Clinico laboratory assessment of Late Sequel in Childhood Cancer Survivors at Pediatric Oncology Department South Egypt Cancer Institute

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Abstract

Background: **Background:** Improved survival after childhood cancer was attributed to intensive, aggressive therapy. The adverse sequel can manifest months to years after completion of treatment. There is a little information about the late adverse effects of both childhood cancer and its therapy.

Aim: - Screening and assessment of late treatment –related complications that resulted from both childhood cancer and its therapy by using selected laboratory studies in addition , providing monitoring for early identification and intervention for treatment related complications.

Materials and Methods: A prospective study carried out on the period from January 2014 to December 2018. The study included 219 survivors of childhood cancer aged up to16 years at the time of diagnosis and survived for at least 2 years off of cancer therapy. They were 127 males and 92 females. The study included a complete history and clinical examination, with specific laboratory investigations to detect organ toxicity.

Results: The median age at diagnosis was 5(range, 14months-17 years old) and the median current age was10 (range, 4.4 -23 years old).The median time elapsed at end of therapy was 3.6 (2-15 years old) and the median time elapsed after diagnosis was 5 (4 -16 years old).The adverse laboratory late effects included positive HCV in 27 patients (12.3%), positive HBV in 7 patients (3.2%) and thyroid dysfunction in 40 patients (18.2%).

Conclusion:

- The higher percentage of acquired hepatitis during treatment necessitate adherent screening of the blood products at the same time, the higher percentage of subclinical hypothyroidism require good follow up for early detection and management.

Key words: Childhood cancer, follow-up, late effects, survivors, laboratory investigations.

Introduction:

"Late effects" are defined as therapy- related complications or adverse effects that persist or arise 2 years after completion of treatment. The 5 years cure rate for childhood cancer is now nearly 80%, and for some cancers, such as acute lymphoblastic leukemia and Hodgkin's disease, cure rates exceed 90% . [(6)]

Nearly two-thirds of all of childhood cancer survivors will suffer some late effects, and the endocrine system is commonly involved. Care of the childhood cancer survivor is shifting from merely the detection of relapse to an improved understanding of the long-term sequeale of cancer treatment ***[13)]*.**

The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Children, Adolescent, and Young Adult Cancers (COG LTFUG), most recently updated in 2006, provide a summary of late effects of surgery, radiation, chemotherapy,and stem cell transplant [(4)].

Progress in therapy has made survival into adulthood a reality for most children, adolescents, and young adults diagnosed with cancer today. Notably, this growing population remains vulnerable to a variety of long-term therapy-related sequeale. Systematic ongoing follow-up of these patients, therefore, is important for providing for early detection of and intervention for potentially serious late-onset complications. In addition, health counseling and promotion of healthy lifestyles are important aspects of long-term follow-up care to promote risk reduction for health problems that commonly present during adulthood ***[(9)]*.**

The laboratory investigations are one of the main tools for detection of late effects in childhood cancer survivors, used for detection of these late effects, also for follow up and monitoring of these late effects which include the detection of endocrinal late effects such as thyroid disorders and infertility, hepatitis and anemia.

Aim

Screening and assessment of late treatment –related complications in our survivors resulting from therapy for childhood cancers at Pediatric Oncology

Department at South Egypt Cancer Institute by using selected laboratory studies in addition , providing monitoring for early identification and intervention for treatment related complications.

Patients and Methods:

Survivor's selection

A prospective study was carried out on children with cancer who survived for at least 2 years off of cancer therapy at the Pediatric Oncology Department, SECI, Assiut University. The study included pediatric survivors up to 18 years with all types of malignancies and survivors for at least 2 years off of cancer therapy. The survivors were subjected to the following:

Detailed history, complete physical examination and full laboratory investigations such as complete blood count (CBC), Liver function test s(LFTs), kidney function tests (KFTs), hepatitis markers, hormonal studies including thyroid function tests and sex hormones. Bone marrow aspirate and biopsy (for patients with hematological malignancy, transformation of MDS and secondary malignancies due to therapy) and selected radiological modalities.

