Ewing tumours: Outcome in children, adolescents and adult patients

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Introduction

Age as prognostic factor in cancer patients

In cancer patients, patient age may impact on outcome. This may be attributed to different biological properties of both diseases and patients in different groups. While paediatric as well as geriatric oncology have become recognised subspecialties, adolescent and young adult (AYA) cancer medicine is only beginning to form, with the first adolescent cancer units recently established in the UK [1].

The AYA age group probably needs special attention in cancer medicine: The American Survival, Epidemiology, and End Results (SEER) registry data demonstrate that cure rates from cancer have improved much less in recent years in the AYA compared to all other age groups. This has, among other factors, been contributed to a lack of participation in clinical trials [2–4].

However, even in those patients registered on cancer trials, AYA cancer patients may experience disadvantages compared to adults or children, as trials are mainly designed for one or the other age group, respectively, while there are almost no trials designed specifically for AYA patients. Even in diseases occurring in all age groups, like acute lymphoblastic leukaemia (ALL), trials addressing adults often prescribe less intensive treatments than those addressing children, reflecting the common view that adults are more likely to experience serious side effects with more intensive treatments. As highlighted in several publications regarding acute lymphoblastic leukaemia in adolescents and young adults, such less intensive treatments may lead to lower remission rates. This means less AYA patients are cured from their disease when enrolled in 'adult' rather than 'paediatric' treatment protocols [5,6]. But even within the same treatment protocol, outcome differences between cancer patients of different age groups may be observed. Thus, further analyses of factors potentially contributing to such outcome differences seem warranted. Possible contributors to this outcome differential could be found in age-related differences of the biology of the disease, of the patients' needs and attitudes, of drug metabolism and tolerance, but also of medical patient handling, or, in other words, of the doctors' attitude towards their patients.

Age-related prognosis in Ewing tumours

Ewing tumours (ET) occur with an annual incidence of 3 per million per year in the Caucasian population. As the median age at diagnosis is 15 years, and as about 50% of cases are observed in the AYA population, ET concerns all paediatric, medical, and adolescent oncology [7,8]. Population based data from the U.S. SEER registry from 1984 to 1995 have shown that the prognosis for patients with ET was inversely correlated with age: Patients diagnosed with an ET aged 5–9 years had a 71% 5-year survival, those aged 10–19 had a 56% 5-year survival, and patients aged 20–39 years at diagnosis had a 45% 5-year survival, respectively [9].

The reasons for this observation have largely remained speculative. All of the potential contributors might be involved to some degree: Biology of both tumour and/or patients, and/or patients' and doctors' attitude to treatment might differ between age groups. Older patients with ET present with larger tumours at diagnosis, and have more commonly pelvic or metastatic tumours [10–12]. Results from U.S. NCI trial INT-0091 (CCG-7881 and POG-8850) showed that the addition of ifosfamide-etoposide improved survival for younger, but not for older patients over 17 years. As treatment intensity did not differ between age groups, this might hint towards biologic differences of tumour response in different age groups [13].

Chemotherapy regimen – type and age related prognosis in Ewing tumours

Reports of some, but not all studies on adult ET patients being treated on chemotherapy regimens

similar to paediatric protocols seem to demonstrate a prognosis comparable to the prognosis of children on such protocols. Verrill's group have treated Ewing's patients aged 16–48 years with an intensive 'paediatric-type' regimen and found that age did not influence survival, while tumour volume did [12]. Similarly, in the CESS 86 study, age did not impact on survival [14].

However, other reports of adults on paediatric trials found an inferior outcome for older patients [10,13, 15,16]. One of these, the INT-0091 (CCG-7881 and POG-8850) trial, could not explain these outcome differences by differences in dose intensity between age groups. However, multivariate analysis taking into account other proven risk factors like tumour volume, gender, or tumour site, were not reported [13].

Institution-related prognosis in Ewing tumours

In surgical oncology, 'surgeon volume', 'hospital volume' and 'physician volume' as surrogate parameters for the experience of an individual or institution have recently received some attention as possible indicators of treatment quality [17–21]. Such data seem to indicate that in clinical oncology, large experience with a specific disease or situation may improve patients' outcome. Multi-centre clinical trials for rare disease should overcome the disadvantages of small patient numbers in single institutions: By incorporating experience from many centres into a treatment outline, the best suitable approach should be available in all participating institutions. Still, interpretation of treatment guidelines, individualised supportive care approaches, and others may contribute to different outcome in centres participating in the same trial. In the setting of controlled multi-centre oncology trials, not much information is available regarding outcome differences between participating institutions.

