

# **IMMUNOHISTOCHEMICAL EXPRESSION OF CD133 STEM CELL MARKER IN PRIMARY OSTEOSARCOMA**

Thesis  
Submitted for Partial Fulfillment  
Of Master Degree in Pathology

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**2015**

## *Acknowledgement*

*First, thanks are all directed to **ALLAH** for helping me to complete this research.*

*I would like to express my deepest gratitude to **Pro. Dr. Nahed Samy Khamis**, Professor and Head of Pathology Department , Faculty of Medicine, Ain Shamas University, for her great support and continuous encouragement through the whole work under her guidance and supervision.*

*Also, I am deeply indebted to **Pro. Dr. Manal Mohamed El Mahdy**, Professor of pathology, Faculty of medicine, Ain shams University, for her great effort, support and guidance throughout the whole work.*

*My sincere regards and gratefulness for **Dr. Nermeen Salah Youssef**, Assistant professor of pathology, Faculty of medicine, Ain shams University, for her kind care, unlimited help and her great effort throughout this work.*

*Also, I would like to express my deep gratitude and thanks to **my husband, my daughters and my mother** who helped me a lot to complete this work.*

## List of Abbreviations

ABC	ATP-binding cassette transporter
AC133	Antibody clone 133
AIP	Aptaf-1 interacting protein
AJCC	American Joint Committee on Cancer Staging
Aptaf-1	Apoptotic protease activating factor 1
<b>ATP</b>	Adenosine triphosphate
Bcl2	B-cell lymphoma
Bcl-XL	B-cell lymphoma-extra large
BCRP	Breast cancer resistance protein
CD133	Cluster of Differentiation molecule 133
CIS	Cisplatin chemotherapeutic agent
CSCs	Cancer stem cells
CT	Computed Tomography
CXCR4	C-X-C chemokine receptor type 4 stem cell marker
DAB	Diaminobenzidine
<b>DNA</b>	Deoxyribonucleic acid
DOX	Doxorubicin chemotherapeutic agent
EpCAM	Epithelial cell adhesion molecule
ES	Embryonic stem cell
ESA	Epithelial specific antigen molecule
FC	Flow cytometry
FLIP	FLICE-inhibitory proteins
GBM	Glioblastoma multiforme

H&E	Hematoxylin and Eosin stain
HS	Highly significant
IAP	Inhibitors of apoptosis proteins
IF	Immunofluorescence
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal stem cell
MTX	Methotrexate chemotherapeutic agent
NS	Non significant
OS	Osteosarcoma
PBS	Phosphate - buffered saline
PET	Positron Emission Tomography
PFS	Progression-free survival
Pgp	P-glycoprotein
RB1	Retinoblastoma 1 gene
RNA	Ribonucleic acid
ROC	Receiver operating characteristic curve
RT-PCR	Real-time polymerase chain reaction
S	Significant
Saos2	Sarcoma osteogenic cell line 2
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SP	Side population cell
TNI	Tumor Necrosis Index
TNM	Tumor size, Lymph node and Metastasis Staging
WHO	World Health Organization

# Contents

## *Page*

<b>Introduction.....</b>	<b>1</b>
<b>-Aim of the work.....</b>	<b>4</b>
<b>-Review of Literature</b>	
Chapter 1: Normal anatomy.....	5
Chapter 2: Osteosarcoma .....	13
Chapter 3: Cancer stem cells.....	56
Chapter 4: CD133.....	65
<b>-Material and methods.....</b>	<b>70</b>
<b>-Results.....</b>	<b>78</b>
<b>-Discussion.....</b>	<b>119</b>
<b>-Conclusion.....</b>	<b>130</b>
<b>-Recommendation.....</b>	<b>131</b>
<b>-Summary.....</b>	<b>132</b>
<b>-References .....</b>	<b>134</b>
<b>-Arabic summary.</b>	

## List of Tables

<b>Table NO.</b>	<b>Title</b>	<b>Page</b>
<b>Table (1)</b>	Enneking's surgical staging system of bone sarcoma.	<b>45</b>
<b>Table (2)</b>	TNM Classification of bone tumors.	<b>46</b>
<b>Table (3)</b>	Enneking's criteria for surgical margins in musculoskeletal tumors.	<b>50</b>
<b>Table (4)</b>	Demographic & Descriptive analysis for osteosarcoma cases.	<b>78,79</b>
<b>Table (5)</b>	Frequency of different age groups within studied osteosarcoma cases.	<b>80</b>
<b>Table (6)</b>	Comparison between both groups as regarding the mean age.	<b>86</b>
<b>Table (7)</b>	Correlation between patients' age and CD133 in each group.	<b>87</b>
<b>Table (8)</b>	Difference between the two groups regarding sex.	<b>87</b>
<b>Table (9)</b>	Correlation between sex and CD133 expression in each group.	<b>88</b>
<b>Table (10)</b>	Correlation between histopathological types of osteosarcoma and CD133 in each group.	<b>90</b>
<b>Table (11)</b>	Difference between the two groups regarding tumor site.	<b>92</b>
<b>Table (12)</b>	Correlation between tumor site and CD133 in each group.	<b>93</b>
<b>Table (13)</b>	Difference between the two groups regarding tumor grade.	<b>95</b>
<b>Table (14)</b>	Correlation between tumor grade and CD133 expression in each group.	<b>96</b>

