Original Paper, PET/CT.

The Role of 18F-FDG PET/CT in Follow up After Treatment in Childhood Langerhans Cell Histiocytosis.

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ABSTRCAT:

Objectives: To demonstrate the value of FDG PET/CT in follows up after treatment of patients with childhood Langerhans cell histiocytosis (LCH). **Patients and Methods**: A retrospective analysis of thirty pediatric patients with histopathologically proven LCH from September 2013 till November 2016 with follow up for 36 months. All patients received specific therapy for LCH in the form of chemotherapy &/or surgical resection. Analysis criteria at initial assessment included the following: any focal FDG uptake was considered abnormal when it was greater than that of hepatic uptake or in presence of abnormal changes on CT with any degree of FDG uptake. **Results**: 21 patients (70 %) presented with multi-system disease (bone as well as LNs &/or liver, lungs, soft tissue and skin), 6 patients (20%) had uni-focal lesions and 3 patients (10%) presented by multi-focal lesions. Follow up FDG PET/CT after therapy detected metabolic changes earlier than structural changes detected by CT. At the end of study 21 patients (70%) were disease free with nine patients (30%) had residual active disease. No statistically significant difference could be detected in relation to overall survival in relation to disease extent or risk group. **Conclusion**: F-18 FDG PET/CT is valuable in detection of response therapy. Survival was better in patients with unifocal disease and those of low risk group.

Key Words: Langerhans Histiocytosis & PET/CT.

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INTRODUCTION:

Langerhans cell histiocytosis (LCH)is a granulomatous disorder characterized by clonal proliferation of cells that share phenotypic characteristics with the primary antigen presenting cells of the epidermis known as Langerhans cell [(1)].

LCH shows wide age range. It occurs in newborn to the childhood, with annual childhood incidence of 2.2 to 6 cases per million. The disease is more common and more severe in younger population with median age of presentation of about 24 months. In infants there is slight predominance in males yet male to female ratio is close to one [(2)].

LCH is shows diverse presentation, ranging from a solitary lesion with self-remission to an extensive life-threatening multi-system disease. The severity of the disease tends to be more in the younger population. Extensive multi-system LCH (with or without organ failure) is seen mostly in the very young age. Multi-focal restricted single-system LCH is often diagnosed in children between 2 and 5 years, while half of the uni-focal bone disease occurs in children over 5 years [(3)].

LCH may involve a single system (SS), which may be a single site (uni-focal) or involve multiple sites (multi-focal), or may involve multiple systems (MS) which may involve a limited number of organs or be disseminated. Involvement of specific organs such as the liver, spleen, and hematopoietic system separates multisystem LCH into high (HR) and low risk (LR) groups, where risk indicates the risk of death from disease [(4)].

Depending on the site and extent of disease treatment of LCH may include surgical curettage, chemotherapy and/or radiation therapy. The most commonly used systemic chemotherapy regimen is the combination of vinblastine and prednisone for 12 months.

MATERIALS AND METHODS:

FDG PET/CT scans of thirty children with childhood Langerhans cell histiocytosis were included. Data were retrospectively collected in the period from 2013 till 2016. They were referred for FDG PET/CT for staging for pathologically proven Langerhans cell histiocytosis.

Clinical information were extracted from the medical records, including age, sex, detailed pathology, disease extent at diagnosis, Risk of mortality at diagnosis, imaging findings, treatment details, response to treatment and disease status. Data were entered into a computerized database. Study end points included date of last follow-up or date of death.

Patients Criteria and Study Design: The current study was a retrospective analysis of thirty patients with histopathological proven Langerhans cell histiocytosis (LCH) who was under treatment and/or regular follow up at the National Cancer Institute during the period from September 2013 till 2016. The age of patients encountered in the study ranged from 2.7 months to 9 years with a mean of 2.7 ± 2.0 years. They included 22 males (73.3%) and eight females (26.7%). All patients were referred to the Oncology and Nuclear Medicine Department to perform F18-FDG PET/CT for initial staging, restaging and/or assessment of treatment response within two weeks of chemotherapy.

All patients received specific therapy for LCH in the form of chemotherapy &/or surgical resection according to the standard institutional protocol.

