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Evaluation of Overall Survival (OS) and Event-Free Survival (EFS) of Paediatric Sarcoma Patients at a Single Institution

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Abstract: *Aims:* To evaluate OS and EFS of paediatric sarcoma patients with an interest in comparing metastatic cases with non-metastatic cases, and compiling statistics on treatment methods.

Methods: Information was obtained from patient notes in the Schiehallion ward. These contained information about diagnosis, treatment, prognostic indicators, and outcomes for each patient.

Results: 56 patients, 2001-2008. *Osteosarcoma:* 11 patients, 7♂, 4♀; age range: 4-16; = 10; OS = 64%, EFS = 55%; Primary site of disease: Femur (47%), Tibia (41%), Humerus (5.5%), Scapula (5.5%), Other (1%); Metastatic Rate = 27% (OS = 0%). *Ewing's sarcoma:* 24 patients, 10♂, 14♀; age range: 1-16; = 12; OS = 71%, EFS = 58%; Primary site of disease: Pelvis (29%), Femur (22%), Paraspinal (16%), Chest Wall (10%), Tibia (10%), Other (13%); Metastatic Rate = 21% (OS = 40%; EFS = 40%); *Alveolar rhabdomyosarcoma:* 10 patients; OS = 80%, EFS = 60%; Metastatic Rate = 20% (OS = 100%; EFS = 100%). *Embryonal rhabdomyosarcoma:* 11 patients; OS = 73%, EFS = 73%; Metastatic Rate = 0%.

Conclusions: Our results reflect access to an experienced and innovative paediatric sarcoma service with close links to a national Sarcoma MDT. The data falls in line with other studies in terms of age of onset, location of primary tumour, metastatic rate, site of metastases, and prognosis for all cancer types. Limb salvage surgery is greatly favoured over amputation for both osteosarcoma and Ewing's sarcoma. Females have a more favourable prognosis in osteosarcoma and a slightly poorer prognosis in Ewing's sarcoma. Yorkhill's overall survival rates are currently better than the UK-wide statistic for three of the four tumours examined.

Keywords: Children, Osteosarcoma, Ewing's Sarcoma, Rhabdomyosarcoma, Outcome, Glasgow.

1. INTRODUCTION

When we compare recent statistics on cancer incidence in the UK we see that childhood cancer (0-14 years) is very rare. There are approximately 143 new cases of cancer diagnosed per one million each year of the population for this age group [1]. In comparison, the age group of teenage and young adults (15-24 years) has 272 new cancer diagnoses per one million population each year, whereas the incidence rate for the combined population of the UK is approximately 5,242 per one million each year [2,3].

Soft tissue sarcomas, that is, neoplasms of connective and supportive tissue, account for approximately 6.5% of all childhood cancers [4]. Of these, more than half are rhabdomyosarcomas [5].

Bone cancers account for approximately 10% of all malignant neoplasms in children and fall into two main categories: osteosarcoma and Ewing's sarcoma [6].

1.1. Osteosarcoma

This is an aggressive and highly malignant bone tumour that has one of the lowest survival rates for children. In the UK, osteosarcoma has an incidence rate of about 3 people per one million of the general population, and it affects males more than females with a ratio of 1.4:1 [7]. Although the cause of the cancer is currently unknown, the correlation between age of onset and the most common sites of onset – the proximal tibia and the distal femur – suggests a relationship to maximum osteoblastic activity [8]. There are a couple of known genes – the retinoblastoma gene and the p53 gene – that have been reported to increase susceptibility to development of an osteosarcoma [8].

Osteosarcomas usually form compact, whiteish, hard tissue that grows rapidly in a circular-like mass towards the periosteal surface, where it can spread to adjacent soft tissues. The tumour then often spreads through the blood stream and becomes metastatic – the most common site being the lungs. The histological diagnosis depends on the presence of malignant connective tissue stroma with cells that form new bone or osteoid [9]. Variants on the basis of histological

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differences have been identified and include osteoblastic, fibroblastic, chondroblastic, and telangiectatic. Other variants include intraosseous well-differentiated (low-grade), small-cell, multifocal, surface (peripheral), para-osteal (juxtacortical), periosteal, and high-grade surface [10] (Table 1).