<b>Table (15)</b>	Difference between the two groups regarding TNM stage of surgically resected OS	<b>98</b>
<b>Table (16)</b>	Correlation between pTNM stage of surgically resected OS cases and CD133 expression in each group	<b>98 &amp; 99</b>
<b>Table (17)</b>	Difference between the two groups regarding AJCC tumor stage	<b>99</b>
<b>Table (18)</b>	Correlation between AJCC staging and CD133 expression in each group	<b>100</b>
<b>Table (19)</b>	Difference between the two groups regarding margin, infiltration of the surrounding soft tissue and CD133 expression	<b>101</b>
<b>Table (20)</b>	Correlation between CD133 expression and margin and infiltration of the surrounding soft tissue in group 1	<b>102</b>
<b>Table (21)</b>	Correlation between CD133 expression and surgical resection margins in group 2	<b>102</b>
<b>Table (22)</b>	Comparison between both groups as regarding the mean of TNI	<b>102</b>
<b>Table (23)</b>	Correlation between TNI and mean of CD133 expression for all patients	<b>103</b>
<b>Table (24)</b>	Correlation between TNI and mean of CD133 expression in group 1	<b>103</b>
<b>Table (25)</b>	Correlation between TNI and median of CD133 expression in group 1	<b>104</b>

## List of Figures

<b>Figure No.</b>	<b>Title</b>	<b>Page</b>
<b>Figure (1)</b>	Important anatomic landmarks for tumor diagnosis in long bones	<b>6</b>
<b>Figure (2)</b>	Cross section of mature bone	<b>7</b>
<b>Figure (3)</b>	Diagram demonstrates bone cells.	<b>10</b>
<b>Figure (4)</b>	Osteoclast resorbing bone	<b>11</b>
<b>Figure (5)</b>	Osteosarcoma, causing swelling in the distal femur	<b>20</b>
<b>Figure (6)</b>	X-ray of distal femur showing sunburst and Codman triangle	<b>21</b>
<b>Figure (7)</b>	MRI illustrates extensive destruction of the distal third of the tibia and extraosseous soft tissue extension.	<b>22</b>
<b>Figure (8)</b>	Small cell OS in proximal femur, axial nonenhanced CT image	<b>22</b>
<b>Figure (9)</b>	Gross specimen of osteosarcoma	<b>26</b>
<b>Figure (10)</b>	Osteoblastic osteosarcoma presenting as dense, granular to sclerotic grossly bone-producing lesion	<b>26</b>
<b>Figure (11)</b>	Chondroblastic osteosarcoma. The cartilage component is sufficiently large and well organized to be clearly seen grossly	<b>27</b>
<b>Figure (12)</b>	Microscopic picture of osteoblastic osteosarcoma containing pleomorphic malignant cells and coarse neoplastic woven bone	<b>28</b>
<b>Figure (13)</b>	Microscopic picture of chondroblastic osteosarcoma with neoplastic cartilage merging with tumor bone	<b>29</b>
<b>Figure (14)</b>	Microscopic picture of fibroblastic osteosarcoma containing fascicles of malignant spindle cells adjacent to deposits of neoplastic bone	<b>30</b>



<b>Figure (15)</b>	Gross appearance of a telangiectatic osteosarcoma	<b>31</b>
<b>Figure (16)</b>	Microscopic picture of telangiectatic osteosarcoma.	<b>32</b>
<b>Figure (17)</b>	Microscopic picture of small cell osteosarcoma, round cell type (high power photomicrograph)	<b>34</b>
<b>Figure (18)</b>	Microscopic picture of small cell osteosarcoma, short spindle cell type epithelioid-like pattern	<b>34</b>
<b>Figure (19)</b>	Microscopic picture of low grade central osteosarcoma	<b>35</b>
<b>Figure (20)</b>	Parosteal osteosarcoma involving the bones of the forearm grossly.	<b>36</b>
<b>Figure (21)</b>	Microscopic picture of parosteal osteosarcoma.	<b>37</b>
<b>Figure (22)</b>	Gross of surface lesion mass	<b>38</b>
<b>Figure (23)</b>	Periosteal osteosarcoma, high-powered photomicrograph.	<b>39</b>
<b>Figure (24)</b>	High grade surface osteosarcoma involving the distal femur grossly.	<b>40</b>
<b>Figure (25)</b>	Microscopic picture of high grade surface osteosarcoma.	<b>40 &amp; 41</b>
<b>Figure (26)</b>	Enneking's criteria for surgical margins	<b>50</b>
<b>Figure (27)</b>	Model of tumor progression and maintenance according to cancer stem cell hypothesis.	<b>58</b>
<b>Figure (28)</b>	Possible mechanisms leading to OS initiation.	<b>64</b>
<b>Figure (29)</b>	Sex distribution among osteosarcoma cases.	<b>80</b>
<b>Figure (30)</b>	Age distribution within osteosarcoma cases	<b>81</b>
<b>Figure (31)</b>	Type of osteosarcoma among studied	<b>82</b>