The findings of the PET/CT were compared with skeletal survey, computed tomography (CT) and/or magnetic resonance imaging (MRI) findings within time interval less than 3 months. The choice of methods depended on tumor location. All procedures were approved by the institutional review board. Follow up using PET/CT and/or diagnostic CT was done for 36months.

F18-FDG PET/CT:

F18-FDG PET/CT study was done using a dedicated PET/CT scanner (Discovery MI, GE). This machine integrates a PET scanner with a dual-section helical CT scanner and allows the acquisition of co-registered CT and PET images in one session.

Patient Preparation and Imaging Technique:

All patients fasted for at least 4 h before the injection of 0.1-0.15mCi/kg (3.7-5.5 MBq /kg) 18F-FDG. Blood glucose levels did not exceed 150 mg/dL. Scanning started 45-60 min after tracer injection (acquisition time: 1-2 min/bed position). Intravenous contrast agent was administered in most patients. Initially, patients were examined in the supine position with arms elevated, and CT scanning was started with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. The CT scans were acquired during breath holding within the normal expiration position and reached caudally to the mid thighs.

PET over the same region was performed immediately after acquisition of the CT. Attenuation correction of PET images was performed by using attenuation data from the low dose CT component of the examination.

Images were interpreted at a workstation equipped with fusion software (Advantage Window (AW); GE) that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images in any percentage relation. Interpretation was accomplished by 2 experienced nuclear medicine physicians. Maximum standardized uptake value (SUV max) of each involved site was determined for semi-quantitative analysis using a spherical region of interest tool.

Analysis criteria of PET/CT:

Focal FDG uptake was considered abnormal when it was greater than that of hepatic uptake or in presence of abnormal changes on CT with any degree of FDG uptake. Criteria of treatment response assessment.

Complete metabolic response (CMR): Complete resolution of FDG uptake, with FDG uptake less than the liver and indistinguishable from that of the surrounding background.

Partial metabolic response (PMR): a decrease of greater than or equal to 25% of the initial study.

Stationary disease (SD): a decrease of less than 25% of the initial study.

Progressive disease (PD): lesions show an increase of greater than or equal to 25% or development of a new lesions.

Statistical Analysis:

Data were statistically described in terms of mean, standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. Correlation between various variables was done using Pearson moment correlation equation. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22 for Microsoft windows.

RESULTS:

In the present study, thirty children with Langerhans cell histiocytosis had age ranged between 2.7 months to 9 years; the mean age of onset was 2.7 ± 2.0 years with median of 26.4 months. Most of the children were between one to five years old. While only eight were below one year (26.7%) and three were older than five years (10%).

Twenty two patients were males (73.3%) and eight female patients (26.7%) with male to female ratio 2.75:1.

Disease extent: Twenty one patients (70%) presented with multi-system disease. Six patients (20%) had unifocal lesions and only three patients (10%) presented by multi-focal lesions as in ***Table (1)***.

Table 1: Distribution of disease extent in thirty patients with LCH.

Frequency	Number	Percent
Uni-focal	6	20%
Multi-focal	3	10%
Mutli-system	21	70%
Total	30	100%

Risk of mortality at diagnosis: Twenty three patients (76.7%) had low risk (LR) of mortality and only seven patients (23.3%) had high risk (HR) state.

Site distribution and quantification of metabolic activity as detected by initial FDG PET/CT:

Bone lesions: Twenty four patients (80%) had osseous involvement. twenty one patients (87.5%) had skull involvement. Four patients (13.3%) had vertebral lesions, eight patients (26.7%) had rib lesions, five patients (16.7%) had scapular lesions, six patients (20%) had long bone lesions, two patients (6.7%) had sternal lesions and seven patients (23.3%) had pelvic bone lesions. The highest mean SUV max is seen in skull, pelvic bones, vertebrae and long bones as in ***Table (2)***.

Lymph node lesions: Twenty three patients (76.7%) had lymph node involvement. Twenty one patients (70%) had cervical lymph nodes. Cervical nodes was the only nodal site in eleven patients (36.7%), while only one patient (3.3%) had isolated mediastinal nodal site and another patient (3.3%) with isolated axillary nodal involvement.

The other ten patients (33.3%) had multiple nodal site involvement. The highest mean SUV max of lymph node lesions is mediastinal and abdominal lymph nodes as in ***Table (3).*** **Pulmonary, hepatic and soft tissue involvement**: One patient (3.3%) had lung, hepatic and soft tissue lesions, these were in addition to bone and nodal lesions. The SUV max of the lung lesions was 0.6, the SUV max of the hepatic lesions was 1.5 and the SUV max of the soft tissue lesions was 0.7.