This report summarises the experience of a large multi-centre, multinational study group in Ewing tumour treatment, focussing on differences in outcome related to patient age and type of treating institution.

The CESS and EICESS Ewing tumour trials

The multi-centre Cooperative Ewing's Sarcoma Studies CESS 81 and CESS 86 were undertaken by the German/Dutch/Austrian/Swiss 'Gesellschaft für Pädiatrische Onkologie und Hämatologie' (GPOH). The successor trial, the European Intergroup Cooperative Ewing's Sarcoma Study EICESS 92 was jointly performed by the GPOH and the United Kingdom Children's Cancer Study Group (UKCCSG). All three studies prescribed neoadjuvant multi-drug chemotherapy, surgery and/or radiotherapy, followed by adjuvant chemotherapy for all ET patients. Chemotherapy in all trials was based on alkylating agents (ifosfamide, cyclophosphamide), doxorubicin, actinomycin D, and vincristine, with additional etoposide in a subgroup of high-risk patients in EICESS 92 [14,22,23].

While CESS 81 was initially aimed at the paediatric population under the age of 18 years, CESS 86 included patients up to the age of 25, and EICESS 92 was open to patients aged 0 to 35 years. There were no specific aged-related treatment stratifications. In addition to the primary study patient population, patients who fulfilled exclusion criteria, e.g. older age at diagnosis, but had no contraindications towards the prescribed treatment and who consented to treatment and data analyses, were treated according to the protocols and registered in the CESS/EICESS registry. Thus, outcome data are available on patients of a broad age range. Altogether, for this report, 1426 patients could be analysed: 181 from Cess 81, 468 from CESS 86, and 777 from EICESS 92, respectively. The study population contains both patients with localised and patients with metastatic disease. The median patient age at diagnosis was 15 years, with a range from 2 months to 54 years. Twenty-four percent of patients were under 10 years at diagnosis, 56% were between 10 and 20 years of age, and 20% were over 20 years, respectively. Thus, the whole spectrum of age groups was represented, see Fig. 1.

Patients were registered from 195 institutions: 88 were paediatric oncology type, and 107 were non-paediatric. Among the latter, there were 91 medical oncology institutions, and 16 other institutions, like interdisciplinary cancer centres, and others. Of all 1426 patients, 1045 (73%) were registered from and

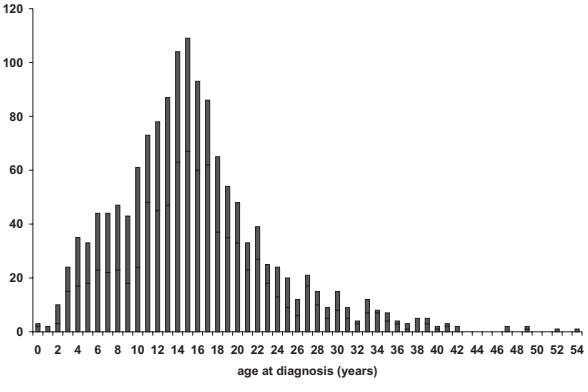

Fig. 1. Age distribution in Ewing tumour patients. CESS/EICESS data, $n = 1426$.

treated in paediatric institutions. 292 patients (21%) were treated in medical oncology, and 89 patients (6%) in other institutions, respectively. The median number of patients registered per institution in this rare disease was 19, with a minimum of one patient registered in one institution, and a maximum of 67 patients registered by one centre. Eight institutions had registered more than 30 patients each, accounting for a total of 373 patients (26%).

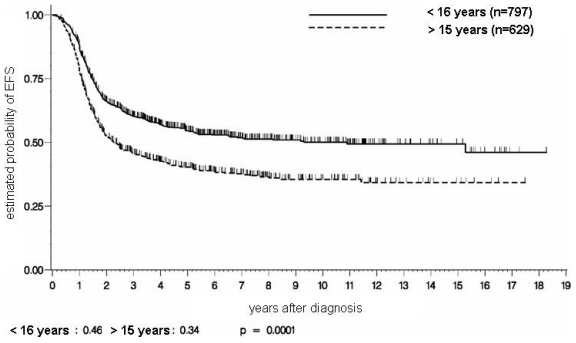

Fig. 3. EFS in relation to patient age at diagnosis (<16 versus 16 or older; $n = 1426$).

