Primary lymphoma of bone in Egyptian population: a retrospective study with emphasis on prognostic factors and treatment outcome

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Abstract: Background: Primary bone lymphoma (PBL) is a rare disease with lacking data on the prognostic factors or the treatment outcome. **Patients and Methods**: We retrospectively collected data from twenty three patients with PBL referred to the department of Clinical Oncology, Tanta University Hospitals from 2000 to 2013 to better understand the outcome of this disease in Egyptian population. **Results:** Median age was 48 years (range, 26–68) with male predominance (52.2%). The most frequent location was the femur and pelvis (26.1% and 17.4%, respectively). 17 patients (73.9%) were treated with radiotherapy either alone or in combination with chemotherapy while 6 patients were treated with chemotherapy alone**.** The overall response rate was 82.6%**.** The 5-year and 15-year overall survival (OS) was 82.6% and 69.6%, respectively. Freedom-from treatment failure (FFTF) was significantly higher with normal LDH level (P = 0.001), female gender (P = 0.001), ECOG performance status < 2 (P = 0.001), low grade tumors (P = < 0.0001), and combined modality therapy (P = 0.05). OS was significantly higher in female (P = 0.04), < 40 years (P = 0.003), lack of B symptoms (P = 0.001), normal LDH level (P = < 0.005), and combined modality therapy (P = 0.01). On multivariate analysis, only age < 40 years and the use of combined modality therapy were independent prognostic factors for better OS and FFTF. **Conclusions:** Our data showed that age < 40 years and combined modality therapy were independent prognostic factors for better OS and FFTF in Egyptian patients with PBL.

1. Introduction

Primary bone lymphoma (PBL) is not a common disease [1], representing about 5% of non-Hodgkin lymphomas (NHL) [2, 3] and 3% of all bone malignancies [4].

The definition of PBL in the new version of "WHO pathology and genetics classification of soft tissue and bone tumor"[5] in 2013 is single or multiple tumor in the bone consisted of malignant lymphocytes, not associated with invasion or involvement of other extranodal malignant lymph nodes outside the area.

There is no specific age predominance, with a median age of onset ranging from 40–60 years old. PBL is more frequent in male than in female (1.0–1.8:1), and also was found in children [1,2]. The most common histpathological subtype is diffuse large B-cell lymphoma (DLBCL) [6, 7, 8].

According to 2013 WHO, the independent prognostic factors of worse overall survival and progression free survival are soft tissue extension and worse international prognostic index (IPI) score [6].

Due to paucity of the studies with respect PBL, most of the data are derived from retrospective analyses over decades [9]. Furthermore, recent studies are largely from Europe, United States, and Asia with sparse data from African population. Here we retrospectively collected and analyzed data from twenty three patients with PBL who were referred to the Department of Clinical Oncology, Faculty of Medicine, Tanta University Hospitals from January 2000 to January 2013, in order to better understand the characteristics, prognostic factors and treatment outcome in Egyptian population.

2. Patients and Methods
Design of the Study

This study is a retrospective single institution study**.** The Ethics Committee in Faculty of Medicine, Tanta University, granted study approval.

Data collection:

This retrospective study was conducted at the Clinical Oncology Department, Faculty of Medicine, Tanta University Hospitals from January 2000 to January 2013. Twenty-three with confirmed measurable PBL were enrolled. All patients were chemotherapy and radiotherapy-naïve patients with their age ranged between 18 and 70 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; measurable disease; available treatment data as well as follow-up data.

Pretreatment evaluation

All patients had their medical histories recorded including presenting symptoms, sites of involvement, presence of B symptoms, as well as pretreatment stage. Physical workup information including chest X-rays, routine laboratory studies, bone marrow biopsy, contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis and magnetic resonance imaging scan and were also collected. The clinical stage was determined by Ann Arbor staging criteria [10]. Stage IE was defined as a solitary bone lesion without lymph node involvement; stage IIE as a solitary bone lesion with regional lymph nodes involvement; and stage IV was the presence of multiple bone lesions with or without regional lymph node involvement.

Received treatment

Patients received various treatments according to physician discretion. Four patients received radiation therapy alone, 6 received chemotherapy alone, and 13 received combined modality therapy.