Table 2: Quantification of metabolic activity of skeletal lesions in thirty patients with LCH.

Site	Number of cases	Percent	Mean SUV max	Minimum SUV max	Maximum SUV max
Skull	21	70%	4.4 (±2.1 SD)	1.2	9.1
Pelvic bones	7	23.3%	3.5 (±2.4 SD)	1.8	7.3
Vertebrae	4	13.3%	3.4 (±0.8 SD)	2.5	4.5
Long bones	6	20%	3.4 (±2.5 SD)	1.2	8.4
Ribs	8	26.6%	2.4 (±1.0 SD)	1.7	4.7
Scapular	5	16.7%	3.2 (±3.3 SD)	1.0	9.0
Sternum	2	6.7%	2.0 (±0.7 SD)	1.5	2.5

Table 3: Quantification of metabolic activity of nodal lesions in thirty patients with LCH.

Site	Number of cases	Percent	Mean SUV max	Minimum SUV max	Maximum SUV max
Mediastinal LNs	5	16.7%	5.7 (±3.3 SD)	2.2	9.1
Abdominal LNs	5	16.7%	6.7 (±5.5 SD)	2.5	15.8
Axillary LNs	5	16.7%	3.0 (±1.9 SD)	0.7	5.9
Cervical LNs	21	70%	2.4 (±1.5 SD)	1.2	8.2

Semi-quantitative assessment of treatment response using PET/CT in 24 patients with Langerhans cell histiocytosis. FDG PET/CT revealed marked metabolic changes early in disease course of osseous lesions which is more evident in vertebrae, ribs and long bones in 88.4%, 52.3% and 38.4% respectively as seen in ***Table (4)***.

Table 4: Semi-quantitative Assessment of treatment response in osseous lesions using PET/CT in thirty patients with LCH.

Site	No. cases	CMR	PMR	SD	PD	Maximum SUV max	Mean SUV max	Decrease in Mean SUV max
Vertebrae	4	3	1			1.6	0.4(±0.8SD)	88.4%
Ribs	8	2	4	1	1	2.6	1.2(±0.9SD)	52.3%
Long bones	6		4	1	1	3.3	2.0(±1.1SD)	38.4%
Skull	21	8	2	4	7	8.9	3.2(±3.1SD)	29.2%
Pelvic bones	7	2	2	1	2	7.7	2.8(±3.0SD)	20.4%
Sternum	2		1		1	2.6	1.8(±1.1SD)	10%
Scapulae	5	1		3	1	8.8	3.4(±3.4SD)	3.7%

While in lymph node lesions metabolic changes are seen in mediastinal and abdominal lymph nodes in 61.4% and 41.1% respectively as in ***Table (5)***.

Table 5: Semi-quantitative Assessment of treatment response in lymph node lesions using PET/CT in thirty patients with LCH.

Site	No. cases	CMR	PMR	SD	PD	Maximum SUV max	Mean SUV max	Decrease in Mean SUV max
Cervical LNs	21	4	1	12	4	10.7	2.4(±2.4SD)	0.4%
Mediastinal LNs	5	2	1	2		4.1	1.6(±1.7SD)	61.4%
Axillary LNs	5	2	1	1	1	6.5	2.6(±2.9SD)	14.4%
Abdominal LNs	5	2	2		1	8.7	4.3(±4.1SD	41.1%

Response assessment: Follow up with FDG PET/CT revealed metabolic changes in osseous lesions earlier than skeletal survey in 11 out of 16 patients (68.8%) whereas diagnostic CT showed improvement in 8 out of 12 patients (66.7%) as seen in ***Table (6) and Figure (1: A & B).***

Table 6: Comparison between FDG PET/CT, Skeletal survey and diagnostic CT in response assessment.

		PET/CT		
	Total	**Metabolic response**	**Concordant**	**Additional lesions**
Skeletal Survey	16	11(68.8%)	4(25%)	1(6.3%)
CT	12	8(66.7%)	2(16.7%)	2(16.7%)

Fig. 1 (A): Axial CT-FDG PET and fused PET/CT of Skull shows FDG avid lytic bone lesions.