Outcome in relation to age, and to type of treating institution

Overall outcome

The event free survival (EFS) calculated according to Kaplan and Meier 10 years after initial diagnosis was 0.44 (confidence interval CI 0.41 to 0.47) with a median follow up of 8 (range, 1 to 21) years. Overall survival (OAS) after 10 years was 0.53 (CI 0.49 to 0.55).

Impact of patient age on outcome

Outcome differed between age groups; younger patients had a better prognosis than older patients. In patients aged under 11 years, 10-years EFS was 0.51, in those aged 11 to 15, EFS was 0.49, in those aged 16 to 20 years, EFS was 0.37, and in patients over 20 years of age, EFS was only 0.34, $P = 0.0001$, see Fig. 2. The most significant prognostic difference according to age occurred when patients were separated into two roughly equally large groups, with a split at the median age of 15 years. Those patients aged 15 or younger (<16 years) at diagnosis had an EFS of 0.50, those older than that an EFS of 0.35, respectively, $P = 0.0001$, see Fig. 3. This also remained true when controlling for the strongest overall predictor of outcome, i.e. metastatic stage at diagnosis: Younger patients (<16 years) with localised disease had a superior outcome compared to older patients with localised disease, 0.57 versus 0.44, $P = 0.0001$.

Impact of the type of treating institution

Patients treated in paediatric oncology type institution had a better EFS compared to those treated elsewhere, see Fig. 4. When confining the analysis to patients aged above 15 years, patients treated in non-paediatric units still fared worse, see Fig. 5. In contrast, patients aged over 19 did not seem to benefit very significantly when treated in paediatric institutions, see Fig. 6. In contrast, the most pronounced difference of outcome between paediatric and non-paediatric institutions was observed in the AYA group of aged between 16 and 19 years, see Fig. 7.

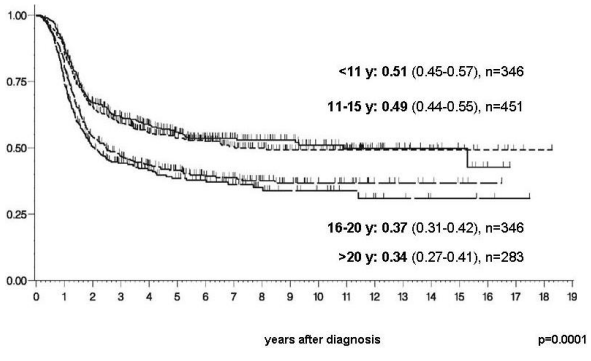

Fig. 2. 2 EFS in relation to patient age at diagnosis (⩽10, 10–15, 16–20, >20 years; $n = 1426$).

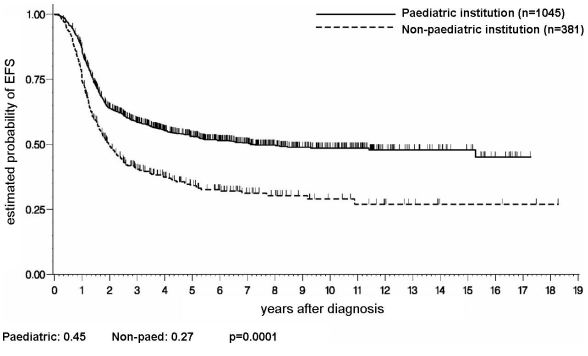

Fig. 4. EFS (figures given at 10 years) in relation to treating institution ($n = 1426$).

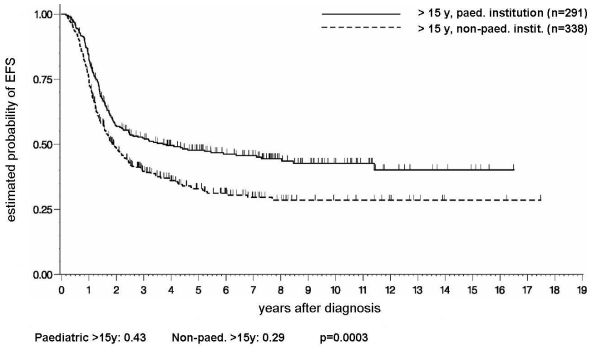

Fig. 5. EFS (10 y) of patients aged over 15 years in relation to treating institution ($n = 629$).