Table 1: A study based on 1046 Patients Detailed the Skeletal Distribution

Site	Number of patients	%
Femur	521	50
Tibia	269	26
Humerus	102	10
Fibula	54	5
Pelvis	40	4
Skull	15	1.5
Radius	11	1
Rib	10	1
Vertebra	9	>1
Clavicular	4	>1
Hand	4	>1
Scapula	3	>1
Foot	3	>1
Ulna	1	>1

Table Adapted from Paediatric Oncology – Clinical Practices and Controversies [11].

Patients will present with pain, usually gradually increasing, with swelling of the affected area becoming more prominent. Often, patients and their families will associate the pain with a recent sports injury or it may be assumed to be caused by simple ‘growing pains’. Once they present to hospital, a plain X-ray is normally the first diagnostic image taken where a lesion with new bone formation will be seen. Often there will be breakage of the tumour into the cortex and adjacent soft tissue [11]. The initial X-ray image will be complemented by CT and/or MRI scanning as well as a radionuclide bone scan to gain a description of the primary tumour and to detect any metastatic deposits. The MRI and bone scan will also be able to detect any ‘skip’ lesions, that is, tumour deposits in other areas of the affected bone, that are known to occur in approximately 5% of cases [12]. The main sites for metastases are the lungs (98%), other bones (37%), pleura (33%), and heart (20%) [13] (Table 2).

In comparison to other cancers, the prognosis for osteosarcoma is quite poor. With modern treatment, and with patients who have a localised lesion, the 5

year survival rate is somewhere between 60-80% [15]. If metastases are present at the time of diagnosis, the 5 year survival rate drops to between 15-30% [15].

Table 2: Treatment for Osteosarcoma takes place Over a Number of Phases [14]

Phase 1	<u>Neo-adjuvant chemotherapy:</u> Once osteosarcoma has been diagnosed the patient is given chemotherapy with the aim of attempting to shrink the primary tumour and kill any cancer cells that may have metastasised.
Phase 2	<u>Surgery:</u> The aim of surgery is to remove as much of the primary surgery as possible whilst keeping the body working as best it can. This is much simpler in limbs, where either an amputation or limb-salvage surgery can be performed, rather than in other places in the body such as the pelvis or spine. Limb-salvage surgery may be possible using a metal implant and false joint, or using an autologous bone graft.
Phase 3	<u>Pathology:</u> After surgery, the tumour is examined by a pathologist to check if all of it has been removed successfully and to see if the chemotherapy drugs are having any impact.
Phase 4	<u>Adjuvant Chemotherapy:</u> The patient will then go on to receive a further regimen of chemotherapy drugs normally lasting for a period of 18 weeks.
Phase 5	<u>Further Surgery:</u> This may be necessary to remove secondary tumours that might have spread to other parts of the body.

However, this figure is closer to 40% if the metastases are confined to only the lungs or if all tumours, including metastases, have been completely removed [15]. Chemotherapy is an essential component in treatment, especially in high-grade osteosarcomas, where without it, the cancer is very likely to recur [15]. Certain factors have been linked to a more favourable diagnosis, including:

- being younger
- being female
- the primary tumour site being in an arm or leg
- the tumour being completely resectable
- normal blood alkaline phosphate levels and LDH levels
- good tumour response to chemotherapy [15]

1.2. Ewing's Sarcoma

Ewing's sarcoma is a malignant bone tumour that belongs to a family of small round-cell tumours including neuroblastoma, poorly differentiated rhabdomyosarcoma, and Askin tumour (primitive neuroectodermal tumour – PNET – of the chest wall) [16]. It affects slightly less than 2 people per million of the general population with a peak incidence between 10 and 20 years of age [17]. Although it is thought of as childhood cancer, recent research shows that over half of all cases present in patients over the age of 15 [17]. It accounts for about 6% of all primary malignant tumours in bone and around 40% of all the primary bone cancers diagnosed in the young people in the UK [16,17]. Again, like osteosarcoma, the exact causes of Ewing's sarcoma are unknown but with the peak incidence being around the time of most rapid bone growth, a link between the two can be deduced.