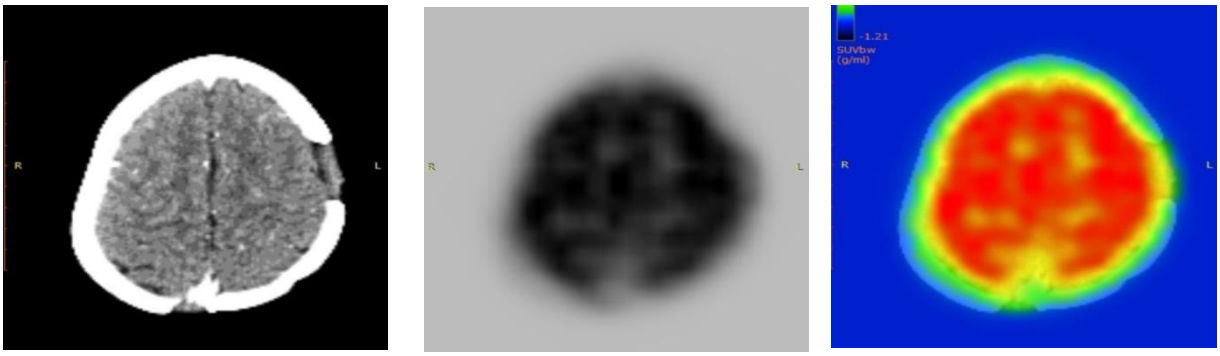

Fig. 1 (B): Post therapy Axial CT-FDG PET and fused PET/CT of Skull shows marked metabolic regression with residual lytic bone lesions in CT.

Disease outcome: At the end of study, twenty one patients (70%) had marked metabolic regression, while nine patients (30%) had residual disease with mild metabolic regression. A significant correlation was found between disease out come and risk of mortality (P value=0.028) as seen in ***Table (7).***

Table 7: Correlation between risk of mortality at diagnosis and disease outcome in thirty patients with LCH.

	Low risk	High risk	P value=0.028
Good metabolic response	19 (90.5%)	2 (9.5%)	
Residual disease	5 (55.6%)	4 (44.4%)	

Univariante analysis revealed no statistically significant correlation between disease outcome and either of age at diagnosis (P=0.160), patient sex (P=0.715), disease extent (P=0.707), SUV max of the leading lesion in initial PET scan (P value=0.365), post therapy SUV max of the leading lesion (P value=0.565) or percent change in SUV max (P value=0.423) as seen in ***Table (8).***

Table 8: Univariante analysis of different parameters with disease outcome in thirty patients with LCH.

	Disease Outcome
Age at diagnosis	(P value=0.160)
Sex	(P value=0.715)
Disease extent	(P value=0.707)
Initial SUV max	(P value=0.365)
Post therapy SUV max	(P value=0.565)
Percent change in SUV max	(P value=0.423)

Correlation with risk of mortality: Positive correlation was found between risk of mortality and disease extent (P value=0.053) as seen in ***Table (9).***

Table 9: Correlation between risk of mortality and disease extent in thirty patients with LCH.

	Low risk	High risk	P value=0.053
Uni-focal	9 (37.5%)	0 (0%)	
Multi-focal	5 (20.8%)	1 (16.7%)	
Multi-system	10 (41.7%)	5 (83.3%)	

While no statistically significant correlation could be found between risk of mortality and either of age at diagnosis (P=0.293), Patient sex (P=0.897), SUV max of the leading lesion in initial PET scan (P value=0.362), post therapy SUV max of the leading lesion (P value=0.149) or percent change in SUV max (P value=0.149) as in ***Table (10)***.

Table 10: Univariante analysis of different parameters with risk of mortality in thirty patients with LCH.