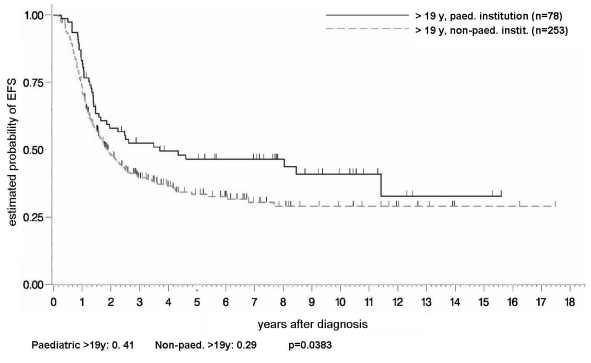

Fig. 6. EFS (10 y) of patients aged over 19 years in relation to treating institution ($n = 331$).

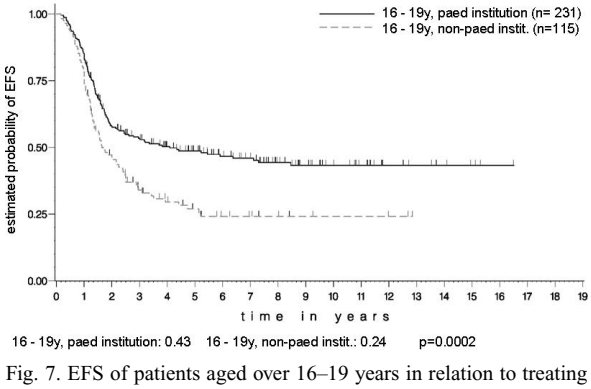

Fig. 7. EFS of patients aged over 16–19 years in relation to treating institution ($n = 346$).

Obviously, risk factors other than age might have been distributed unequally between types of institutions, thus leading to alterations of outcome. Thus we controlled for some established risk factors, the most important one being stage at diagnosis. When confining our analyses to patients without metastases at diagnosis, results remained basically unchanged, see Fig. 8.

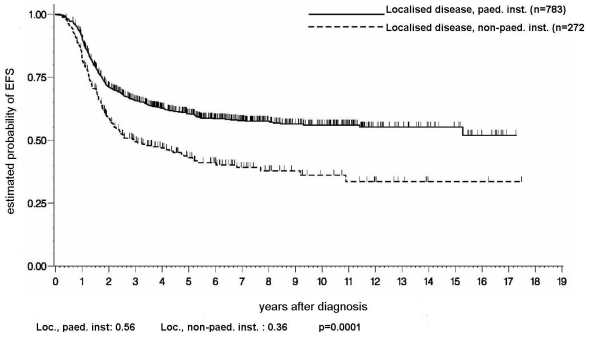

Fig. 8. EFS (10 y) of patients with localised disease in relation to treating institution ($n = 1005$).

Table 1
Risk profiles of patients in paediatric versus non-paediatric institutions (n = 1356)

Variable	Value	Paed.	Non-paed.	*P*-value
Stage	metastatic	25%	29%	0.162
Site	axial	55%	59%	0.147
Volume	⩾100 ml	65%	72%	0.013
Transcript type	non-1	49%	31%	0.089
Response	poor	23%	34%	0.002

Table 2
Multivariate Cox analyses of potential risk factors (n = 1309, 656 events, model. chi-square $P = 0.0001$ for both models)

Variable	Label	Risk ratio	*P*-value
Model one: Stage, site, tumour volume, and patient age			
Stage	metastatic	2.24	0.0001
Site	axial	1.55	0.0001
Volume	⩾100 ml	1.42	0.0001
Age	>15 years	1.41	0.0001
Model two: Stage, site, tumour volume, patient age, and type of institution			
Variable	Label	Risk ratio	*P-value*
Stage	metastatic	2.27	0.0001
Site	axial	1.54	0.0001
Volume	⩾100 ml	1.42	0.0001
Age	>15 years	1.17	0.1003
Type of institution	non-paediatric	1.43	0.0006

Table 1 shows the available risk profiles of patients in paediatric versus non-paediatric institutions. There are only two significant differences: Patients in non-paediatric institutions presented with larger tumours at diagnosis, which might have contributed to inferior

outcome, and showed less response to chemotherapy, which might be due to different tumour biology, treatment intensity, or patient's or physician's treatment compliance.