Ewing's sarcoma originates from the intramedullary cavity and often breaks through the cortex and extends into the surrounding soft tissue [18]. The tumour tissue is seen to be a greyish-white with areas of haemorrhage and necrosis [18]. Histologically it is characterised by densely packed, regularly shaped, small cells with round or oval nuclei, often showing translocations between chromosomes 11 and 31 [19]. The classic differential diagnosis that can mimic Ewing's on radiological imaging is osteomyelitis [20]. Other differentials that must be ruled out include rhabdomyosarcoma, neuroblastoma, peripheral neuroectodermal tumour (PNET), small-cell osteosarcoma, and primary lymphoma of bone [20] (Table 3).

Table 3: A Study Based on 300 Patients Demonstrated the Distribution of Ewing's Sarcoma

Site	Number of patients	%
Pelvis	60	20
Femur	58	19
Fibula	32	11
Tibia	31	10
Rib	30	10
Vertebra	23	8
Scapula	19	6
Foot	7	2
Ulna	5	1.67
Clavicular	5	1.67
Skull	4	1
Radius	3	1
Sternum	1	>1

Table Adapted from *Paediatric Oncology – Clinical Practices and Controversies* [20].

Patients will commonly present with pain and swelling that may worsen rapidly over a short period of time. Again, like osteosarcoma, the first diagnostic imaging taken is normally a plain X-ray where a 'moth-eaten' pattern of bone destruction along with a parallel 'onion skin' appearance of new periosteal bone formation is seen [16,20]. Pathological fractures will be seen in approximately 5% of cases [20]. Further imaging in the form of CT or MRI will be undertaken to look for the presence of metastases, which, because of the highly aggressive nature of the tumour, are very common. The estimate of metastases at diagnosis is 25% [21].

Treatment for Ewing's sarcoma is similar to that of osteosarcoma with one major difference: whereas osteosarcoma is a very radio-resistant lesion, Ewing's is very radio-sensitive and therefore radiotherapy plays a big role. Neo-adjuvant chemotherapy will be administered with the aim of shrinking the primary tumour and destroying any potential metastatic spread. Then surgery will be undertaken, the complications of which depend on the site of the primary tumour. If the tumour is in one of the limb bones, complete resection (either by amputation or by a limb-sparing procedure) will be less complicated than if the primary site is in one of the flat bones of the body, such as the pelvis. After surgery, the removed tumour will be examined by a pathologist and the decision to undergo radiotherapy will be taken. Radiotherapy will be administered if either the whole tumour has not been removed or if more than 10% of the tumour remains alive when examined under microscope [22]. Adjuvant chemotherapy will normally continue regardless of radiotherapy treatment and further surgery may have to be carried out at a later date to remove any metastatic spread, for example, in the lungs.

Overall, the 5-year survival rate for Ewing's sarcoma when the patient has presented with a localised tumour is estimated to be around 70% [23]. If the patient presents with metastatic disease the 5-year survival drops to between 15% and 30% [23]. This figure is slightly higher if the metastases are only confined to the lungs. Other prognostic factors include are mentioned in Table 4 [24].

1.3. Rhabdomyosarcoma

Rhabdomyosarcoma is a highly malignant tumour that is thought to arise from mesenchymal cells that would further develop into striated muscle [25]. Due to its embryological nature, they are the most common

Table 4: Other Prognostic Factors [24]

Site of tumour	Distal extremities have the best prognosis with central sites such, as the pelvis and sacrum, the worst.
Age	Patients younger than 15 have a better prognosis than those that present after 15 years of age.
Gender	Girls have a better prognosis.
Serum lactate dehydrogenase	Increased serum LDH levels at time of diagnosis are associated with poorer prognosis.

form of malignant soft-tissue tumour in infants and young children, accounting for about 3% of all childhood cancers [26,27]. It shows a peak incidence at around three years old [28]. There are four distinct types of rhabdomyosarcoma, described in Table 5.

Table 5: Types of Rhabdomyosarcoma

Type	Features
Embryonal	<ul style="list-style-type: none"> along with botryoid rhabdomyosarcoma, accounts for approximately two thirds of all rhabdomyosarcomas primarily a tumour of early childhood resembles striated muscle
Botryoid	<ul style="list-style-type: none"> the term botryoid means ‘grape-like’ and is applied to embryonal rhabdomyosarcomas with a polypoid configuration and a myxoid consistency occurs in mucosa-lined organs
Alveolar	<ul style="list-style-type: none"> accounts for about one quarter of rhabdomyosarcomas arises in voluntary muscle typically presents between ages of 10-20 years
Pleomorphic	<ul style="list-style-type: none"> rarest subtype tends to arise in limbs of both children and adults

Table Adapted from Woolf’s Pathology: Basic and Systemic [29].

