

**Role of Positron Emission Tomography In Detecting  
Primary Site in patients with Metastatic Cancer Of  
Unknown primary**

**Thesis**

Submitted For The Fulfillment Of Master Degree In

Nuclear Medicine

*By*

***Ekram Ali Ahmed***

*M.B.B.Ch*

Under Supervision Of

***Professor Dr. Hosna Mohamed Moustafa***

*Professor of Nuclear Medicine Department*

*Faculty Of Medicine - Cairo University*

***Dr. Hitham Fouad***

*Lecturer Of Nuclear Medicine*

*Faculty Of Medicine - Cairo University*

***Dr. Khalid Mohammed Taalab***

*Consultant Of Nuclear Medicine*

*Military Medical Academy*

Faculty Of Medicine

Cairo University

2009

# بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي  
خَلَقَ (1) خَلَقَ الْإِنْسَانَ  
مِنْ عَلَقٍ (2) اقْرَأْ وَرَبُّكَ  
الْأَكْرَمُ (3) الَّذِي عَلَّمَ  
بِالْقَلَمِ (4) عَلَّمَ  
الْإِنْسَانَ مَا لَمْ يَعْلَمْ (5)

صدق الله العظيم

---

## *Acknowledgements*

*I would like to express my deepest thanks to my professor Dr. Hosna Moustafa, It was a great honor to work under her kind guidance. I have learnt a lot from her, no words could express my grateful appreciation to her kind support and supervision.*

*I would like to Acknowledge the generous help, cooperation , valuable time, Skills and support of Dr. Khalid Taalab.*

*I would particularly like to acknowledge the help, valuable advice and encouragement of Dr. Hitham Fouad.*

*Lastly I would like to express my gratitude to my family especially my mother, my son, and particularly my husband for unlimited help throughout this work and through all my life.*

---

## Table of contents

<i>Table of contents</i> .....	<i>i</i>
<i>List Of Figures</i> .....	<i>v</i>
<i>List Of Tables</i> .....	<i>vi</i>
<i>List Of Abbreviations</i> .....	<i>vii</i>
<b><i>Introduction</i></b> .....	<b><i>1</i></b>
<b><i>Aim of the work</i></b> .....	<b><i>3</i></b>
<b><i>Chapter 1: Cancer of unknown primary</i></b> .....	<b><i>5</i></b>
<i>Definition</i> .....	<i>5</i>
<i>Incidence and epidemiology</i> .....	<i>5</i>
<i>Aetiology and risk factors</i> .....	<i>6</i>
<i>Early diagnosis</i> .....	<i>6</i>
<i>Referral</i> .....	<i>6</i>
<i>Pathology</i> .....	<i>6</i>
<i>Diagnostic Pathology</i> .....	<i>6</i>
<i>Histological types</i> .....	<i>7</i>
<i>Biology</i> .....	<i>12</i>
<i>Chromosomal Abnormalities</i> .....	<i>13</i>
<i>Oncogenes And Proteins</i> .....	<i>13</i>
<i>Tumor Suppressor Genes And Proteins</i> .....	<i>13</i>
<i>Angiogenesis</i> .....	<i>17</i>
<i>Multigene Expression Profiling</i> .....	<i>19</i>
<b><i>Chapter 2:Diagnostic evaluation of CUP</i></b> .....	<b><i>24</i></b>
<i>Diagnostic evaluation for the identification of primary site</i> .....	<i>24</i>
<i>Diagnostic evaluation</i> .....	<i>25</i>
<i>1-Clinical evaluation</i>	
<i>2-Laboratory Studies and Serum Tumor markers</i> .....	<i>26</i>