Radiotherapy: 17 patients (73.9%) were treated with radiotherapy megavoltage equipment either alone or in combination with chemotherapy. Radiotherapy was delivered to the entire bone in 11 cases while localized treatment to the lesion with individually shaped portals was given in 5 cases with daily fractions of 1.8 CGy on 5 consecutive days a week. A median total dose of 43.2 Gy (range 21.6-55.8 Gy) was applied, and immobilization techniques were used as required.

Chemotherapy: A total of 19 patients had received combination chemotherapy either alone or in combination with radiotherapy. Chemotherapy alone was applied in the form of CHOP regimen in 4 patients which consisted of cyclophosphamide, adriamycine, vincristine and prednisone, and the cycle was repeated every 3 weeks or RCHOP (CHOP plus rituximab) in 2 patients. Patients without progressive disease (PD) or unacceptable toxicity continued treatment up to 4- 6 cycles. Three of these patients received CNS (central nervous system) prophylaxis with intrathecal methotrexate. Thirteen patients had received combined modality therapy in the form of either 2-6 cycles CHOP (8 patients) or RCHOP (5 patients) chemotherapy, before radiation therapy.

Patients Assessment and follow-up

Assessment of treatment response was recorded. The physicians assessed tumor response according to Cheson criteria also know as the International Workshop to Standardize Response Criteria in 1999 (IWC) [11]. The PET/CT review efficiency of some patients was based on the revised edition of malignant lymphoma remission criteria in 2007[12]. The occurrence and nature of any adverse events were recorded. Toxicity grading was based on the WHO Toxicity criteria [13]. Late complications were scored

according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema [14].

After completion of treatment, patients were assessed by physical examination, chest radiography, and serial axial CT or MRI every 3 - 4 months. Biopsy was performed from new recurrent sites of the disease with histopathological examination, and was documented at the time of initial occurrence.

Primary and Secondary Endpoints

The primary endpoints of the study were prognostic factors and the evaluation of response rate. Secondary end points were the disease-free survival and overall survival. Disease progression was defined as increases in the size of previously present disease or the appearance of new disease site as determined by serial axial CT or MRI.

Statistical Analysis:

Twenty three patients were recruited in the study between January 2005 and January 2015. The date of this analysis was October 2017.

Overall-survival (OS) rates were calculated from the start of therapy to the time of the last follow-up visit or death using the Kaplan-Meier method [15] with SPSS [Statistical package] (version 12.0). Disease - free survival was the time went by from the date of beginning of therapy to the date of first evidence of disease recurrence or death in the absence of disease recurrence. Overall survival and disease-free survival were compared by the Kaplan–Meier method [15] with statistical significance assessed by the log-rank test. Mean and standard deviation were estimates of quantitative data. Chi-square or Likelihood Ratio was used for qualitative data. All P values were two-tailed; a value of ≤ 0.05 was considered significant.

3. Results

Patients' characteristics:

From January 2000 through January 2013, we collected and analyzed data of 23 patients with biopsy-confirmed PBL who were treated at the department of Clinical Oncology, Tanta University Hospital. Patient characteristics were listed in table 1. There was a slight predominance of the male sex (52.2%) with median age of 48 years (range, 26–68). Two major sites of origin could be distinguished at diagnosis. The most frequent location was the femur (26.1%). The second frequent site was PBL originating in the pelvis (17.4%). Fourteen patients (60.9%) had performance status 1. Nine (39.1%) patients had elevated LDH at diagnosis. More than half of the patients (78.3%) had DLBCL histological subtype followed by diffuse, mixed, small and large cell histological subtype in two patients (8.7%). B symptoms were reported in four patients (17.4%). PBL could be considered as a

localized disease, with the exception of polyostotic   involvement (Table 1).