Although the exact cause of rhabdomyosarcoma is unknown, there have been a number of identified conditions that have been shown to increase the risk with developing a rhabdomyosarcoma along with other tumours:

- Li-Fraumeni syndrome
- Pleuropulmonary blastoma
- Neurofibromatosis type 1 (NF1)
- Beckwith-Wiedemann syndrome
- Costello syndrome
- Noonan syndrome [30]

The most common locations for development of rhabdomyosarcoma are the head and neck including parameningeal sites (including the nasopharynx, middle ear, paranasal sinuses), and the genitourinary tract including bladder, prostate, vagina, vulva, uterus, and paratesticular regions [31] (Table 6).

Table 6: Most Common Locations for Development of Rhabdomyosarcoma

Site of Primary Tumour	Incidence
Parameningeal	16
Orbit	10
Head/Neck	10
Genitourinary (All)	23
Extremity	19
Other	22

Table Adapted from The Liddy Shriver Sarcoma Initiative [31].

Patients present with signs and symptoms that depend on the site of the tumour listed in Table 7.

Table 7: Signs and Symptoms for Tumour

Site of primary tumour	Signs/Symptoms
Trunk, limbs, groin	<ul style="list-style-type: none"> a mass or swelling may or may not be painful
Eye	<ul style="list-style-type: none"> the eye can bulge out strabismus
Ear, nasal sinuses	<ul style="list-style-type: none"> headache earache sinus congestion
Bladder, prostate	<ul style="list-style-type: none"> haematuria
Vagina	<ul style="list-style-type: none"> vaginal bleeding
Abdomen, pelvis	<ul style="list-style-type: none"> abdominal pain vomiting constipation
Bile ducts	<ul style="list-style-type: none"> jaundice

Table Adapted from The American Cancer Society [32].

Imaging used in the diagnostic process includes X-rays, MRI, and CT scans. A biopsy of the tumour will be taken, either via surgery or a needle procedure, and the diagnosis will be confirmed by a pathologist. Once the type of rhabdomyosarcoma has been determined, further imaging will be taken, including bone scans, to look for the presence of metastases and stage the disease. Finally, the patient will be placed into a clinical group along with being stratified into a risk category that determines their treatment regimen and the aggressiveness of this treatment.

The risk group that patients are assigned differentiates the 5-year survival rates for rhabdomyosarcoma (Table 8).

Table 8: 5-Year Survival Rates in Rhabdomyosarcoma in Risk Group Patients

Risk group	5-year survival rate
Low Risk	for children, survival rate is over 90%
Intermediate Risk	survival rates range from 60-80%
High Risk	survival rates range from 20-40%

Table Adapted from The American Cancer Society [33].

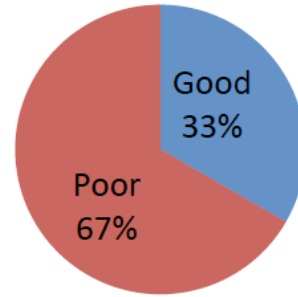
As with other types of cancer, the treatment for rhabdomyosarcoma follows a similar regimen of neo-adjuvant chemotherapy, surgery to remove the tumour, adjuvant chemotherapy with or without radiotherapy, and potential further surgery to remove any metastases.

2. RESULTS

There were 56 paediatric patients included in this study in the timeframe from 2001 to 2008. The patients were selected on the basis of a diagnosis of either osteosarcoma, Ewing's sarcoma, or rhabdomyosarcoma (Table 9).

