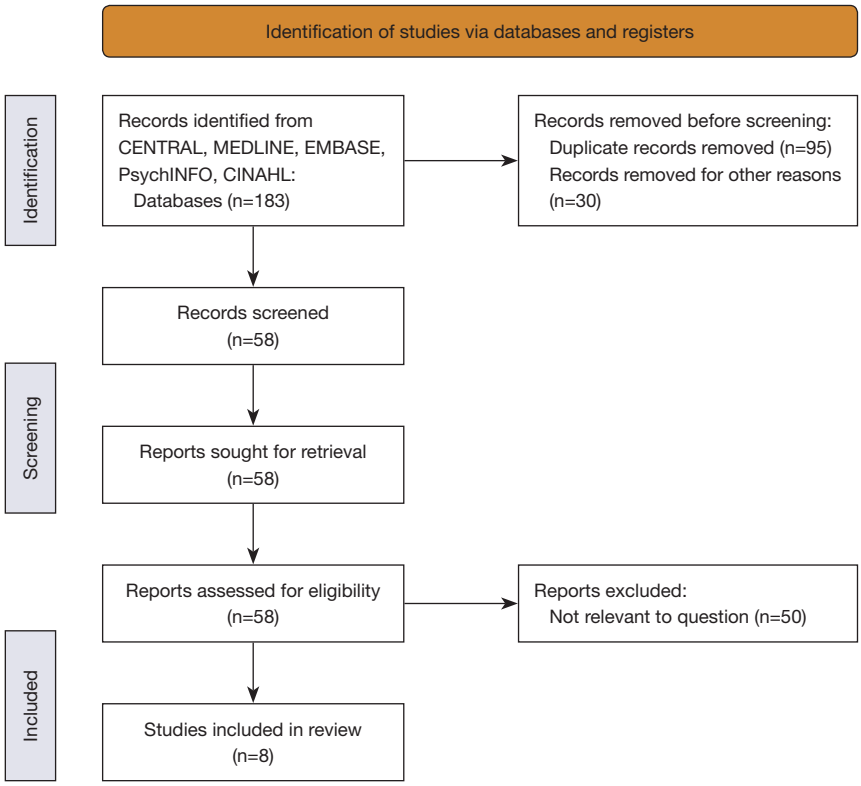

Figure 1 Literature review flowchart and search strategy.

acquisition protocols did not demonstrate a change to the rate of incidental findings.

Results

A total of 8 studies were selected for inclusion in the study which equated to a total of 10,068 PET scans performed in eight separate institutions. Of these, 487 incidental findings were reported. Two hundred and ten true positive pathologies were demonstrated on histopathology on further investigation of these incidental findings. This equates to a true positive rate of 2.1% and a false positive rate of only 1.1%.

Table 3 shows the breakdown of studies analysed including false positive and negative rates. There was significant variability in the rates of true and false positives as well as significant differences in the number of patients lost to follow-up. The explanation for this is not entirely clear but the studies do hint at disease factors in particular, such as untreatable disease, or multiple comorbidities as causes for non-investigation. The significance of a large number of patients lost to follow-up is difficult to analyse. The literature supports a cut-off of <5% loss to follow-up as leading to little bias, whereas a loss to follow-up of >20% leads to significant bias (14). All bar two of the included studies had a greater than 5% loss to follow-up with up to 63% loss to follow-up in one study. This is a significant source of bias which would affect the overall rates of true incidental positives. If all patients lost to follow-up are assumed to have true positive incidental findings, as in a worst-case-scenario, the rate would rise to 3.7% (15).

Table 4 demonstrates the areas of incidental uptake for the studies with most lesions being colorectal in origin (N=66), lung (N=42), and head and neck (N=24) in descending order. The different methods of data acquisition are compared in *Table 5* which includes the bed/cradle position time, acquisition time, and resolution where this data was provided. Where the data was not provided, all attempts were made to contact the author listed in the publication. The known scan acquisition protocols were similar between studies that reported them, with the main differences being scan acquisition time and FDG dose. These differences do not appear to influence the rate of incidental findings.

