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Alveolar echinococcosis: From a deadly disease to a well-controlled infection. Relative survival and economic analysis in Switzerland over the last 35 years☆

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***Background/Aims*: Alveolar echinococcosis (AE) is a serious liver disease. The aim of this study was to explore the long-term prognosis of AE patients, the burden of this disease in Switzerland and the cost-effectiveness of treatment.**

***Methods*: Relative survival analysis was undertaken using a national database with 329 patient records. 155 representative cases had sufficient details regarding treatment costs and patient outcome to estimate the financial implications and treatment costs of AE.**

***Results*: For an average 54-year-old patient diagnosed with AE in 1970 the life expectancy was estimated to be reduced by 18.2 and 21.3 years for men and women, respectively. By 2005 this was reduced to approximately 3.5 and 2.6 years, respectively. Patients undergoing radical surgery had a better outcome, whereas the older patients had a poorer prognosis than the younger patients. Costs amount to approximately €108,762 per patient. Assuming the improved life expectancy of AE patients is due to modern treatment the cost per disability-adjusted life years (DALY) saved is approximately €6032.**

***Conclusions*: Current treatments have substantially improved the prognosis of AE patients compared to the 1970s. The cost per DALY saved is low compared to the average national annual income. Hence, AE treatment is highly cost-effective in Switzerland.**

***Keywords*: Cost-effectiveness; Alveolar echinococcosis; Treatment; Survival; DALY**

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Abbreviations: AE, alveolar echinococcosis; DALY, disability-adjusted life years; CE, cystic echinococcosis; YLD, years lived with disability; YLL, years of life lost; GDP, gross domestic product.

1. Introduction

Human alveolar echinococcosis (AE), a hepatic disease resembling liver cancer, is caused by the larval stage (metacestode) of the fox tapeworm *Echinococcus multilocularis*. The parasite is distributed in the northern hemisphere, the endemic area stretching from North America through central and eastern Europe to central and East Asia including northern parts of Japan [1–3]. In humans, the metacestode can grow over years before

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symptoms such as abdominal pain, jaundice, hepatomegaly and weight loss might occur. Untreated, AE may result in severe hepatic dysfunction and metastases in other organs with high mortality. The average survival rate 10 and 15 years after diagnosis of untreated patients, has been reported to be as low as 29% and 0%, respectively [4].

The parasite is highly endemic in Switzerland where it naturally cycles between foxes and various rodent species [5]. Humans acquire the disease by the ingestion of parasite eggs directly or indirectly from fox faeces or from other infected definitive hosts such as dogs. Recently, the fox population in central Europe has increased significantly, which has been accompanied by an invasion of urban areas by foxes due to increases in the anthropogenic food supply. The prevalence rate of *E. multilocularis* in foxes in the core endemic region of central Europe has been recorded to range between 35% and 65% [2,3,5,6]. This high prevalence together with the increasing urban fox population inevitably will result in increases in the environmental contamination with *Echinococcus* eggs leading to an increased risk of transmission to humans [5]. Accordingly, current data suggest that the incidence of AE also significantly increased from approximately 0.10 cases per 100,000 between 1993 and 2000 to 0.26 cases per 100,000 between 2001 and 2005 [7]. Improved diagnostic accuracy, due to modern imaging techniques such as computerized tomography [8] was unlikely to fully account for this increase. The increase in incidence occurred after an approximately 4-fold increase in the fox population between 1980 and 1990. The latency period of human AE is thought to be approximately 10–15 years [4] which corresponds well to the observed increase in human AE some 10–15 years after the fox population started to rise in Switzerland [7].

With behaviour similar to that of a malignant tumour, AE can be a devastating human disease. Treatment often requires radical surgery and/or life long antiparasitic chemotherapy [4,9]. Relative survival analysis is accepted as the method of choice for population-based cancer survival studies although a randomised clinical trial would be the preferred method to assess clinical efficacy [10]. However, as AE is a rare disease in Europe such clinical trials would be very difficult to conduct. Hence, multivariate survival analysis could indicate likely survival when the background prognostic factors (such as patient age) are removed. Any changes in the survival rates for recently diagnosed patients could also give important clues to treatment efficacy as new patient management strategies are introduced. Therefore, a major objective of this study was to analyze long-term changes in the prognosis of AE-affected patients as an indicator of the effectiveness of modern treatment protocols.