2.1. Osteosarcoma Treatment

Chemotherapy Response



Surgery Type

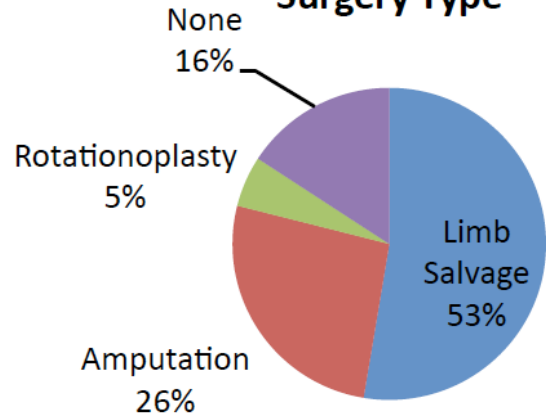
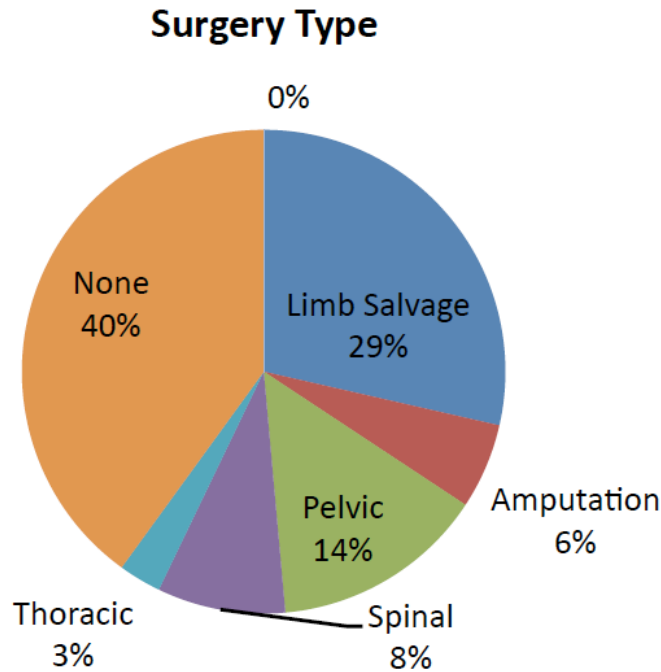


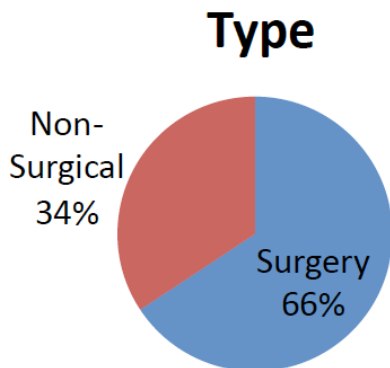
Table 9: Detailed Results of 56 Paediatric Patients included in this Study in the Timeframe from 2001 to 2008

	Osteosarcoma	Ewing's Sarcoma	Alveolar Rhabdomyosarcoma	Embryonal Rhabdomyosarcoma
No. of patients	11	24	10	11
Male	7	10	-	-
Female	4	14	-	-
Age range	4-16	1-16	-	-
Mean age	10	12	-	-
Overall survival (%)	64	71	80	73
Event free survival (%)	55	58	60	73
Primary site of disease (%)	Femur: 47 Tibia: 41 Humerus: 5.5 Scapula: 5.5 Other: 1	Pelvis: 29 Femur: 22 Paraspinal: 16 Chest wall: 10 Tibia: 10 Other: 13	-	-
Metastatic rate (%)	27	21	20	0
Overall survival with metastases (%)	0	40	100	n/a
Event free survival with metastases (%)	0	40	100	n/a

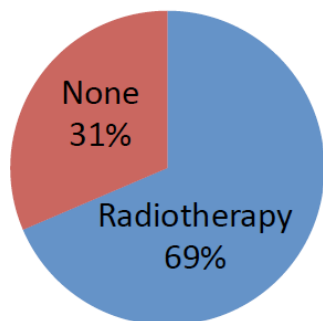
2.2. Ewing's Sarcoma Treatment



2.3. Rhabdomyosarcoma Treatment



Radiotherapy



3. DISCUSSION

3.1. Overall Survival and Event-Free Survival

In the period from 2001 through to October 2008, there were 11 patients diagnosed with Osteosarcoma.

7 of these patients survived for more than five years and only one had disease recurrence providing an overall survival of 64% and event-free survival of 55%. This compares to other UK studies putting overall survival at 59% and a European rate at 66% [34]. In the metastatic group there were 3 patients all of whom died, giving an overall survival rate of 0%.