---

<i>3-Radiological studies.....</i>	<i>30</i>
<i>A-Chest radiographs and plain films.....</i>	<i>30</i>
<i>B-Contrast radiographic studies.....</i>	<i>31</i>
<i>C-Mammography.....</i>	<i>31</i>
<i>D-Computed tomography .....</i>	<i>32</i>
<i>E-Magnetic resonance imaging.....</i>	<i>33</i>
<i>4-Diagnostic endoscopy.....</i>	<i>33</i>
<i>5-nuclear medicine examination.....</i>	<i>34</i>
<i>Planar and SPECT scintigraphy</i>	
<i>A-[67Ga]citrate scintigraphy.....</i>	<i>35</i>
<i>B-[99mTc]Pertechnetate scintigraphy.....</i>	<i>36</i>
<i>C-[99mTc]MDP bone scintigraphy.....</i>	<i>36</i>
<i>D-[99mTc]sestamibi scintigraphy.....</i>	<i>38</i>
<i>E-[111In]pentetreotide scintigraphy.....</i>	<i>39</i>
<i>F-[99mTc]EDDA/HYNIC-octreotate scintigraphy.....</i>	<i>41</i>
<i>Positron emission tomography.....</i>	<i>41</i>
<i>A-[18F]FDG-PET.....</i>	<i>45</i>
<i>B-[18F]DOPA-PET.....</i>	<i>50</i>
<i>C- [68Ga]DOTA-NOC and [68Ga]DOTA-TOC.....</i>	<i>52</i>
<b><i>Chapter 3:PET and PET/CT.....</i></b>	<b><i>53</i></b>
<i>Brief History of PET.....</i>	<i>53</i>
<i>Information Provided By PET Images.....</i>	<i>54</i>
<i>Standardized Uptake Value.....</i>	<i>55</i>
<i>Technical Considerations.....</i>	<i>57</i>
<i>Positron Physics.....</i>	<i>57</i>
<i>PET Imaging System.....</i>	<i>58</i>
<i>Factors That Degrade PET Images.....</i>	<i>60</i>

---

<i>Spatial Resolution</i> .....	56
<i>Attenuation</i> .....	62
<i>Attenuation Correction</i> .....	62
<i>Available Instrumentation</i> .....	62
<i>PET/CT imaging technology</i> .....	63
<i>PET/CT Operation And Protocols</i> .....	64
<i>CT-Based Attenuation Correction</i> .....	75
<i>Positron Emission Tomography Radioisotopes and Radiopharmaceuticals</i> .....	82
<i>Other tracers than FDG</i> .....	86
<i>PET/MRI</i> .....	86
<i>Patient Preparation and Radiation Safety</i> .....	76
<i>Image Acquisition and Interpretation</i> .....	79
<i>Normal FDG uptake</i> .....	80
<i>Pitfalls And Artifacts</i> .....	81
<i>Limitation Of PET Imaging</i> .....	87
<i>Technical Limitations</i> .....	87
<i>Other Limitations</i> .....	88
<i>Head And Neck</i> .....	92
<i>Myocardium</i> .....	94
<i>Gastrointestinal Tract</i> .....	95
<i>Genitourinary</i> .....	96
<i>Muscular Activity</i> .....	98
<i>Thymus Uptake</i> .....	100
<i>Bone Marrow</i> .....	100
<i>Splenic Uptake</i> .....	101
<i>Benign Pathologic Causes Of 18F-FDG Uptake</i> .....	102

<b>Chapter 4: Clinical application of PET and PET/CT in diagnosis of CUP.....</b>	<b>105</b>
<i>Role Of PET/CT In Unknown Primary Tumors.....</i>	<i>116</i>
<b>Chapter 5:patient and methods.....</b>	<b>125</b>
<i>Introduction .....</i>	<i>125</i>
<i>Material and methods .....</i>	<i>129</i>
<i>Data analyses .....</i>	<i>131</i>
<i>PET imaging.....</i>	<i>132</i>
<i>Statistical analysis.....</i>	<i>132</i>
<i>Results.....</i>	<i>136</i>
<i>Discussion.....</i>	<i>146</i>
<i>Conclusion .....</i>	<i>149</i>
<i>Limitation.....</i>	<i>149</i>
<i>Recommendation.....</i>	<i>150</i>
<i>Summary and conclusion</i>	