Table 1. Patients and tumor characteristics of the 23 patients with PBL

Patient Characteristics	No.	%
Sex		
Male	12	52.2
Female	11	47.8
Age, years		
Median	48	
Range	26-68	
ECOG performance status		
0	7	30.4
1	14	60.9
2	2	8.7
Histology		
DLCL	18	78.3
Diffuse, mixed, small and large	2	8.7
Follicular, mixed, small and large cleaved	1	4.3
Diffuse, small cleaved	1	4.3
Lymphoma, NOS	1	4.3
Tumor location		
Femur	6	26.1
Pelvis	4	17.4
Tibia/fibula	3	13.1
Humerus	2	8.7
Spine	2	8.7
Mandible	1	4.3
Skull	1	4.3
Scapula	1	4.3
Polyostotic	3	13.1
LDH		
Normal	14	60.9
High	9	39.1
Stage		
I	17	73.9
II	2	8.7
IV	4	17.4
B symptoms		
No	19	82.6
Yes	4	17.4
IPI score		
0	9	39.1
1	7	30.4
2	4	17.4
3	2	8.7
4	1	4.3
5	0	0
Treatment		
CMT	13	56.5
Radiotherapy alone	4	17.4
chemotherapy alone	6	26.1
CMT; radiotherapy dose		
Minimum	21.6 Gy	
Maximum	55.8 Gy	
Median	43.2 Gy	
CMT; chemotherapy regimen		
CHOP	8	
R CHOP	5	

ECOG; Eastern Cooperative Oncology Group, LDH; Lactate dehydrogenase, CMT; Combined modality treatm

The majority of the study cohort (73.9%) presented with stage I disease where stage IV was reported in 17.4%. Most patients had a low IPI score, with 20 patients (86.9%) having an IPI score of ≤ 2. Pain was the main presenting symptom in most cases (60.9%), followed by mass in 3 patients (13.1%).

Bone fracture was encountered in PBL in femur in 2 patients (8.7%). (Table2). Median time from onset of symptoms to diagnosis was the longest for polyostotic involvement (65 days) and as compared to 35 days in PBL of the femur. Thirteen (56.5%) patients had received combined modality therapy (CMT).

Received treatment:

Most patients (83.3% in the chemotherapy alone arm, 75% in the radiotherapy alone arm, and 76.9% in the CMT arm) received the full dose of the scheduled treatment protocols. Treatment delays of seven days or more happened more often in the CMT arm than in the radiotherapy alone arm and the chemotherapy alone arm (only 1 patient in the chemotherapy alone arm compared to 2 patients in the CMT arm) but without statistically significant difference (p = 0.94), (Table 3). Dose reductions were not often. Overall, only 5 patients (21.7%, 5/23) received at least one dose reduction (Table 3). There was no statistically significant difference between the treatment arms in the percentage of patients with dose reductions (25% in the radiotherapy alone arm compared to 16.7% in the chemotherapy alone arm and 23.1% in the CMT arm; p = 0.98). The mean radiotherapy doses for all patients in the radiotherapy alone and CMT arms were 44 Gy and 43.2 Gy respectively.

Response to Treatment

The overall response rate (CR+PR) was 82.6% (19/23) of all patients and the disease control rate (CR+PR+SD) was 86.9% (20 patients). Seventeen patients (73.9%) developed complete response and 3 patients (13.1%) had disease progression (Table 4). No patients went through amputations.

Survival

All our patients were followed up regularly, with no one had lost follow up in this study. Patients were followed for a median of 132 months, range; 1 – 180 months (SD = ± 36.6 months). The 5-year and 15-year DFS rate were 82.4% and 64.7%, respectively (Fig.1). The 5-year and 15-year OS rate were 82.6% and 69.6%, respectively (Fig.2).

Prognostic Factors

On univariate analysis, IPI score did not significantly affect OS (P = 0.18), cancer-specific survival (CSS) (P = 0.34), or FFTF (P = 0.21). Freedom-from treatment failure (FFTF) was significantly higher in patients with normal LDH level (P = 0.001), female patients (P = 0.001), patients with ECOG performance status < 2 (P = 0.001), patients with histopatholgical low grade tumors (P = < 0.0001), and in patients who had received combined modality therapy (P = 0.05).

OS was significantly higher in patients with age <40 years (P = 0.003), female patients (P = 0.04), patients with lack of B symptoms (P = 0.001), patients with normal LDH level (P = < 0.005), and in patients who had received combined modality therapy (P = 0.01). No differences were observed regarding CSS except for female gender (P = 0.04). On multivariate analysis, only age < 40 years and the use of combined modality therapy were independent prognostic factors for better OS, CSS, and FFTF.