Results:

Survivor characteristics

The median age at diagnosis was 5(range, 14months-15 years) and the median current age was 10(range, 4.4 -18 years).The median time elapsed after end of therapy was 3.6 (2-4 years) and the median time elapsed after diagnosis was 5 (4 -9 years) **(Table 1).**

One hundred and twenty seven were males (58%) and ninety two were females (42%) with male to female ratio 1.08:1. Thirteen male participants had a history of smoking (7 HL and 6 ALL) , positive family history of cancer in five survivors (2 ALL and 3 solid tumors), only7 survivors received hepatitis B virus vaccine (one WT and 6 ALL after finishing treatment) who were hepatitis B surface antigen negative ,180(88%) survivors had health insurance coverage.

Regarding the diagnosis, the majority of our survivors diagnosed as hematological malignancies 126 (57.4%), sixty-three survivors (28.7%) had leukemia 59 (26.9%) ALL, 4 (1.8%) AML and 63 survivors (28.7%) had lymphoma (20 (9.1%) HL and 43 (19.6%) NHL. Ninety three (42.6%) diagnosed as solid tumors ,30 survivors (13.7%)had WT and 17 survivors (7.8%) had NB, 16 survivors (7.3%) had soft tissue sarcomas, 12 survivors had bone sarcomas 10 (4.6%) OS and 2survivors (1.8%) ES), 11 survivors (5.3%) had GCT and four survivors(1.8%) had HB, one survivor (0.7%) had colonic adenocarcinoma, one survivor (0.7%) had histocytosis and one survivor (0.7%) had brain tumor figure (1).

With respect to treatment, 105(47.4%) received CTH alone, 36 (16.2%) received CTH and RTH, 55 (24.75%) received CTH and surgery and 23 (9.85%) received triple therapy. No bone marrow transplantation.

Table 1: Demographic characteristics of the studied 219Childhood Cancer Survivors

Variable	Nu (%)
Age at Diagnosis : Median (range)	5yrs (14 months-15 years)
Current Age : Median (range)	10yrs(4.4 -18 years)
Time elapsed	
After Diagnosis	5 (4-9 years)
Treatment Completion	3.6 (2-4 years)
Sex	
Males	127 (58%)
Females	92 (42%)
Diagnosis	
hematological malignancies	126(57.4%)
solid tumors	93(42.6%)
Clinical presentation	
No complaint	65 (29.6%)
With complaint	154 (70.3%%)
Abdominal pain	5(2.28%)
chest infection	59 (26.9%)
bone pain	20 (8.8%)
dental caries	60 (24.9 %)
secondary amenorrhea	2 (0.91%)
poor school achievement	13(5.9%)
Growth Curve	
Normal	152 (69.4%)
Abnormal	67 (30.6%)

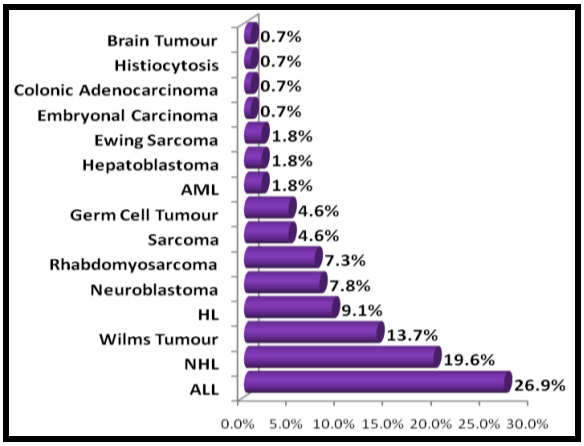

Fig. 1: Distribution of the 219 Survivors according to Diagnosis

During screening of late effect ,no complaint in 65 survivors (29.6%) and 154 (70.4%) presented with complaint, 59 (26.9%) of survivors had simple chest infection and were given supportive treatment, 5 survivors (2.3%) presented by abdominal pain, 60 (24.9 %) of survivors had dental caries and were given a dental consultation for management .Ten survivor (4.5%) presented by chronic otitis media and were given ENT consultation for management ,Twenty (8.8%) survivors complain of severe bone pain. Two females were complaining from secondary amenorrhea

(one HL and 1 GCT). 13 (5.9%) survivor presented by memory impairment and poor school achievement

Regarding growth and nutritional assessment of our survivors, there is normal growth curve in152 (69.4%) and abnormal growth curve in 67 (30.6%) in the form of obesity in 42 (19.2%), malnutrition 10(4.6%), short stature 6(2.7%) and malnutrition and short stature 9.