المخلص العربي

---

## List of figures

<i>Figure 1: Patient with 6-mm neuroendocrine tumor (NET) of the pancreas confirmed by surgery.....</i>	<i>34</i>
<i>Figure 2: Secondary hepatic lesions in a patient with unknown primary carcinoid that is demonstrated by [99mTc]EDDA/HYNIC-TOC (duodenum). ....</i>	<i>37</i>
<i>Figure 3: Secondary hepatic and bone lesions in a patient with unknown primary carcinoid that is demonstrated by [18F]DOPA-PET-CT (head of the pancreas).....</i>	<i>39</i>
<i>Figure 4: Secondary hepatic and bone lesions in a patient with unknown primary adenocarcinoma that is demonstrated by [18F]FDG-PET-CT (hilum of the right lung).....</i>	<i>40</i>
<i>Figure 5: Positron emission followed by the disintegration of a positron-electron couple.....</i>	<i>49</i>
<i>Figure 6: Diagram shows positron annihilation resulting in back-to-back photons.....</i>	<i>52</i>
<i>Figure 7: Schematic of a simple PET scanner detecting an event.....</i>	<i>53</i>
<i>Figure 8: Schematic shows factors that degrade PET images.....</i>	<i>55</i>
<i>Figure 9: Attenuation effects. PET emission images were obtained with (left) and without (right) attenuation correction.....</i>	<i>57</i>
<i>Figure 10: Typical imaging protocol for combined PET/CT.....</i>	<i>65</i>
<i>Figure 11: Graph shows bilinear scaling function used to convert CT numbers to linear attenuation values at 511 keV.....</i>	<i>68</i>
<i>Figure 12: Glucose and fluorodeoxyglucose structure.....</i>	<i>70</i>
<i>Figure 13: Early metabolic paths of glucose and FDG.....</i>	<i>70</i>

---

<i>Figure 14: Normal FDG-PET whole-body scan.....</i>	<i>80</i>
<i>Figure 15: Asymmetric salivary gland uptake (projection view).....</i>	<i>84</i>
<i>Figure 16: Symmetric salivary gland uptake.....</i>	<i>85</i>
<i>Figure 17: Thyroid inflammation.....</i>	<i>86</i>
<i>Figure 18: (A) Cardiac uptake.....</i>	<i>87</i>
<i>Figure 19: Stomach uptake.....</i>	<i>88</i>
<i>Figure 20: Cecal uptake. ....</i>	<i>89</i>
<i>Figure 21: Dilated urinary bladder.....</i>	<i>90</i>
<i>Figure 22: Renal activity.....</i>	<i>90</i>
<i>Figure 23: Muscle uptake.....</i>	<i>92</i>
<i>Figure 24: Brown fat uptake.....</i>	<i>92</i>
<i>Figure 25: Bone marrow.....</i>	<i>93</i>
<i>Figure 26: Spleen uptake.....</i>	<i>94</i>
<i>Figure 27: 18F-FDG uptake in lymph nodes attributed to tuberculosis.</i>	<i>95</i>
<i>Figure 28: Scar tissue from recent surgery.....</i>	<i>95</i>
<i>Figure 29: Intense aortic uptake due to inflammation.....</i>	<i>95</i>
<i>Figure 30: Breast uptake, lactating female.....</i>	<i>96</i>
<i>Figure 31: Left pharyngeal T1 squamous cell cancer (SCC). Axial CT with contrast.....</i>	<i>110</i>
<i>Figure 32: Carcinoma of unknown primary.....</i>	<i>114</i>
<i>Figure 33: Unsuspected second primary.....</i>	<i>115</i>

## List of tables

<i>Table 1: Immynoperoxidase markers.....</i>	<i>9</i>
<i>Table2: Most common imaging studies for cancer of unknown primary.....</i>	<i>23</i>
<i>Table3:Most relevant tumor markers guiding the diagnosis of CUP..</i>	<i>25</i>
<i>Table4:The most commonly used markers and their corresponding primaries.....</i>	<i>26</i>
<i>Table5: Proposed radiopharmaceuticals for detecting cancer of unknown origin.....</i>	<i>33</i>
<i>Table 6: Metabolism or function disturbed in cancer and the PET tracer used for their study.....</i>	<i>72</i>
<i>Table7: Common PET radioisotopes.....</i>	<i>73</i>
<i>Table8:. Estimated radiation dose with intravenous administration of FDG in a 70-kgpatient .....</i>	<i>79</i>
<i>Table9:descriptive statistics.....</i>	<i>133</i>
<i>Table 10:sex .....</i>	<i>133</i>
<i>Table 11: Data on 39 patient with CUP syndrome.....</i>	<i>133</i>
<i>Table12:PET results feed back cross tabulation.....</i>	<i>137</i>
<i>Table 13:Chi square testes.....</i>	<i>138</i>
<i>Table 14:Symmetric measures.....</i>	<i>138.</i>
<i>Table 15:Lung cancer gold standard cross tabulation.....</i>	<i>139</i>
<i>Table 16:Chi square testes.....</i>	<i>139</i>
<i>Table 17:Symmetric measures.....</i>	<i>140</i>
<i>Table 18:Liver cancer gold standard crosstabulation.....</i>	<i>141</i>
<i>Table 19: Chi square tests.....</i>	<i>141</i>
<i>Table 20:Symmetric measures.....</i>	<i>141</i>
<i>Table 21:Breast cancer gold standard crosstabulation.....</i>	<i>142</i>