	Risk of mortality
Age at diagnosis	(P value=0.293)
Sex	(P value=0.897)
Initial SUV max	(P value=0.362)
Post therapy SUV max	(P value=0.149)
Percent change in SUV max	(P value=0.149)

Survival rates:

Overall survival: All our thirty patients were alive by the end of the study whereas progression free survival was 20% as seen in ***Figure (2).***

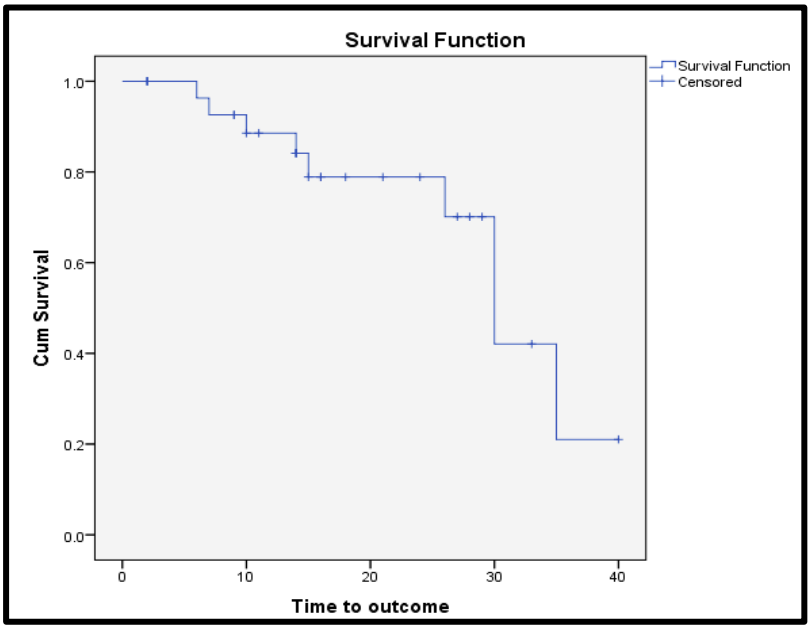

Figure 2: Progression free survival in thirty patients with LCH.

Progression free survival in relation to disease extent: It was 70% in patients with uni-focal disease, 65% in patients with multi-focal disease and 35 % in patients with multi-system disease. The difference between the three groups was statistically insignificant (P value= 0.432) as seen in ***Figure (3)*.**

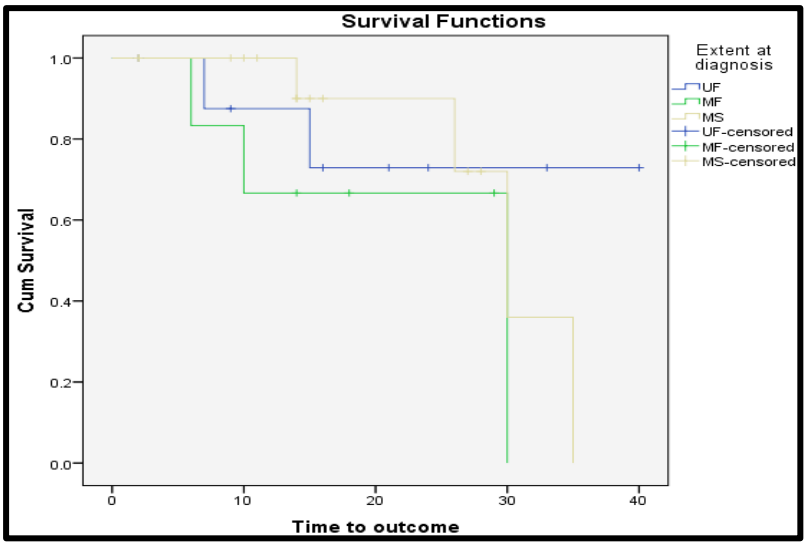

Figure 3: Progression free survival with correlation to disease extent.

Progression free survival in relation to risk of death: Low risk group showed progression free survival rate of 55% while high risk group showed progression free survival of 25%. The difference between groups was statistically insignificant (P value= 0.304) as seen in ***Figure (4)*.**