Toxicity

Most common grade 3-4 hematological toxicities in the combined modality therapy arm (n=13) were neutropenia in 3 patients (23.1%), with one (7.7%) patient suffered from febrile neutropenia, and one (7.7%) patient developed grade 3-4 thrombocytopenia. Grade 3-4 diarrhea in 3 patients (23.1%), nausea in 2 patients (15.38%) and mucositis in 1 patient (7.7%) were the most common Grade 3-4 non hematological toxicity. One patient (16.7%) had grade 3-4 neutropenia while one additional patient (16.7%) had diarrhea and another one suffered from nausea and mucositis added in later cycles in the chemotherapy arm (n=6). Only one patient had grade 3-4 diarrhea in the radiotherapy arm (n=4). Six patients from 23 (26.1%) were hospitalized for treatment-related toxicity. There was no treatment-related death.

Late events after therapy

Late events after therapy were evaluated and summarized in table 6. After about 10 years of follow-up CMT produced significantly less diarrhea (p = 0.02), as well as less incidence of second malignancy (p = 0.001). Other late events including pulmonary toxicity (p = 0.11), Hypothyroidism (p = 0.07), cardiac complications (p = 0.38), and Hyperthyroidism (p = 0.19) were more frequent in the radiotherapy alone arm but this difference was not statistically significant (all p = NS) (Table 6).

Table 2. Clinical picture at diagnosis in the 23 patients with PBL

Symptoms and signs	No	%
Pain	14	60.9
Mass	3	13.1
Bone fracture	2	8.7
B symptoms (fever, night sweats and loss of weight)	4	17.4
Others	2	8.7

Table 3. Therapy parameters in patients with PBL by treatment arm

Parameters	Radiotherapy alone arm N=4		Chemotherapy alone arm n=6		Combined-modality therapy arm N=13		P value
	No.	%	No.	%	No.	%	
Dose reduction for any reason No Yes	3 1	75 25	5 1	83.3 16.7	10 3	76.9 23.1	0.98
Treatment delay, days 0 1 – 6 ≥ 7	3 1 0	75 25 0	4 1 1	66.6 16.7 16.7	9 1 3	69.2 7.7 23.1	0.94

Table 4. Tumor response in the 23 Patients with PBL

Evaluable patients	N=23	
	No.	%
Complete response (CR)	17	73.9
Partial response (PR)	2	8.7
Stable disease (SD)	1	4.3
Progressive disease (PD)	3	13.1

**Table 5. Hematologic and non-hematologic Grade 3 & 4 toxicity in the management of the 23 patients with PBL**

Event	Number of Events After Therapy						P-value
	Radiotherapy alone arm N=4		Chemotherapy alone arm N=6		Combined-modality therapy arm N=13		
	No.	%			No.	%	
Hematologic Toxicity Neutropenia Febrile neutropenia Thrombocytopenia	0 0 0	0 0 0	1 0 0	16.7 0 0	3 1 1	23.1 7.7 7.7	0.05 0.03 0.03
Non-hematologic Toxicity Diarrhea Nausea/vomiting Mucositis	1 0 0	25 0 0	1 1 1	16.7 16.7 16.7	3 2 1	23.1 15.38 7.7	0.11 0.35 0.12