*Table 22: Chi square tests..... 142*

*Table 23: Symmetric measures..... 143*

*Table 24: Cancer colon gold standard crosstabulation..... 143*

*Table 25: Chi square tests..... 144*

*Table 26: Symmetric measures..... 144*

*Table 27: Cancer rectum gold standard crosstabulation..... 145*

*Table 28: Chi square tests..... 145*

*Table 29: Symmetric measures..... 145*

---

## List of abbreviations

<b><i>CUP</i></b>	<i>Carcinoma Of Unknown Primary</i>
<b><i>IHC</i></b>	<i>Immune Histochemistry</i>
<b><i>CEA</i></b>	<i>Carcinoembryonic Antigen</i>
<b><i>CDX2</i></b>	<i>Cdx2 gene in gastric cancer.</i>
<b><i>PSA</i></b>	<i>Prostate Specific Antigen</i>
<b><i>CLA</i></b>	<i>Cutaneous Lymphocyte-Associated Antigen</i>
<b><i>EMA</i></b>	<i>Epithelial Membrane Antigen</i>
<b><i>TTF-1</i></b>	<i>Thyroid Transcription Factor 1</i>
<b><i>VIII</i></b>	<i>(Factor 8) (Human) Monoclonal antibody. This antibody reacts with Von Willebrand factor in endothelial cells. It also reacts with megakaryocytes in human bone marrow. Proteolytic enzyme digestion of formalin fixed paraffin embedded tissue sections is required prior to immunostaining.</i>
<b><i>S-100</i></b>	<i>Marker of melanoma</i>
<b><i>HMB-45</i></b>	<i>Staining for diagnoses of melanoma</i>
<b><i>NSE</i></b>	<i>Neuron-Specific Enolase</i>
<b><i>HCG</i></b>	<i>Human Chorionic Gonadotropin</i>
<b><i>AFP</i></b>	<i><math>\alpha</math>-Fetoprotein</i>
<b><i>ER</i></b>	<i>Estrogen Receptors</i>
<b><i>PR</i></b>	<i>Progesterone Receptors</i>
<b><i>CK</i></b>	<i>Cytokeratin</i>
<b><i>LDH</i></b>	<i>Lactate Dehydrogenase</i>

<b><i>c-Myc</i></b>	<i>Cancer gene</i>
<b><i>Ras</i></b>	<i>An oncogene</i>
<b><i>HER-2</i></b>	<i>Human epidermal growth factor receptor-2. Positive Breast Cancer</i>
<b><i>EGFR</i></b>	<i>Epithelial Growth Factor Receptor Mutations In Non Small Cell Lung Cancer</i>
<b><i>VEGF</i></b>	<i>Vascular Endothelial Growth Factor</i>
<b><i>TKIs</i></b>	<i>Monitoring therapeutic response to TKIs in breast cancer by use of imaging peptides</i>
<b><i>PCR</i></b>	<i>Polymerase Chain Reaction</i>
<b><i>c-Kit</i></b>	<i>The transmembrane protein c-kit is a receptor tyrosine kinase (KIT)</i>
<b><i>PDGFR</i></b>	<i>An antibody directed against PDGF receptor <math>\beta</math> enhances the antitumor and the anti-angiogenic activities of an anti-VEGF receptor 2 antibody</i>
<b><i>GISTs</i></b>	<i>Gastrointestinal Stromal Tumour</i>
<b><i>Bcl-2</i></b>	<i>Is An Integral Outer Mitochondrial Membrane Protein That Blocks The Apoptotic Death Of Some Cells Such As Lymphocytes</i>
<b><i>P53</i></b>	<i>A Tumor Suppressor Gene</i>
<b><i>MDM-2</i></b>	<i>Is An Important Negative Regulator Of The P53 Tumor Suppressor</i>
<b><i>p14ARF</i></b>	<i>Is a protein product of the alternative reading frame of the human INK4a locus. It functions as a tumor suppressor protein.</i>
<b><i>KiSS-1</i></b>	<i>Kisspeptin the product of the gene Kiss1</i>