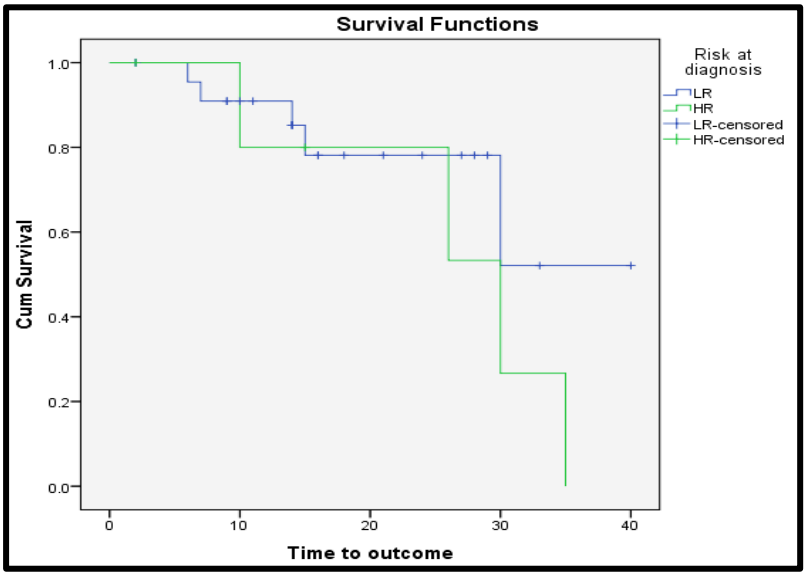

Figure 4: Progression free survival with correlation to risk of death.

DISCUSSION:

The clinical presentation and course of Langerhans cell histiocytosis (LCH) are variable, ranging from an isolated, spontaneously remitting bone lesion to multisystem disease with life-threatening organ dysfunction. Management ranges from a wait and see attitude to intensive multidrug therapy and in some cases bone marrow or liver transplantation. Treatment efficacy is difficult to evaluate. Bone may take months to recover. In patients with multi-organ involvement, treatment may cure skin lesions while failing to improve hematological status. Evidence of improved or resolved lesions is necessary to define a good therapeutic response to chemotherapy. Few authors have demonstrated the usefulness of FDG PET/CT for monitoring of therapeutic response in patients with LCH [(5)].

The present work was designed to evaluate the role of ^{18}F-FDG PET/CT in assessment of treatment response and survival of children with Langerhans cell histiocytosis.

Zhou et al, reported on serial ^{18}F-FDG PET/CT studies and showed variable response rates to therapy between bone and soft tissue lesions. Few lesions were resistant to the chemotherapy requiring additional radiotherapy. Also they stated that osteolytic change although is a common manifestation on CT images, it does not necessarily reflect an active status of a lesion in comparison to the PET findings [(6)].

In our study, PET/CT was able to detect metabolic changes in some osseous and lymph node lesions, the percentage of change of the mean SUV max was evident in vertebrae, ribs, and long bones. Also nodal lesions showed similar heterogeneous metabolic behavior with higher percent change of the mean SUV max in mediastinal and abdominal lymph nodes.

Similarly, ***Phillips et al***, reported that PET scan showed response to treatment via change in SUV before radiographic changes by other modalities were noted in 33/256 lesions (12.9%). They also showed additional lesions 90/256 lesions (35%) [(7)].

Gadner et al, stated that survival is closely linked to the extent of disease at presentation when high-risk organs. They found that recurrences have been found in 10% of patients with unifocal disease, 25% of patients with multi-focal bone LCH and 50% of both low-risk multisystem patients and high-risk multisystem patients [(8)].

In this study, although twenty one patients (70%) had multi-system involvement the overall survival was 100% most of them had residual active disease.

On the other hand, we noticed over all progression free survival (PFS) is only 20%. On further analysis in relation to disease extent PFS was 70% in patients with uni-focal disease, 65% in multi-focal disease and 35% in multi-system disease, yet the difference between the three groups was statistically insignificant. Also, on analysis in relation to risk of death, low risk group showed PFS 55% while high risk group showed PFS 25%. The difference between groups was also statistically insignificant.

Similar results was reported by ***Gadner et al***, they found that patients with low-risk multisystem LCH have a survival rate of almost 100%, but reactivations were shown to be major risk factors as late effects [(9)].

Also ***Donadieu et al***, analyses 27 patients with refractory high-risk organ involvement and resistant multisystem low-risk organ involvement, they revealed progression-free survival rate of 63% and a 5-year overall survival rate of 85% [(10)].

Also ***Simko et al*** showed that infants with single system skin only disease had 89% 3 year progression free survival [(11)].

Regarding nodal involvement ***Ducassou et al*** revealed that cervical nodes are the most frequently involved site with 5 year survival 87% and deaths mostly attributable to hematologic involvement **(12)**.

CONCLUSION:

In conclusion, our results advocate for F-18 FDG PET/CT as a useful tool in identification of metabolically active lesions which help in assessment of treatment response in LCH patients. Progression free survival is related to disease extent and risk stratification.

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