In order to further analyse potential confounders, multivariate Cox regression analyses of outcome were performed. In a first model, stage of disease, tumour site, tumour volume, and patient age were included, representing established risk factors. In a second model, the type of treating institution was additionally introduced into the model. While in model 1, age showed significant impact on outcome, this was lost with the addition of the treating institution in model 2, see Table 2. This might hint towards a significant influence of the treating institution, independent from the other risk factors analysed.

Most recent trial period – EICESS 92

We wondered if the tendency that treatment for adolescents aged 16 to 20 years was more successful in paediatric institutions would hold true in the most recent trial, EICESS 92. In this trial, relatively more patients from non-paediatric institutions were included as compared to the previous trials. Fig. 9 shows that in EICESS 92 differences in outcome were no longer significant, even in the age group of 16 to 19 year old patients. Moreover, multivariate Cox regression analyses performed on the EICESS 92 trial cohort failed to prove any significance for the type of treating institution ($P = 0.1221$, data not shown). Thus it seems, that in this most recent area, non-paediatric institutions produce similar outcome to paediatric-type centres.

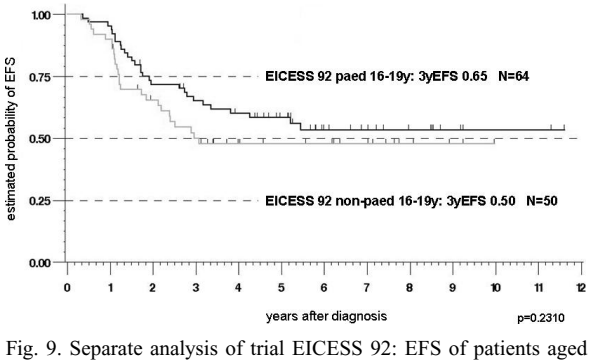

Fig. 9. Separate analysis of trial EICESS 92: EFS of patients aged 16 to 19 years in relation to treating institution ($n = 114$).

Impact of the experience of the institution

Ewing tumour treatment is rather complex, involving diagnostics, chemotherapy, radiotherapy and/or surgery, supportive care, and psychosocial support among others. Thus the experience of the treating institution might be of particular importance for a successful therapy in this disease. Indeed, we found that in our study population those institutions with the largest number of patients registered seemed to produce better event-free survival than institutions with less patients, with a significant difference between the most and the least experienced centres, see Fig. 10.

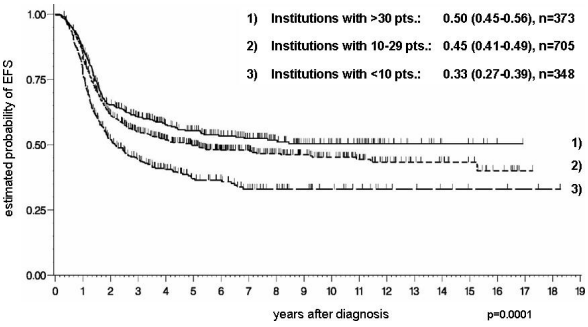

Fig. 10. EFS in relation to the numbers of patient treated per institution ($n = 1426$).

This may at least in part also account for some of the differences observed between types of treating institutions, as the average number of patients treated per institution was highest in the paediatric-type institutions: 1045 patients were treated in 88 paediatric institutions, i.e. an average of twelve patients per institution, and 381 patients were treated in 107 non-paediatric institutions, which equals an average of only four patients per institution.

Discussion

Paediatrics and geriatrics have formed as medical subspecialities, as both children and older persons have their own specific diseases, biology, and psychosocial settings, and as these differ from those of the average 'adult'. In everyday life, between childhood and adulthood, adolescence is identified as an age of its own rights – and problems. This has, more recently, led to the insight that this might hold true for medicine as well, and especially for oncology.