<b>CD34</b>	<i>A cluster of differentiation molecule present on certain cells within the human body. It is a cell surface glycoprotein and functions as a cell-cell adhesion factor.</i>
<b>TSP-1</b>	<i>Human thrombospondin's (TSP-1) C-terminal domain opens to interact with the CD-47 receptor</i>
<b>MMP-2</b>	<i>Matrix Metalloproteinases (MMPs) Are Zinc-Dependent Endopeptidases That Degrade Substances Within The Extracellular Matrix</i>
<b>RT-PCR</b>	<i>The ProtoScript II RT-PCR Kit is designed for the sensitive detection of mRNAs in a two-step process</i>
<b>MOC-31</b>	<i>Monoclonal Antibody Was Reported To Be Useful In Distinguishing Adenocarcinoma From Mesothelioma In Tissue Specimens</i>
<b>PAP</b>	<i>Smear Is A Test That Checks For Changes In The Cervix</i>
<b>GCDFP-15</b>	<i>Immunohistochemistry of a gross cystic disease fluid protein of the breast. A marker of apocrine epithelium and breast carcinomas</i>
<b>ce-CT</b>	<i>Contrast enhanced Computed Tomography</i>
<b>MRI</b>	<i>Magnetic Resonance Imaging</i>
<b>CLA</b>	<i>Cutaneous Lymphocyte-Associated Antigen</i>
<b>EMA</b>	<i>Epithelial Membrane Antigen</i>
<b>HMB-45</b>	<i>Melanocytic Marker</i>
<b>RT-PCR</b>	<i>Reverse Transcriptasepolymerase Chain Reaction</i>
<b>US</b>	<i>Ultrasound</i>

<b><i>SPECT</i></b>	<i>Single Photon Emission Computed Tomography</i>
<b><i>PET</i></b>	<i>Positron Emission Tomography</i>
<b><i>GIT</i></b>	<i>Gastro Intestinal Tract</i>
<b><i>Tg</i></b>	<i>Thyroglobulin</i>
<b><i>CgA</i></b>	<i>Chromogranin A</i>
<b><i>BAP</i></b>	<i>Bone Alkaline Phosphatase.</i>
<b><i>18FFDG</i></b>	<i>fluro-2-deoxy-D-glucose</i>
<b><i>99mTc</i></b>	<i>Technetium</i>
<b><i>MDP</i></b>	<i>Methylene Diphosphonate</i>
<b><i>EDDA</i></b>	<i>Ethylenediaminediacetic Acid</i>
<b><i>67Ga</i></b>	<i>Gallium-67</i>
<b><i>111In</i></b>	<i>Indium</i>
<b><i>HYNIC</i></b>	<i>Hydrazinonicotinyl</i>
<b><i>DOPA</i></b>	<i>Dihydroxyphenylalanine</i>
<b><i>DOPA-NOC</i></b>	<i>Dihydroxyphenylalanine NOC, 1-NaI3-octreotide</i>
<b><i>NET</i></b>	<i>Neuroendocrine Tumor</i>
<b><i>FNAB</i></b>	<i>Fine Needle Aspiration Biopsy</i>
<b><i>FDA</i></b>	<i>Food and Drug Administration</i>
<b><i>SRS</i></b>	<i>Somatostatin Receptor Scintigraphy</i>
<b><i>GEP</i></b>	<i>Primary Gastroenteropancreatic</i>
<b><i>SST2</i></b>	<i>Somatostatin Receptor Type</i>
<b><i>MIBG</i></b>	<i>Metaiodobenzylguanidine</i>
<b><i>TOC</i></b>	<i>Tyr3-octreotide</i>
<b><i>SUV</i></b>	<i>Standardized Uptake Value</i>