In this same period there were 24 patients diagnosed with Ewing's Sarcoma of which 17 lived longer than 5 years and 7 died giving an overall survival of 71%. 14 of the survivors have had no disease recurrence and therefore there is an event-free survival of 58%. Yorkhill's overall survival rate is comparable to UK (55%) and European (62%) studies [34]. In the metastatic group there were 5 patients, 2 of which survived past 5 years giving an overall survival rate of 40%.

There were 10 Alveolar Rhabdomyosarcoma patients with 80% surviving and an Event-Free Survival of 60%. UK figures give a 65% overall survival rate for this subtype of rhabdomyosarcoma [35]. There were 2 patients with metastatic disease, both of whom survived past 5 years with no disease recurrence giving an overall survival and event free survival of 100%.

There were 11 Embryonal Rhabdomyosarcoma patients with an overall survival of 73% and all of those survivors were event-free. UK figures give an 82% overall survival rate for this subtype of rhabdomyosarcoma [35].

Gender

For osteosarcoma, the overall survival rate for males is 57% with an event-free survival of 43%, compared to an overall survival for females of 75% with an event-free survival of 75%. Osteosarcoma has a more favourable prognosis with girls and the data reflects this [15]. The close relationship with growth and the fact that males have a growth spurt at an older age is the most likely reason for this prognostic indicator.

For Ewing's sarcoma, the overall survival rate for males is 80% with an event-free survival of 70%, compared to an overall survival for females of 64% with an event-free survival of 64%.

Treatment Type

For osteosarcoma, one of the main prognostic indicators is response to initial chemotherapy. A 'good' response is defined as one where there is at least 90%

necrosis of the tumour when examined by the pathologist after neo-adjuvant therapy. From our data, 67% of the osteosarcoma patients were judged to have a poor response to their initial chemotherapy.

In our sample there was a 67% overall survival rate in good responders compared to 50% of poor responders.

Regarding surgery type, the most common type of surgery performed was a limb salvage operation with 58% of patients opting for this. Understandably patients want to avoid amputation as best they can but this must be a balancing act between the risks of salvaging a limb versus the risk of not excising the entire tumour.

The 5-year survival rate in our group of patients that underwent limb salvage surgery was 66.7%.

Only 1 patient underwent amputation before 2008 and has had an event free survival of more than five years. Due to the small sample sizes, it is difficult to draw any solid conclusions in our data from limb-salvage vs. amputation.

Looking at the type of surgery performed for Ewing's patients, the most common was to elect for no surgery at all. This was due to a variety of reasons including difficult position of the primary tumour and disease that was cured by chemotherapy and radiotherapy only.

From 2001 to 2008 there is a 100% overall survival in those who have undergone limb salvage surgery. All of these patients had local disease with no metastases.

There is a 50% overall survival in those who did not undergo any surgery, however, there is only a 30% event free survival in that group.

Looking at the data for rhabdomyosarcoma patients, treatment involving surgery versus a non-surgical approach was in the ratio of 2:1. There were a wide variety of surgical procedures performed depending on the site of the original tumour. Sometimes, a non-surgical approach was favoured especially in patients where the tumour was considered non-resectable due to its proximity to vital structures. In other cases, some patients presented with such poor prognosis that their treatment plan was palliative and surgery was considered to be inappropriate.

Radiotherapy was administered in 69% of patients. Sometimes this was adjuvant to surgery and

sometimes this was instead of a surgical procedure. In some of the more recent cases, patients travelled to Florida to receive radiotherapy in the form of proton therapy. Although, to date, there has been no published data as to the efficacy of this new treatment and whether or not its side effects are less than that of conventional radiotherapy.

SUMMARY

Our results reflect access to an experienced and innovative paediatric sarcoma service with close links to a national Sarcoma MDT. The data falls in line with other studies in terms of age of onset, location of primary tumour, metastatic rate, site of metastases, and prognosis for all cancer types. Limb salvage surgery is greatly favoured over amputation for both osteosarcoma and Ewing's sarcoma. Females have a more favourable prognosis in osteosarcoma and a slightly poorer prognosis in Ewing's sarcoma. Yorkhill's overall survival rates are currently better than the UK-wide statistic for three of the four tumours examined.

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