One recent issue of the European Journal of Cancer (December 2003, Vol. 39 Issue 18) has been entirely devoted to adolescents and young adults with cancer, the 'lost tribe', as Maria P. Michelagnoli and colleagues name them in their introduction to the issue [24]. They chose this label for adolescents and young adults (AYA) with cancer, as it seems that the AYA with cancer gets lost in our western health systems: There are specialised paediatric, adult, and

geriatric oncology centres, there are trials specifically designed for these age groups, and drugs developed for them – but not so for the AYA with cancer. Consequently, participation in oncology trials is lower in this age range than in all other ages, and, not surprisingly, cure rates have increased at a much lower pace than in children or adults, or even in old age persons [2–4]. In the same issue, Jeremy Whelan has asked 'Where should teenagers with cancer be treated?' [1]. While the logical consequence has been drawn in the United Kingdom with the establishment of adolescent cancer units, these are not available at many places outside the UK. Moreover, even with teenage cancer units in place, only the first of a number of necessary steps has been taken to establish an effective 'adolescent cancer medicine'. Other steps must follow, e.g. design of treatment schedules and trials specific for the AYA age group, and generally more adolescent cancer research.

As long as this is not the case, we need to ask ourselves how the AYA with cancer should best be treated. Usually, AYAs will be treated along guidelines established for the age group where their specific cancer is observed most commonly. In some diseases, however, the AYA population is the primarily concerned age group, and there are trials at hand designed specifically for this population. Examples are the primary malignant bone tumours, osteosarcoma and Ewing tumours. As these diseases occur primarily in AYAs, trials are specifically designed for this population.

So far, no publications have been available on the effect of the type of treating institution on outcome. The CESS/EICESS data provide the unique possibility to compare outcome data of adolescents and young adults treated on the same protocol, but within different institutions, with regard to their prognosis. In this report, we show that in Ewing tumours, age was an important prognostic factor. However, it also seemed to be of importance where treatment was delivered: AYAs treated in paediatric units seemed to have a better outcome than persons of the same age treated in non-paediatric institutions. One might argue that even in persons aged over 15,the median age of those treated in paediatric institutions will be lower than the median age of patients treated in non-paediatric institutions. However, the largest difference in outcome between types of institutions was observed for the very closely matched AYA age group from 16 to less than 20 years. This might hint towards a difference in efficacy of the treatment rather than a pure effect of age itself. This assumption may be supported by the observation that, in general, histological response is better in patients treated in paediatric institutions.

It remains speculative at present, if this difference in treatment efficacy is related to a biological difference of disease at different ages, or to different treatment intensity. So far, further analyses of drug-dose intensity and other factors potentially reflecting the quality of cancer care delivery between different types of cancer treatment institutions have not been possible in this cohort, mainly due to incomplete data. However, it could be observed that (a) treatment results were better in institutions treating larger numbers of patients, and (b) the largest patient numbers were recruited through paediatric institutions.

Therefore, it is likely that the experience of the institution delivering chemotherapy might be correlated to survival rates. Similar effects have been described for surgically treated tumours as 'surgeon volume effect' on patient outcome [19,20,25], but further analyses of these phenomenon seem warranted.

One recent publication has shown that – surprisingly – older patients tolerated an intensive Ewing tumour chemotherapy as well as children did [26]. As many of the institutions of this report have also treated AYA and adult patients in the EICESS trial, but not in the older trials, we speculated that more recently, experience and hence treatment intensity might have increased in non-paediatric institutions. And indeed, in the most recent trial analysed here, EICESS 92, treatment was virtually equally effective in paediatric and non-paediatric institutions.

Our proposal is that institutions applying complex treatments like those in Ewing tumours should follow established treatment guidelines as closely as possible, and, wherever available, in the framework of a controlled clinical trial. This also means that treatment of such rare diseases should probably best be performed in institutions where some experience and expertise in these rare tumours is available. Last, but not least, we should try to recognise and respect age group-specific needs and circumstances in order to deliver optimum care to all patients regardless whether child, adult or adolescent.

Conflict of interest statement

We confirm that there is no conflict of interests.

Acknowledgement

The authors would like to thank the team of the Münster Ewing Tumour Data Centre for all the data and analyses provided. These analyses would not have

been possible without the support of all participating and documenting institutions, and of all parents and patients who consented to data processing. Thank you!

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