Overall late effects

Regarding the laboratory tests abnormal CBC was found in (21/9.5%) in the form of anemia (17/7.7%) , anemia and leucopenia in two survivor and pancytopenia in two survivor, KFTs and LDH were normal, LFTs were abnormal with chronic liver toxicity (59/26.4%) in the form of increased ALT (30/13.5%),increased AST (19/8.9%), increased ALT and AST in 10 (4.5%) , viral hepatitis was detected in 40 (18.2%) survivors, positive HCV in 27 (12.3%), positive HBV in 7 (3.2%) and positive both HCV&HBV in 6 (2.7%) survivors. Bone marrow aspirate was done in 54(24.6%) survivors with hematological malignancies, BM relapse was found in2 ALL survivors (1.4 %) and normal in 52 (%) **(Table 2).**

Regarding hormonal assay, there was abnormal thyroid function tests in 31 survivors (14.1%) include functional subclinical hypothyroidism in 17 survivor (7.7%) with increased TSH and decrease T3and T4 (9HL, 4ALL, 2STS and 2 NHL). 5 (2.3%) survivors increase T3and T4 (thyroid nodule) and 9 (4.1%) survivors had decrease T3 or T4 (3 survivors and 6 respectively), all these survivors had follow up with endocrinologist and three survivors put on replacement therapy. Sex hormones (LH, FSH) were low in two females survivor (one HL and one GCT) who received replacement therapy and one WT male survivor had low level of testosterone hormone who referred to androlologist. Tumor markers B-HCG and Alpha fetoprotein were normal for survivors with GCT and HB figure (2).

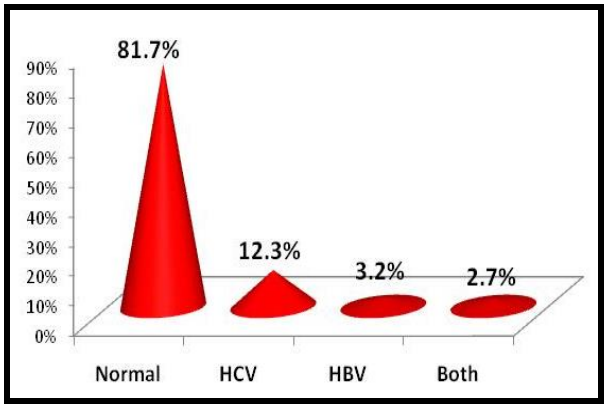

Fig. 2: Distribution of the 219 survivors according to Viral Hepatitis Infection

Table 2: Laboratory Investigations of the studied Childhood Cancer Survivors

Variable	Nn (%)
CBC	
Normal	198(90.4%)
Abnormal	21(9.5%)
Anemia,	17(7.7%)
anemia and leucopenia	2(0.9%)
pancytopenia	2 (0.9%)
LFTs	
Normal	160 (72.6%)
Abnormal	59(26.9%)
Increased ALT	30 (13.5%)
Increased AST	19 (8.9%)
increased ALT and AST	10(4.5%)
viral hepatitis markers	
Normal	179 (81.8%)
Abnormal	40 (18.2%)
Positive HCV	27(12.3%)
Positive HBV	7 (3.2%)
Positive HCV&HBV survivor)	6(2.7%)
Bone marrow aspirate	**54(24.6%)**
Normal	52 (23.7%)
Abnormal	2 (0.9%)
BM relapse	2(0.9%)
Thyroid function tests	
Normal	176 (81.5%)
Abnormal	31 (14.1%)
Increased TSH and decrease T3and	17(7.7%)
T4	5 (2.28%)
Increase T3and T4	9 (4.1%)
decrease T3 or T4	
Sex hormones	
low LH, FSH	2 (0.9 %)
low testosterone hormone	1(0.4%)