Due to the significant heterogeneity demonstrated in the

Table 1 Meta-analysis of proportions

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Ozkol *et al.* (6)	2,370	2.911	2.272 to 3.670	23.53	13.07
Williams *et al.* (7)	609	0.657	0.179 to 1.673	6.05	12.26
Fuertes *et al.* (8)	2,290	0.83	0.500 to 1.293	22.74	13.06
Oozeer *et al.* (9)	299	3.01	1.385 to 5.637	2.98	11.29
Garcheva *et al.* (10)	1,408	0.426	0.157 to 0.925	13.98	12.87
Malik *et al.* (11)	591	4.23	2.756 to 6.181	5.88	12.23
Strobel *et al.* (12)	589	9.508	7.262 to 12.169	5.86	12.23
Ishimori *et al.* (13)	1,912	1.151	0.722 to 1.737	18.99	13
Total (fixed effects)	10,068	1.754	1.507 to 2.030	100	100
Total (random effects)	10,068	2.298	1.077 to 3.961	100	100

Table 2 Tests for heterogeneity

Test for heterogeneity	Static value
Q	157.4717
DF	7
Significance level	P<0.0001
I^2 (inconsistency)	95.55%
95% CI for I^2	93.16 to 97.11

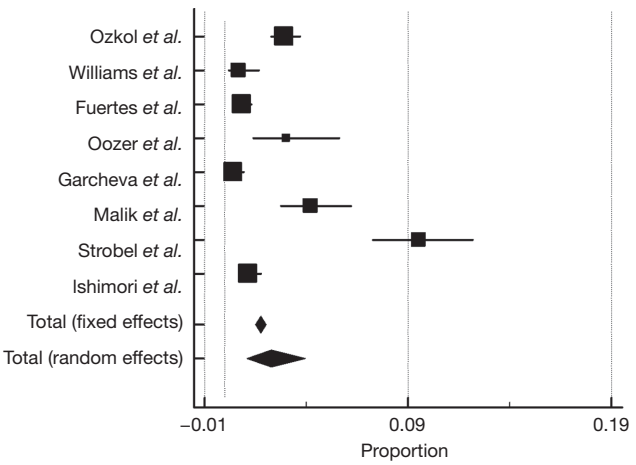

Figure 2 Forest plot of meta-analysis of proportions.

subgroups, a random effects model was used for the meta-analysis which supports a weighted finding of an effect size of 2.29% (95% CI: 1.08–3.96).

One hundred and sixty-six patients were lost to follow-up or did not have complete investigation of the incidental findings. This number represents 34% of total incidental findings and the significance is that the final number of true positives could be underestimated. When the number of patients lost to follow-up are analysed as a subgroup, and the individual false positive rates are applied, the predicted true positive rate increases substantially. A further subgroup meta-analysis of proportions demonstrates a new effect size of 3.22% (95% CI: 1.68–5.24). This would be equivalent to 1 in 30 patients having a missed diagnosis of a second primary disease, were it not for PET/CT staging.

Discussion

The results demonstrate that a significant number of patients with a single neoplastic process may have a second incidental finding which may not be clinically apparent. The importance of positron emission tomography in these patients is to highlight secondary disease which may otherwise go unchecked, potentially leading to treatment failure from unsuspected secondaries, second primary disease progression due to non-treatment, or unnecessary treatment of a primary disease in patients who may have an untreatable second disease.

In Australia, the fee for a whole body FDG PET study is AU$953.00 (16). This is arguably a negligible number of health Dollars for what could significantly alter the course of the patient journey. This is a journey which can often include

Table 3 Breakdown of total scans, incidental positive findings, true and false negatives, and patients not investigated or lost to follow-up

Author	Number of scans	Incidental positives	True positives	False positives	Not investigated
Ozkol *et al.* (6)	2,370	121	69 (2.9%)	5	47
Williams *et al.* (7)	609	76	4 (0.7%)	24	48
Fuertes *et al.* (8)	2,290	27	19 (0.8%)	8	0
Oozeer *et al.* (9)	299	40	9 (3.0%)	20	11
Garcheva *et al.* (10)	1,408	11	6 (0.4%)	0	5
Malik *et al.* (11)	591	64	25 (4.2%)	31	8
Strobel *et al.* (12)	589	69	56 (9.5%)	13	0
Ishimori *et al.* (13)	1,912	79	22 (1.2%)	10	47
Totals	10,068	487	210	111	166