In addition, treatment of this disease represents a considerable, but as yet unknown financial burden. Estimates of the burden of disease of cystic echinococcosis (CE) a related disease, caused by *Echinococcus granulosus* have been substantial both in localized endemic areas and globally [11]. Estimates for disease burden of AE have been reported only from one highly endemic region in China [12,13], but there are no estimates for disease burden in the central European endemic area. Because AE has a greater clinical severity and a poorer prognosis the burden of disease of individuals diagnosed with this condition is likely to be higher compared to individuals with CE. In addition, burden analysis can provide an estimate of the cost-effectiveness of present treatment protocols for AE-affected patients.

Studies have shown that periodic treatment of fox populations with anti-helmintic treated baits can result in substantial reductions in the prevalence of *Echinococcus* in foxes [14]. However, the cost-effectiveness of such strategies in terms of the reduction in AE incidence has not yet been evaluated. An estimate of the burden of AE in Switzerland, in terms of both monetary and non-monetary methods [15], can provide an objective measure against which costs of control strategies such as periodic baiting of foxes can be measured.

2. Methods

2.1. Patient data

The patient data were retrieved from the database established by Schweiger et al. [7]. Among others, relevant variables extracted for this study included date and clinical presentation of AE, all surgical and anti-helminthic treatments in the in- and outpatient setting, time off from work, and long-term disability due to AE or its treatment.

Income losses were calculated from the estimated absenteeism from work during treatment and the patient's occupation. Patients, who were not working at the time of AE diagnosis or thereafter, were assumed to have no income loss. A total of 155 patient records, spanning the period 1967–2005, were available where all known costs could be calculated. The annual incidence of disease was based on the latest available figure spanning the AE epidemic emerging over the past 5 years [7] so that economic costs would reflect the recent burden of disease in Switzerland. Long-term records were used to estimate the clinical outcomes including premature mortality, morbidity and long-term effect on the health of the individuals.

2.2. Survival analysis

In order to estimate excess mortality in the population due to AE, relative survival analysis was performed. The data were entered and analyzed in R (The R Foundation for Statistical Computing, http://CRAN.R-project.org) using the relative survival package [16]. Swiss life tables were used to estimate the expected survival rates. Additive survival models were used which assumed that the hazard of every individual can be split into two components. The first component consists of the normal population hazard, which depends on the subject's age, gender, cohort year and location and can be determined based on standard life tables of the population in question. The second component is the excess hazard or risk associated with the disease, in this case infection with AE. In total, 329 patient records were suitable for analysis where details of the patient's age, gender and time of diagnosis, date of death or loss to follow were known. These cases were recorded from 1963 to 2005. A multifactorial relative survival model was

constructed where the covariates were the patient's gender, age at diagnosis, year of AE diagnosis, radical surgery undertaken and PMN score [7,9]. Radical surgery was assumed when it was indicated in the patient's record. Otherwise it was assumed not to have taken place where there was either no record of the surgery or where only non-radical or palliative surgery was undertaken. It was possible to assign PMN scores to 242 patient records. The PMN score was analyzed in two ways. First, as a categorical variable with score I, II, IIIa, IIIb, IV and unknown. For a second analysis, the unknown data were given the mean of PMN scores from the corresponding period of time and the variable was analyzed as a continuous variable with PMN scores IIIa and IIIb were given a value of 3 and 3.5, respectively [7].

Using the relative survival model, the hazard function for patients diagnosed in 2005 was calculated and the estimated survival times were based on the relative survival curves. Excess hazard compared to the Swiss population norms was assumed to be due AE, even where the actual cause of death in the hospital records was not AE. Estimated survival times and 10-year survival rates were also calculated for each 5-year interval between 1970 and 2000 to analyze any changing trends in survival of AE patients and to estimate the survival time before the use of chemotherapy. All the results are reported as centered on patients 54 years of age as this is the long-term average age at diagnosis of Swiss AE patients [7].