Number of late effect and severity grading

Among the 219 survivors, 102 (46.5%) had late effect and 117 (53.4%) had no late effects.one late effect was present in 60 (58.8%), Two late effects were present in 33 survivors (32.3%) and 3 late effects were present in 9 survivors (8.8%). Sixty nine survivors (67.6%) had grade 1 (mild) late effects and 30 (29.4%) had grade 2 (moderate). Grade 3 or more late effects were found in 3 (3%) survivors. No deaths among the 209 survivors

Pattern of Late effects according to diagnosis

ALL Survivors (59/26.9%)

Abnormal CBC , BMA (4/2.3%). Endocrine system 8 (13.5%), abnormal TFT increased TSH and decrease T3and T4(8/13.5 %), ,chronic liver disease 2 (3.3%), positive HCV 10 (16.9%) , positive HBV 4 (6.7%) .

AML Survivors (4/1.8%)

Chronic liver disease in 3(75%), positive HCV 1(25%), endocrine system with abnormal TFT increased T3 (1/25%).

NHL Survivors (43/19.6%)

Chronic liver disease 5 (11.6%), positive both HBV and HCV 4 (9.3%), positive HCV 7(16.2%), positive

HBV 1(2.3%), abnormal TFT 7 (16.2%) , and anemia 5 (11.6%).

HL Survivors (20/9.1%)

Anemia 4 (20%), leucopenia 1(5%). GIT 2 (10%), chronic liver disease 1(5%), positive HCV 1(5%), abnormal TFT 8(40 %) .

WT Survivors (30/13.7%)

Chronic liver disease (3/10%) , positive HCV 3(10%), positive HBV (2/6.6%), positive both HCV and HBV (1/3.3%) , anemia (1/3.3%), .Endocrine system 5(16.6%), increased T3 and T4 1 (3.3%), increased T3 3 (10%), male infertility 1(3.3%),

Neuroblastoma Survivors (17/7.8%)

Anemia (1/5.8%), GIT 7 (41.1%), chronic liver disease 2 (11.7%), positive HCV 3 (17.6%),. Endocrine system 2 (11.7%) .

Sarcomas Survivors (31/13.6%)

Endocrine system 4(12.9%), increased T3 in 1 ,decreased T3 and T4 in 3(9.6%),GIT in 3(9.6%),chronic liver disease 1 (3.3%) , increased ALT and AST 1(3.3%) , positive HCV 1(3.3%) ,CNS 1(3.3%) .

Germ cell tumor Survivors (11/5%)

GIT 2(18%), chronic liver disease 1(9%), positive HCV in one survivor (9%), endocrine system 1 (9%) with increased T3 and T4.

Hepatoblastoma Survivors (4/1.8%)

GIT 2(50%), chronic liver disease 1(25%) (increased ALT and AST), positive HCV &HBV in one survivor (25%), endocrine system increased T3 and T4 in 1 (25%) .

Brain tumor Survivor (1/0.7%)

Table 3: Late Laboratory effects among 219 survivors of childhood cancer at the time of follow up at the end of treatment

Diagnoses	BM	Endocrine	GIT
ALL (59/26.9%)	4 (2.3%)	8 (13.5%)	14(23.7%)
NHL (43/19.6%)	anemia5 (11.6%)	7(16.2%)	14 (31%)
HL (20/9.1%)	anemia 4,leucopenia 1,5(5%)	8(40%)	2(10%)
WT (30/13.7%)	anemia1 (3.3%)	5(14%)	13(43.3%)
Sarcomas (31/13.6%)	----------	4 (12.9%)	3 (9.6%)
NB (17/7.8%)	anemia 1(5.8 %)	2(0.34%)	7(41.1 %)
GCT (11/5%)	----------	1(9%)	2(18%)
AML (4/1.8%)	----------	1(25%)	4(100%)
HB (4/1.8%)	----------	1(25%)	2(50 %)
Total	16(7.3%)	37(16.8%)	61(27.8%)

Statistical analysis

Data were verified, coded by the researcher and analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA) *. Descriptive statistics: Means, standard deviations, medians, ranges and percentages were calculated. Test of significances: chi-square test was used to compare the difference in distribution of frequencies among different groups. Independent t-test analysis was carried out to compare the means of dichotomous data. For variables with more than two categories; ANOVA test was calculated to test the mean differences of the data that follow normal distribution, post-hoc test was calculated using Bonferroni corrections. A significant p value was considered when it is equal or less than 0.05.