Table 4 Breakdown of sites of individual true positive lesions

Site of second primary	Ozkol	Williams	Ishimori	Fuertes	Oozeer	Malik	Garcheva	Strobel	Totals
Colorectal	16		4	23		17	1	5	66
Thyroid	8	1	6			2			17
Lung	7	2	7					26	42
Kidney	6							1	7
Prostate gland	6								6
Ovarian	6						1		7
Stomach	4					1		1	6
Uterus and cervix	4								4
Head and neck	2		1			2	4	15	24
Salivary glands	2					1			3
Oesophagus	2		2					5	9
Pancreas	2		1						3
Breast	2		2					1	5
Spleen	2								2
Muscle	1								1
Thymus	1							1	2
Adrenal gland	1								1
Pituitary gland	1								1
Lymphatic nodule	1	1				1		1	4
Brain						1			1
Site not reported					11				11

Table 5 Data acquisition protocols

Study	Fasting time	FDG dose	Post-dose waiting time	Bed positions	Acquisition time per bed position	Resolution	FOV	Pixel size	Scanner
Ozkol *et al.* (6)	6 hours	5 MBq/kg	45–90 min	NR	3 minutes	NR	NR	NR	Siemens Biograph 6 LSO
Williams *et al.* (7)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fuertes *et al.* (8)	6 hours	2.4–2.7 MBq/kg	60 min	NR	NR	NR	NR	NR	GE Discovery ST & Siemens Exact HR+
Oozeer *et al.* (9)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Garcheva *et al.* (10)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Malik *et al.* (11)	6 hours	350–400 MBq	55–92 min	NR	2.5 minutes	6.5 mm	NR	3.91 mm	GE Discovery ST & GE Advance
Strobel *et al.* (12)	4 hours	350 MBq	NR	8 to 9	3 minutes	NR	NR	NR	GE Discovery LS
Ishimori *et al.* (13)	4 hours	8.14 MBq/kg	60 min	6 or more	5 minutes	4.5 mm	50 cm	3.91 mm	GE Discovery LS

multiple admissions to hospital, numerous investigations, operative interventions, as well as chemotherapy and/or radiotherapy treatments, the cost of which can and often does run into the tens of thousands of dollars. A dedicated cost-benefit analysis would be required to give an objective breakdown of any cost savings; however, it is at most a modest increase in the overall cost of treatment.

The average radiation dose from an FDG PET scan is estimated to be 12.2 millisieverts (mSv) (17). A whole body CT scan is estimated to impose a radiation dose between 4-24 mSv, compared to 0.04 mSv for a chest X-ray. There is an estimated increase in the possibility of cancer of 1 in 2,000 for each 10mSv radiation exposure (18). This is a considerably smaller dose of radiation than would be expected to be given during the course of cancer treatment. However, treatment doses are delivered in an exact manner and imaging should be performed judiciously to prevent excess radiation exposure.

The age-standardised incidence of colorectal malignancies in Australia as measured in 2013 is 58 cases per 100,000 persons (19). The equivalent incidence for this study would be in the order of over 650 cases per 100,000 persons. The significantly large proportion of colorectal incidental findings is worrying. Given that this is not a typical area of investigation for head and neck cancer secondaries, an incidental primary would not necessarily be picked up in this population. This is yet another reason to consider performing FDG PET as a first line staging investigation. Furthermore, with a false positive rate of 1.1%, FDG PET provides a modality which does not pose a large risk of forcing patients to undergo unnecessary examination or investigation of positive results.

The authors recognise the limitations of attempting to perform a large scale, multicentre investigation of all incidental FDG PET findings such as the logistics of performing the appropriate histopathological investigations, performing intention-to-treat analyses on patients lost to follow-up, as well as the appropriate referral pathways for these second primaries. Despite this, such a study would allow the accurate delineation of the true positive incidental rates and what the longer-term follow-up data on these patients is. This would in turn allow for improved investigation and treatment of all cancer patients. The authors support the pursuit of a large-scale, multicentre prospective study to investigate this further.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/ajo-21-17

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/ajo-21-17). The authors have no conflicts of interest to declare.

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.

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