	cases.	
<b>Figure (32)</b>	Anatomical site of osteosarcoma in studied cases.	<b>82</b>
<b>Figure (33)</b>	Grading of osteosarcoma in studied cases.	<b>83</b>
<b>Figure (34)</b>	Staging of osteosarcoma in studied cases.	<b>84</b>
<b>Figure (35)</b>	The high and low CD133 expression in group1and group2 cases.	<b>86</b>
<b>Figure (36)</b>	Comparison between group 1 and 2 regarding sex.	<b>88</b>
<b>Figure (37)</b>	CD133 expression in relation to sex among OS cases in group 1.	<b>89</b>
<b>Figure (38)</b>	CD133 expression in relation to sex among OS cases in group 2.	<b>89</b>
<b>Figure (39)</b>	CD133 expression regarding different types of OS in group1.	<b>91</b>
<b>Figure (40)</b>	CD133 expression regarding different types of OS in group 2.	<b>91</b>
<b>Figure (41)</b>	Tumor sites in group 1 and group 2.	<b>92</b>
<b>Figure (42)</b>	Frequency of CD133 expression in relation to tumor site in group 1.	<b>94</b>
<b>Figure (43)</b>	CD133 expression in relation to tumor site in group 2	<b>94</b>
<b>Figure (44)</b>	Relationship between group 1and 2 regarding tumor grade among OS cases	<b>95</b>
<b>Figure (45)</b>	Relationship between CD133 expression and tumor grade in group 1	<b>97</b>
<b>Figure (46)</b>	Relationship between CD133 expression and tumor grade in group 2	<b>97</b>
<b>Figure (47)</b>	A scatter plot describes correlation between tumor necrosis index and mean of CD133 expression in all patients.	<b>103</b>
<b>Figure (48)</b>	A scatter plot describes correlation between tumor necrosis index and mean of CD133 expression in group1.	<b>104</b>
<b>Figure (49)</b>	ROC curve of TNI for predicting its effect	<b>105</b>

	on CD133 in group 1.	
<b>Figure (50)</b>	Control positive cytoplasmic CD133 stain in epithelial cells lining tubules in normal kidney tissue (CD133 X 200).	<b>106</b>
<b>Figure (51)</b>	High power view of previous figure (H&E X 100).	<b>106</b>
<b>Figure (52)</b>	High power view of previous figure shows strong positive cytoplasmic CD133 stain in 90% of neoplastic cells (CD133 X 100).	<b>107</b>
<b>Figure (53)</b>	Osteoblastic osteosarcoma, high grade, shows strong positive cytoplasmic CD133 in 90% of neoplastic cells (CD133 X 200).	<b>107</b>
<b>Figure (54)</b>	High power view of previous figure shows strong positive cytoplasmic CD133 stain in 90% of neoplastic cells (CD 133 X 400).	<b>108</b>
<b>Figure (55)</b>	High power view of previous figure shows moderate positive cytoplasmic CD133 stain in 50% of neoplastic cells (CD133 X 100).	<b>108</b>
<b>Figure (56)</b>	Chondroblastic osteosarcoma, high grade, (H & E X200).	<b>109</b>
<b>Figure (57)</b>	High power view of previous figure (H & E X400).	<b>109</b>
<b>Figure (58)</b>	Chondroblastic osteosarcoma, high grade, with CD133 staining of the previous case shows moderate positive cytoplasmic stain in 90% of neoplastic cells (CD133 X200).	<b>110</b>
<b>Figure (59)</b>	High power view of previous figure shows moderate positive cytoplasmic CD133 stain in 90% of neoplastic cells (CD133 X400).	<b>110</b>
<b>Figure (60)</b>	Fibroblastic osteosarcoma, high grade (H&E X 40)	<b>111</b>
<b>Figure (61)</b>	High power field of the previous case (H & E X 100)	<b>111</b>
<b>Figure (62)</b>	Fibroblastic osteosarcoma, high grade,	<b>112</b>