Discussion:

Advanced oncotherapy and better supportive care have led to increased survival of childhood malignancy patients over the past few decades. Over 80 per cent children with cancer survive more than five years from diagnosis in various centers and are cured of the disease . [14] [15]

Better long-term survival is also accompanied with late or long-term effects of cancer treatment. It is believed that a third to half of childhood cancer survivors will experience a late/long-term effect of cancer therapy, of which up to half may be life-threatening [11].

The screening and treatment of late effects in survivors of childhood cancer remain an under-researched area in most regions of the world [16].

This study conducted on 219 childhood cancer survivors. The majority of our survivors diagnosed as hematological malignancies comprised 57.4% and solid 42.6% with the highest proportion for ALL which matched with [1] that hematological malignancies 51.5% versus 48.5% solid and not matched with Indian study where hematological malignancies comprised 25% .

With respect to specific diagnosis , 30.9% had leukemia , 28.7% had lymphoma,21.% had WT, 7.8% had NB and 23% had others diagnosis which more or less similar to [8] where 39.4% had leukemia ,35 (14.5%) had lymphoma and 46% had others diagnosis .The male-to-female ratio in our study was 1.08: 1 which matched with [8] where ratio was. 1.5:1

In our study, The median time elapsed after end of therapy was 3.6 (2-4 years) and the median after diagnosis was 5 (4 -9 years) which is short when compare with other studies in the United States [14] and The Netherlands [7] where a follow-up period of over 15 years from diagnosis.

In Brazil, this is one of the few studies conducted in childhood cancer survivors developed by the US NCI in a survivor population of childhood cancer. The LAE were observed in 27.4% of the survivors, with acute lymphoid leukemia and lymphoma being the most prevalent initial diagnoses in this group. Hypothyroidism was the main dysfunction observed in the survivors who presented changes in the endocrine-metabolic system.

Among our survivors, 102 (46.5%) had late effect and 117 (53.4%) had no late effects which less than ***(8)*** in his study where 144 (59.8%) had at least one late effect and 97 (40.2%) had no late effects and studies in the United States [14] and The Netherlands where the late effect present in 62.3% and 74.5%, respectively .

The majority of the affected survivor had one late effect (58.8%), 32.3% had two late effects and 8.8% had three late effects. Which not matched with study by ***(Han et al., 2009)*** who reported that two or more late effects were present in 60 survivors (24.9%).

Regarding severity, Sixty-one survivors (25.3%) had grade 1 and 83 (34.4%) had grade 2 and Grade 3 or more late effects were found in 10.8% of survivors which less than studies conducted by [12] this can explained by short follow up period in our study after diagnosis .ALL survivors had the highest late effects and germ cell tumorshad the lowest risk for late effects.

There have been many reports documenting endocrine, especially thyroid, abnormalities are the commonest in childhood cancer survivors [2] [14] , Our findings were not consistent with prior reports, GIT system(39.2%), the most affected followed by growth(30.6%) and endocrine(15.5%) .

Long-term hepatotoxic effects following chemotherapy are not common. Viral infections such as hepatitis A virus, HBV and Cytomegalovirus may be acquired during the treatment for cancer either due to immunosuppression or related to transfusions which may lead to chronic active hepatitis, fibrosis and cirrhosis. Certain drugs such as methotrexate, actinomycin D, 6 mercaptopurine and thioguanine are also implicated as causes for chronic liver disease [18] . In our study viral hepatitis was detected in 40 (18.2%) which very high in comparison with other studies [14] [9] this can explained by high percent of hematological malignancies (57.4%) in our survivors who received intensive prolonged CTH .positive HCV (27/12.3%) then positive HBV (7/3.2%), common in ALL (10, 4 respectively) which matched with other Egyptian study where 28.6% of survivors had hepatitis C antibodies ***(19)*** **.** This result can explained by the high incidence of ALL in our study, aggressive CTH which lead to sever prolonged bone marrow suppression and frequent blood transfusion which may be not irradiated and reactivationof hepatitis.