2.3. Disability-adjusted life years (DALY) estimates

The disability-adjusted life year in its simplest terms can be considered a loss of healthy years of life and is a non-monetary measure of disease burden. It consists of two components: years lived with disability (YLDs) and years of life lost (YLLs). YLDs were calculated according to standard methods [17]. Standard age weightings were used and a discount rate of 3% applied. The disability weights of liver cancer were used [11,13]. For patients diagnosed with AE a disability weight of 0.2, the same as for liver cancer (Dutch disability weight for disease free liver cancer) [18,19] was assigned. This disability weight was assumed for the length of the follow-up period. YLLs were estimated from the life expectancy of patients calculated from relative survival analysis, and DALYs were calculated by adding the YLDs and YLLs. For the scenario that no treatment would be available, the YLLs were estimated from the survival curve from 1970 where the survival analysis indicated a considerably shortened life expectancy. However, present incidence rates were used. In this scenario, YLDs were also calculated based on the last two–three years of life having a disability weight of pre-terminal liver cancer, and the rest of life living with the disease a weight of terminal liver cancer (0.239 and 0.809, respectively) [17,18]. From the financial estimates of the cost of treatment, the cost per DALY saved was estimated and hence the cost-effectiveness of treatment.

2.4. Financial estimates

Financial estimates were based on the actual costs of treatments and loss of income due to disability. The costs of treatment were estimated from the case records and the amount charged for the treatment. All the patients with known costs were used and discounted to present day costs at a discount rate of 3%. Income loss was estimated from the time off from work during treatment and follow-up. This was calculated as the baseline scenario. For comparison, a second scenario was calculated based on any shortened life expectancy resulting in savings to pension costs. Here the average pension cost was assumed to be approximately 70% of the pre-retirement income. An exchange rate of CHF 1 = €0.60, the rate of May 2007, was used to estimate € equivalents.

2.5. Data analysis

All data were entered onto an Excel spreadsheet. A simple model was derived which added the various cost estimates for individuals and then added them across the population. Long-term costs such as repeated outpatient costs and laboratory monitoring was discounted at 3% per year from the age of diagnosis to the estimated life expectancy. Monte-Carlo techniques were used to model data variability. Probability distributions were assigned to costs based on the variability of the data using bootstrapping resampling techniques with replacement from the observed data. In total, 10,000 bootstrap replicates were calculated. Each replicate was entered into the cost model to gain an overall estimate of the cost. The annual incidence rate used was based on bootstrap estimates of the actual numbers of cases recorded over the period 2000–2005. Total costs were the sum of the surgical and medical treatment costs, the diagnostic costs and the loss of income resulting from illness due to the AE and were estimated from the 155 case records reported above.

3. Results

3.1. Survival model

The relative survival model clearly indicates that the year the subject presented with AE and the age of the subject has significant effects on the relative hazard function (Table 1). Gender was not significant. The overall goodness-of-fit is insignificant ($p = 0.84$), implying a reasonable fit of the data to the model. Recently diagnosed patients had the lowest relative risk of mortality. For each year there is an approximate 7.9% decrease in the AE-associated hazard. Likewise, younger patients had a lower relative risk compared to older patients. Table 2 and Fig. 1 give the estimates of the 10-year survival rate and life expectancy of AE patients of age 54 compared to Swiss population norms. Here it can be seen that recent cases have a very good prognosis, with a life expectancy, which is shortened by only about 3 years. It can also be seen that treatment substantially improved the prognosis, as cases diagnosed in 1970 had a life expectancy of approximately 6 and 10 years for men and women, respectively. If radical surgery was undertaken there was an independent decrease in the relative hazard compared to those patients in which it was not undertaken. The proportion of patients undergoing radical surgery was 14.8%, 29.3%, 37.3%

Table 1
Parameters of the relative survival model and their significance

	Estimate	Std. error	Z value	Pr(>|Z|)
Age of patient at time of diagnosis	0.02906	0.0125	2.322	0.0202
Year of diagnosis	−0.0794	0.0239	−3.325	0.0009
Radical surgery undertaken	−1.1862	0.4715	−2.516	0.0119
Gender (male)	0.14611	0.34755	0.420	0.6742
PMN score	−0.03916	0.15846	−0.247	0.8048

Table 2
Estimated 10-year survival rate and median life expectancy of AE-positive patients compared to the general population