Table 6. Late events after therapy

Event	Number of Events After Therapy						P-value
	Radiotherapy alone arm N=4		chemotherapy alone arm N=6		Combined-modality therapy arm N=13		
	No.	%			No.	%	
Second malignancy	1	25	1	16.7	0	0	0.001
Cardiac	1	25	1	16.7	2	15.38	0.38
Pulmonary Grade < 3 Grade > 3	0 1	0 25	1 0	16.7 0	1 0	7.7 0	0.11
Hypothyroidism	1	25	0	0	2	15.38	0.07
Hyperthyroidism	1	25	0	0	1	7.7	0.19
GIT	1	25	0	0	0	0	0.02
Other	0	0	1	16.7	2	15.38	0.28
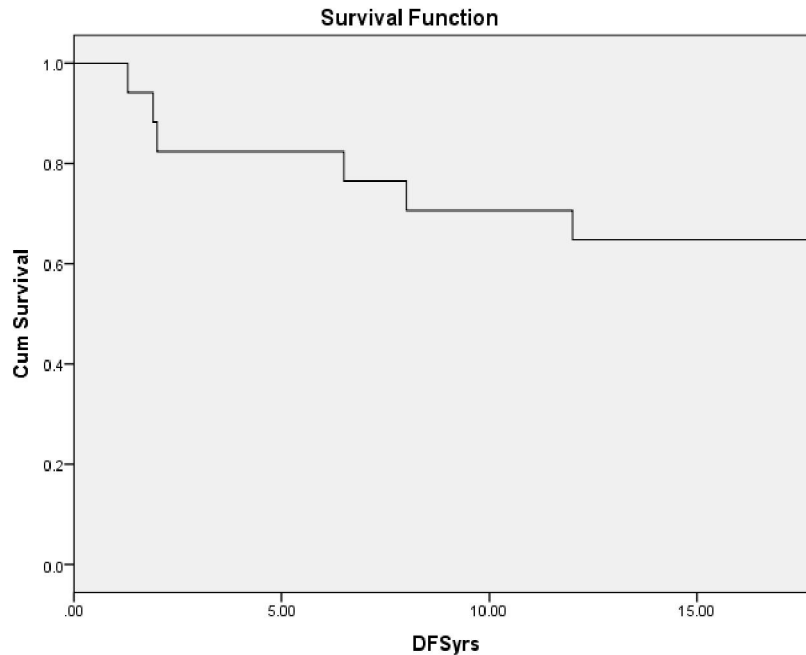
Figure. 1. Kaplan–Meier curves for DFS in patients with PBL.
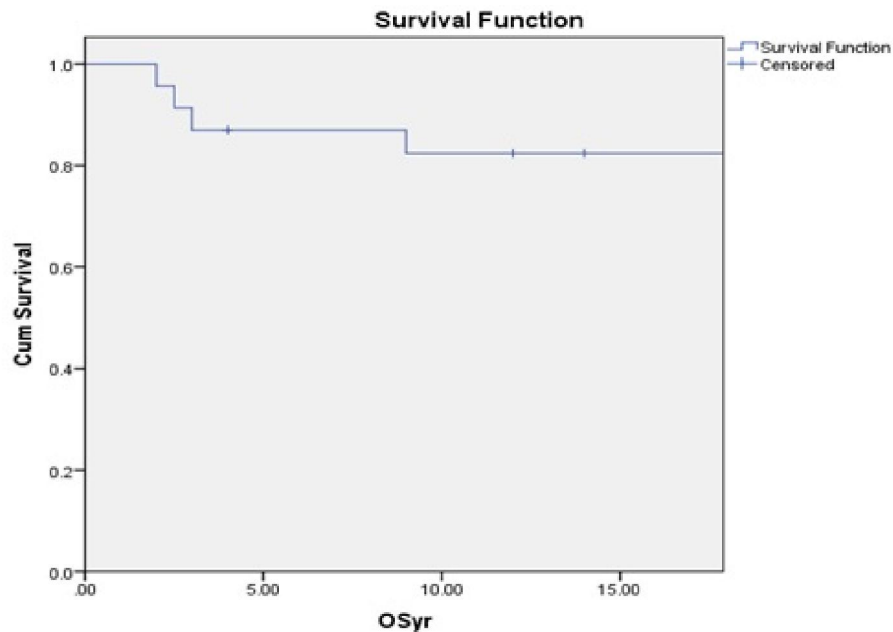
Figure. 2. Kaplan–Meier curves for overall survival time in patients with PBL.

4. Discussion

To our knowledge, there is no published major prospective randomized study applying to PBL in our country. This study is a retrospective single institution study evaluating the definition, clinical characteristics, treatment modalities, and prognosis of PBL. Our report summarizes the experience of the department of Clinical Oncology, Faculty of Medicine, Tanta University Hospitals in the management of 23 patients with PBL over the last 13 years from January 2000 to January 2013. Patients were treated with chemotherapy or radiotherapy either alone or in combination.

Long bones are the most common site of involvement with PBL [2, 16, 17, 18], but with the change of the definition, multiple sites of bone invasion have also been included within the scope of this disease. The spine or pelvis was suggested as the most

common affected parts [7, 8]. Other studies from China and Japan showed that the pelvis was the most common site of PLB involvement [1, 19, 20, 21].