The incidence of thyroid dysfunction depends on the dose of radiation, the length of follow-up and the biochemical criteria used to make the diagnosis. Only persons who had received radiotherapy to the brain and head and neck region and who are susceptible to hormonal dysfunction were screened for thyroid function.

Abnormal thyroid function was detected in (27.9%).functional Subclinical hypothyroidism was seen in (7.7%)mainly in hematological malignancies due to cranial and mantle radiotherapy which more than two Indian studies [10] . Which can explain by difference in diagnosis and number of the survivors.

Young adult Hodgkin lymphoma survivors who were treated with high doses of radiation to the thyroid gland are at substantially increased risk for the development of a spectrum of abnormalities of the thyroid. especially female survivors are at particularly high risk for developing hypothyroidism and thyroid nodules [5].

Hypothyroidism is the most commonly reported abnormality of the thyroid gland after radiation exposure, but hyperthyroidism and development of thyroid nodules occur as well. The association between hypothyroidism and higher radiation doses has been well established. ***(3)***

In a study from south India, male and female gonadal dysfunctions were seen as the common late toxic effects. Oligospermia/azoospermia was seen in 89% males, and gonadal dysfunction, amenorrhea or oligomenorrhoea were seen in 78% females. All had received combination chemotherapy that included alkylating agents ***(17)*** **.** That agree with Yoon et al., 2017 were observed azospermia and oligospermia in 37.5% and 12.5% of male survivors treated with alkylating agents, while a quarter of female survivors required sex hormone replacement ***(20)***

In this study gonadal function not done for the most of our survivor due to many factors such as some work up for this not available in our institute, young age of the our survivor and short time of follow up ,Sex hormones (LH, FSH) were low in two females survivor who complain from amenorrhea (one HL and one GCT) who received replacement therapy and one WT male survivor had low level of testosterone hormone .

Early recognition and treatment can reduce morbidity and mortality in this vulnerable population. The importance of long-term surveillance of those at risk cannot be over emphasized. These endocrine abnormalities may evolve over many years. One of the future challenges will be to better characterize the role of genetic variability in the pathogenesis of these endocrine abnormalities. According to the findings of current and previous studies long term investigation on cancer survivors are recommended regularly and routinely. Therefore, screening them in terms of growth, maturation processes and semen analysis, evaluation of thyroid and parathyroid function tests, measurement of cortisol, prolactin and vitamin D level in blood, assessment of BMI, fasting blood glucose, insulin and lipid profile, at specified intervals after cancer treatment is recommended ***(4)*****.**

The limitations of this study included the small study population size and the short follow-up duration compared with previous studies. It is possible that the prevalence of late effects was underestimated. This could be addressed by continued follow-up of the enrolled survivors. Another limitation was the absence of brain tumor survivors as there is no neurosurgery in our SECI.

Conclusion:

The higher percentage of acquired hepatitis during treatment necessitate adherent screening of the blood products at the same time, the higher percentage of subclinical hypothyroidism require good follow up for early detection and management.

Abbreviations: COG LTFUG (Children oncology group long term follow up guidelines), **SECI** (South Egypt Cancer Institute), CBC (Complete blood count), **LFTs** (Liver function tests), KFTs (Kidney function tests), **MDS** (Myelodysplastic syndrome), **ALL** (Acute lymphoblastic lymphoma), **AML** (Acute myeloid leukemia), HL (Hodgkin lymphoma), **NHL** (Non Hodgkin lymphoma), **WT** (Wilms tumor), **NB**(Neuroblastoma), **GCT** (Germ cell tumor), **HB** (Hepatoblastoma), ES(Ewing sarcoma), **CTH** (Chemotherapy), **LDH** (Lactic dehydrogenase), **ALT** (Alanine transaminase), **AST** (Aspartate transaminase), **TSH** (Thyriod stimulating hormone), **LH** (Lutenizing hormone), **FSH** (Follicle stimulating hormone), **BMA** (Bone marrow aspirate), **RTH** (Radiotherapy).