Date of diagnosis	Ten year survival rate population norms (%)		Ten year survival rates for AE-positive patients		Median life expectancy (years). Swiss population norms		Estimated life expectancy of AE patients (years)	
	Males	Females	Males	Females	Males	Females	Males	Females
1970	87.1	93.6	25.2% (18%, 65.0%)[a]	49.3% (34.1%, 75.0%)[a]	24.4	31.2	6.2 (5.9, 13.1)	9.9 (7.0, 19.1)
1980	88.5	94.8	62.3% (56.8%, 78.2%)[a]	76.2% (67.6%, 86.3%)[a]	26.9	32.4	12.9 (11.2, 19.2)[a]	20.8 (14.2, 24.9)[a]
1990	91.3	95.6	80.2% (76.8%, 86.5%)[a]	87.8% (83.2%, 91.7%)[a]	28.3	32.8	21.1 (20.8, 24.0)[a]	26.0 (23.9, 31.2[b])[a]
2000	92.8	96.1	88.1% (86.1%, 90.6%)[a]	92.7% (90.4%, 94.3%)[a]	28.6	32.9	24.1 (23.9, 25.2)[a]	29.5[b] (29.2[b], 30.9[b])[a]
2005	92.9	96.1	89.7% (88.3%, 91.3%)[a]	94.0% (92.3%, 94.9%)[a]	28.6	32.9	25.1 (24.1, 25.7)[a]	30.3[b] (29.8[b], 31.2[b])[a]

This is for a 54-year-old reference patients with AE.
[a] Figures in brackets represent estimates for patients who do not or have radical surgery, respectively.
[b] Extrapolated (last value carried forward) as it was beyond the end of the survival curve.

and 45.2% in the periods prior to 1975, 1976–1985, 1986–1995 and 1996–2005, respectively. The PMN score was fitted as both a continuous variable (Table 1) and a categorical variable (data not shown). In both instances the PMN score had no significant effect on the relative hazard function.

3.2. Costs

The 155 cases suitable for cost analysis had a mean age at diagnosis of 52.3 years, 36% being male and 43% undergoing radical surgery with the remainder being treated with a combination of non-radical surgery and anti-parasitic chemotherapy. This subgroup was not significantly different from the whole cohort ($n = 329$), having a mean age at diagnosis of 52.6 years with 43% being male and 41% undergoing radical surgery ($p > 0.05$ in each case). Therefore, the sample available for cost analysis was believed to be representative for the whole cohort. The total median treatment cost for each case of AE was estimated to be €103,312 (CIs €90,230–€118,146). In addition, each AE patient lost an average income of € 78,485 (€45,454–€125,614). The median cost per case, when saved pension costs are deducted due to premature mortality, was estimated at €108,762 (€48,302–€178,568), with a total cost per year of €2.0 million (€0.9–€3.5 million). If saved pension costs are not deducted, then the cost per case rises to €182,594 (€144,818–€231,448), with total costs of €3.5 million (€2.5–€4.9 million).

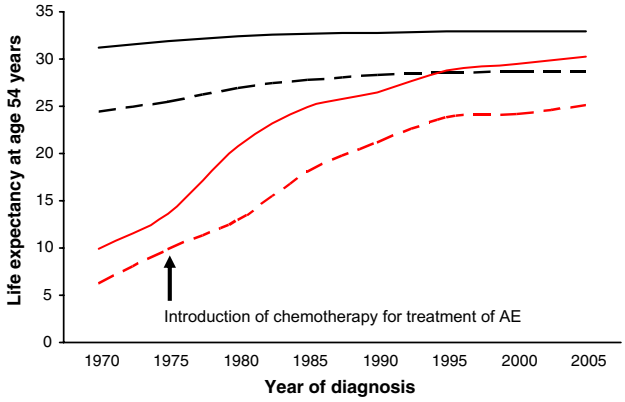

Fig. 1. Improving life expectancy of AE patients (red) compared to population norms (black). Females (solid line) and male (dashed line). [This figure appears in colour on the web.]