	with CD133 staining of the previous case shows strong positive cytoplasmic stain in 98% of neoplastic cells (CD133 X 100).	
<b>Figure (63)</b>	High power view of previous figure shows strong positive cytoplasmic CD133 stain in 98% of neoplastic cells (CD133 X 200).	<b>112</b>
<b>Figure (64)</b>	Telangiectatic osteosarcoma, high grade (H & E X100).	<b>113</b>
<b>Figure (65)</b>	High power view of previous figure (H & E X200).	<b>113</b>
<b>Figure (66)</b>	Telangiectatic osteosarcoma, high grade, with CD133 staining of the previous case shows strong positive cytoplasmic stain in 90% of neoplastic cells (CD133 X40).	<b>114</b>
<b>Figure (67)</b>	Parosteal osteosarcoma, low grade (H & E X100)	<b>114</b>
<b>Figure (68)</b>	High power view of previous figure shows moderate positive cytoplasmic CD133 stain in 70% of neoplastic cells (CD133 X 100)	<b>115</b>
<b>Figure (69)</b>	Osteoblastic osteosarcoma, high grade shows negative CD133 stain (CD133 X100).	<b>115</b>
<b>Figure (70)</b>	Osteoblastic osteosarcoma, high grade with tumor necrosis 85% (H&E X 40).	<b>116</b>
<b>Figure (71)</b>	Osteoblastic osteosarcoma, high grade with CD133 staining of the previous case showing moderate cytoplasmic stain in about 40% (CD133 X 40).	<b>116</b>
<b>Figure (72)</b>	Osteoblastic osteosarcoma, high grade with tumor necrosis 50% (H&E X 40).	<b>117</b>
<b>Figure (73)</b>	Osteoblastic osteosarcoma, high grade with tumor necrosis 50% shows moderate cytoplasmic CD133 stain in about 80% (CD133 X100).	<b>117</b>
<b>Figure (74)</b>	Osteoblastic osteosarcoma, high grade with tumor necrosis 40% shows strong	<b>118</b>

	cytoplasmic CD133 stain in about 85% (CD133 X100).	
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## **Introduction**

Osteosarcoma (OS) is the most common primary, non-hematologic bone malignancy in childhood and adolescence, comprise almost 60% of the common histologic subtypes of bone sarcomas **(Tirino et al., 2011)**.

Sarcomas are widely believed to develop as a result of genetic mutations in mesenchymal progenitor/stem cells. But the accurate cellular origin of most of these tumors remains unknown **(Tang et al., 2008)**.

The cancer stem cells (CSCs) hypothesis predicts that only a small subset of cells within a tumor is capable of initiating a new tumor and sustaining its growth **(Rosen et al., 2009)**. These CSCs are thought to divide asymmetrically, producing an identical daughter stem-like cell and a more differentiated cell, which upon subsequent divisions generates the vast majority of the tumor bulk **(Gibbs et al., 2011)**.

The identification of human CSCs brought a hope for tumor management. Searching for specific surface markers on CSCs is the key to further investigate tumorigenesis, metastasis, recurrence and prognosis of tumors **(Zhang & Li, 2010)**.

Specific cell surface markers required to isolate CSCs in solid tumors have not yet been well established **(Neves & Freitas, 2010)**.

Many studies suggested that CD133 was a specific surface marker for stem cells and CSCs (**Zhang & Li, 2010**). Its interest as a cancer stem marker has grown dramatically since it appeared that it was able to identify a cancer initiating subpopulation in colon (**Gibbs et al., 2005**) and in hepatocellular carcinoma (**Ponti et al., 2005**). Moreover, CD133 cells have also been found melanoma (**Ricci-Vitian et al., 2007**) and in brain (**Tirino et al., 2008**).

CSCs have been already identified in bone sarcomas (**Neves & Freitas, 2010**). Cell cultures, from biopsy samples of primary osteosarcoma and chondrosarcoma tumors, were analyzed and revealed the presence of a subset of cells that displayed a positive reaction for mesenchymal stem cell markers Stro-1, CD105 and CD44 (**Gibbs et al., 2005**). In another study, CSCs were detected and characterized based on a CD133-positive profile in established osteosarcoma cell lines (**Tirino et al., 2008**). Nevertheless, none of the markers used are exclusively expressed by CSCs (**Neves & Freitas, 2010**).

Surgery, when applied early, can be curative, and preoperative chemotherapy has been shown to be effective in the management of localized chemosensitive tumors, significantly increasing the proportion of long-term survivors (**Tirino et al., 2011**). However, the CSCs are naturally resistant to most current chemotherapy due to their quiescent nature. This may explain why traditional chemotherapies can initially reduce the majority of the tumor bulk but fail to eradicate it in