In our series, the long bones were the most frequent site of involvement with approximately 47.9% of cases, which is clearly higher than reported in many other published series [1, 19, 20, 21] and lower than that reported in Beal et al study [2]. The difference between the reported series could be attributed to many factors. Most of the studies [1, 7, 8, 9] were carried out retrospectively, and the period of recruitment ranged from 5 to 15 years suggesting different mechanisms of selection in the reported cohorts. Selection by treatment modality might also be of influence. In comparison with the policy of our study group, which included all treatment strategies, other studies with their primary aim evaluating the role of radiation therapy will inevitably not register combined modality treated patients [22, 23, 24]. Another factor that influences the reported rates for the different PBL sites is whether children have been included in the analysis [25, 26]. In some series, simultaneous involvement of different PBL sites is not reported as a separate entity [1]. It, therefore, remains uncertain whether it was not diagnosed in the first place or was classified as primary long bones lymphoma or primary axial skeleton lymphoma. This represents another reason for a possible variability in the stated rates for PBL.

To describe the extent of the disease, many reports applied the Ann Arbor classification or its modification [10, 27, 28]. Localized stages (IE, IIE) are predominant in our cohort. Beal et al. reported 78%[2], which is comparable to our data (73.9%), whereas another published data is lower (26.2%) [1]. The disease can occur at any age, with a median age of onset at our study was 48 years (range, 26–68). There was just a slight predominance of the male sex (52.2%) for PBL. The median age of onset ranging from 40–60 years old, with most of the literature suggesting that the proportion in male patients was slightly higher than in females (1.0–1.8:1)[1, 2]

The majority of PBL is of B cell non-Hodgkin's lymphoma, the most common type being diffuse large B-cell lymphoma (DLBCL) [6, 7, 8]. We found that more than half of the patients (78.3%) had DLCL histologic subtype. The 5-year and 15-year DFS rate were 82.4% and 64.7%, respectively. The 5-year and 15-year OS rate were 82.6% and 69.6%, respectively. The overall outcome of PBL is variable according to previous reports, 5-year OS of PBL patients were 88%[2], 76%[7], 57.8%[29], 55%[19], and 52.3%[1]. In nodal lymphoma, pathological type is one of the most important prognostic factors [1]. The majority of PBL in our study is of DLBCL in all series, but the OS rate in these patients had no difference as compared with other various pathological subtypes PBL at five years

using univariable and multivariable analyses. However, small sample size makes a comparison difficult. Whether the pathological type has an impact on prognosis of PBL remains an open question. Most other previous studies did not exclude the effect of histological heterogeneity on survival of PBL, although DLBCL accounts for a large proportion (68–83%) [7, 19, 2, 29].

On univariate and multivariate analysis, IPI score did not significantly affect OS in our series of PBL. Some reports concur with this finding where Catlett et al [30], and Alencar et al [16] showed that the survival rate in these patients had no difference when compared between high- IPI score and low IPI score. However, high IPI score had been encountered as a poor prognostic factor of PBL by Ramadan et al. [8], Wu et al. [6] and Huang et al. [19].

In the present study, OS was significantly higher in patients with age <40 years. Similarly, many other studies have suggested that age was an crucial factor affecting the prognosis of PBL [2, 17, 8, 31, 32]. In addition ECOG performance status < 2, in initial presentation was a favorable prognostic factor determining both OS and PFS. This was consistent with other previous reports [7, 33].

We have noted that patients who received CMT had better outcome compared to those who were treated with either modality alone. Many other reports have shown the same finding favoring the use of CMT in management of PBL [2, 18, 7, 34].

On univariate analysis we also found that a normal level of LDH, lack of B symptoms, and female gender were also favorable prognostic factors, but these were not found to be significant on multivariate analysis. Similar results were reported by Beal et al [2]. On multivariate analysis, only age < 40 years and the use of combined modality therapy were independent prognostic factors for OS, CSS, and FFTF. Our prognostic findings were also similar to other series with age <40 years [35] and the use of combined modality therapy [18, 36] found to be associated with an improved OS, CSS, and FFTF rates on multivariate analysis. Although we have a long follow up yet our results are limited by the small number of patients and the retrospective nature of the study.

Further large prospective randomized trials comparing efficacy, toxicity, and quality of life for various treatment modalities are warranted. Better understanding of the tumor biology and identification of biomarkers that predict treatment response should be encouraged.

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