References

1- Amany M A, Heba AS , Douaa MS : **Pattern of Pediatric Tumors at Pediatric Department in South Egypt Cancer Institute**: (2016). Thirteen Years Report J Pediatr Child Nutr **2**(2)100112

2- AndersonNE **: Late complications in childhood central nervous system tumour survivors CurrOpinNeurol**, (2003) **16**(677-683)

3- Armstrong GT, Stovall M, Robison LL :**Long-term effects of radiation exposure among adult survivors of childhood cancer:** (2010), **results from the childhood cancer survivor study.** Radiat Res **174:**840–50.

4- Bhatia S**: Hematology Am SocHematolEducProgram** (2005) . **507**-515.

5- Brignardello E, Felicetti F,: **Endocrine health conditions in adult survivors of childhood cancer:** (2013) , the need for specialized adult-focused follow-up clinics.*Eur J Endocrinol.* 465–72. doi**: 10**.1530/EJE-12-1043

6- Cohen EP and Robbins ME: **Radiation nephropathy.SeminNephrol** (2003), **23**: 486-499.

7- GeenenMM, Cardous-, UbbinkMC : **Medical assessment of adverse health outcomes in long-term survivors of childhood cancer** (2007), JAMA297(2705-2715)

8- HanJ. W. , Kwon S. Y. ,Won S. C : **Comprehensive clinical follow-up of late effects in childhood cancer survivors** shows the need for early and well-timed intervention Annals of Oncology(2009) **20**: 1170–1177.

9- Hudson MM, Mertens AC, Yasui Y : **Health status of adult long-term survivors of childhood cancer:** a report from the Childhood Cancer Survivor Study. (2003) *JAMA.*290 (**12**):1583–1592.

10- Kurkure P, Achrekar S, Dalvi N, Goswami S: **Childhood cancer survivors** – Living beyond cure. Indian J Pediatr (2003**):**.;70:825–8.

11- Miller KD, Pandey M, Jain R, Mehta R : **Cancer survivorship and models of survivorship care**: A review. Am J ClinOncol. (2015) ;**38**:627–33.

12- Oeffinger KC, Mertens AC, Sklar CA : **Obesity in adult survivors of childhood acute lymphoblastic leukemia:** a report from the childhood cancer survivor study group. (2003) J ClinOncol ;**21**:1359-1365.

13- Oeffinger KC, Mertens AC, Hudson MM : **Health care of young adult survivors of childhood cancer**. a report from the Childhood Cancer Survivor Study. *Ann Fam Med.* (2004) **2**(1):61–70.

14- Oeffinger KC, Mertens AC, Sklar CA : **Chronic health conditions in adult survivors of childhood cancer,** (2006)NEngl J Med**355**(1572-1582)

15- Phillips SM, Padgett LS, Leisenring WM, Stratton KK, Bishop K, Krull KR : **Survivors of childhood cancer in the United States.prevalence and burden of morbidity**. Cancer Epidemiol Biomarkers.(2015) Prev .**24**:653–63.

16- Poon LHJ, Yu CP, Peng L : **Clinical ascertainment of health outcomes in Asian survivors of childhood cancer**: a systematic review. J Cancer Surviv. (2019)Jun**;13**(3):374-396.

17- Rajendranath R, Veeraiah S, Ramesh A, Sagar TG: **Late effects of treatment in survivors of childhood cancer from a tertiary cancer center in South India**. (2014) South Asian J Cancer.;3:60–5

18- Sodhi JS, Wani N, Jeelani S :**Occult hepatitis B virus infection as a cause of posttransfusion hepatitis in patients with cancers**. Indian J Gastroenterol(2013):.;**32**:291–6.

19- Tantawy AA, El-Rashidy FH, Ragab IA, Ramadan OA, El-Gaafary MM : **Outcome of childhood acute Lymphoblastic leukemia in Egyptian children: a challenge for limited health resource countries**. Hematology. (2013) ; **18**(4):204-210.

20- Yoon JY, Park HJ, Ju HY : **Gonadal and sexual dysfunction in childhood Cancer survivors.** Cancer Res Treat (2017). ;**49**:1057–64.