3.3. Burden of disease estimates

The estimated YLD per year in the Swiss population is 24.0 (CIs 18.2–30.3). The estimated YLLs is 53.4 (CIs 31.1–79.2) and thus the total number of DALYs lost is 77.6 (CIs 52.1–108.4). In comparison, if no treatment were available, the YLDs would be 30.0 (22.4–37.3) and YLLs would be 380 (223–555), giving a total loss of 409 (249–591) DALYs. Consequently, modern methods of treatment save a net of 332 (171–517) DALYs. As the total medical costs add up to €2.0 million (€1.4–€2.6 million), the costs per DALY saved amount to approximately €6032 (€4187–€10,528).

4. Discussion

The relative survival analysis clearly shows an improved survival rate in subjects with AE whether measured by the median life expectancy or the 10-year survival rate. This almost certainly reflects the improved quality of patient management and experience with this disease. Relative survival analysis was chosen here because the disease is chronic and the average age at diagnosis of AE patients in Switzerland is quite old at

54 years and has not changed over the last 50 years [7]. Thus, a number of patients would expect to die from other causes during the natural history of the disease. This is fully accounted for in the relative survival analysis. Untreated, AE typically exhibits a chronic course. Ammann and Eckert [4] suggested that the disease is fatal in 90% of untreated patients within 10 years. This is supported by the present survival analysis, showing a 10-year survival rates of 25% and 49% (Table 2) for male and female patients, respectively, who were diagnosed in 1970.

The PMN score, perhaps surprisingly, had no significant effect on the relative survival function. This might be a reflection on the effectiveness of chemotherapy as cases with advanced PMN scores usually cannot be treated surgically. However, those cases that were amenable to surgery and underwent radical surgery had a better survival rate than other cases. This is particularly marked in the earlier cases and may reflect that radical surgery can be successful if the lesion is not too extensive.

Constructing double-blind clinical trials for the evaluation of treatment protocols for this disease is difficult because it is a rare disease. However, the results reported here show a rapidly improving prognosis with survival rates approaching those of the normal population. This indicates that modern therapies such as long-term parasitostatic treatment with benzimidazole derivatives and surgery are highly effective. The outlook for patients diagnosed with AE in Switzerland nowadays is relatively good, with an expected shortened lifespan of only 3 years. The probability of surviving 10 years for patients diagnosed at age 54 approaches 90% (for males) and 94% (for females), which favorably compares to the expected 10-year survival rates of 93% and 96%, respectively (Table 2), for healthy individuals.

The analysis in this report did not take into account the actual cause of death in AE-affected patients. The reported cause of death in many of the fatal cases was not AE. Alternatively, these patients could be censored at the time of death rather than being recorded as fatality. In such a scenario only cases actually recorded as death due to AE would be recorded as fatal cases. Human infection with *E. multilocularis* is known to be associated with immunological changes [20–23]. Consequently, even cases where AE was not listed as the cause of death, it could have been a contributory factor and censoring these cases at the time of death would be inappropriate. In addition, relative survival provides a measure of the excess mortality associated with the disease of interest compared to the general population. This is irrespective of whether the deaths are caused directly or indirectly by the disease [24].

The DALY estimates indicate the approximate annual burden of AE in the Swiss population. It was not possible to age weight the YLL component of the DALY as the survival analysis gives an estimate of the mean shortened life expectancy and not the age at death. The overall burden of disease of AE in Switzerland is relatively low as it is still a rare disease. However, the relative survival analysis was used to estimate the life expectancy in the 1970s and the YLL used to calculate the DALY estimate when treatment options were more limited. Thus, in the absence of effective treatment, the numbers of DALYs lost could be as high as 409 DALYs. Consequently modern therapies may be saving as many as 332 DALYs per year at a cost of only €6032 per DALY saved. In terms of the average income per head or GDP (gross domestic product) per head in Switzerland it is very inexpensive as the annual GDP per head is approximately $32,200 (€24,000) [25].

Alveolar echinococcosis has been acknowledged as one of the world's most lethal parasitic zoonoses because of its high fatality rate in untreated patients. In Europe it is a rare disease, but this is not the case in certain communities in China where a prevalence of 5% has been recorded [13]. This study demonstrates that the prognosis has improved for these patients with modern treatment methods, and in the European setting it is cost-effective. These results are not only important from the point of view of European patients but possibly point the way to disease management by chemotherapy in poor and/or very remote communities such as in China where surgical intervention is not possible.

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