Adherence to childhood cancer treatment: a prospective cohort study from Northern Vietnam

Bui Ngoc Lan,1 Anders Castor,2 Thomas Wiebe,2 Jacek Toporski,2 Christian Moëll,2 Lars Hagander3

ABSTRACT

Objectives Global incidence and attention to childhood cancer is increasing and treatment abandonment is a major cause of treatment failure in low- and middle-income countries. The purpose of this study was to gain an understanding of factors contributing to non-adherence to treatment.

Design A prospective cohort study with 2-year follow-up of incidence, family-reported motives and risk factors.

Setting The largest tertiary paediatric oncology centre in Northern Vietnam.

Participants All children offered curative cancer treatment, from January 2008 to December 2009.

Primary and secondary outcome measures Family decision to start treatment was analysed with multivariable logistic regression, and family decision to continue treatment was analysed with a multivariable Cox model. This assessment of non-adherence is thereby methodologically consistent with the accepted definitions and recommended practices for evaluation of treatment abandonment.

Results Among 731 consecutively admitted patients, 677 were eligible for treatment and were followed for a maximum 2 years. Almost half the parents chose to decline curative care (45.5%), either before (35.2%) or during (10.3%) the course of treatment. Most parents reported perceived poor prognosis as the main reason for non-adherence, followed by financial constraints and traditional medicine preference. The odds of starting treatment increased throughout the study-period (OR 1.04 per month (1.01 to 1.07), p=0.002), and were independently associated with travel distance to hospital (OR 0.998 per km (0.996 to 0.999), p=0.004). The results also suggest that adherence to initiated treatment was significantly higher among boys than girls (HR 1.69 (1.05 to 2.73), p=0.03).

Conclusions Non-adherence influenced the prognosis of childhood cancer, and was associated with cultural and local perceptions of cancer and the economic power of the affected families. Prevention of abandonment is a prerequisite for successful cancer care, and a crucial early step in quality improvements to care for all children with cancer.

INTRODUCTION

Low- and middle-income countries have approximately 5% of the global resources to treat and prevent cancer, but 80% of the global cancer disease burden.1 This inequitable distribution implies a prevailing perception of cancer care as insignificant, impossible or inappropriate in developing countries.2 However, both incidence of and attention to childhood cancer is now increasing also outside high-income settings.3 4

Every year approximately 271 000 children worldwide develop cancer.3 6 Currently about 90% of paediatric cancer deaths occur in low- and middle-income countries,7 but the contribution of childhood cancer to child mortality in these settings has long escaped wider public attention.8–10 As fewer children succumb to infectious diseases of infancy and childhood, and countries experience demographic and epidemiological shifts, the relative importance of morbidity and mortality from childhood cancer and other non-communicable diseases will increase. Childhood cancer has ranked among the top 10 causes of death in low-income countries, and top five causes of death in middle-income countries, for children aged 5 to 14 years.7 11 In high-income countries, cancer is the leading cause of death from disease among children and adolescents.12 The number of children in the world with cancer is projected to increase by 30% by 2020, and the global cancer divide will widen.7

Vietnam has recently emerged from a low-income to a lower middle-income country, and is renowned for achieving health outcomes far beyond its income level.13 As a consequence of its successes, the healthcare system is now increasingly challenged by cancer
and other non-communicable diseases, and is starting to adapt to new population needs. In 2006, Vietnam had a postulated overall event-free 5-year survival from childhood cancer14 measuring about a 10th compared with the current 80% in high-income countries.15–17 With the aim of assisting the national development of paediatric oncology, the Lund Vietnam Childhood Cancer Program was inaugurated in January 2008.

There are many reasons why children with cancer die undiagnosed or untreated in low- and middle-income countries, for example, shortage of trained human resources, insufficient infrastructure, low diagnostic capabilities, poor referral systems, inconsistent drug availability and lack of supportive care.11 18 19 Children present in advanced stages of their disease, with malnutrition and other comorbidities, and the treatment is complex and toxic.20 Patients and their families are sensitive to both direct and hidden costs of treatment and disease.7 18 21 In high-income countries, non-adherence to treatment is extremely rare,22 23 but in developing countries non-adherence is a major determinant of childhood cancer survival, and consistently the most common cause of treatment failure.20 22 24 Indeed, the annual number of abandonment events in low- and middle-income countries is nearly equivalent to the total number of new childhood cancer cases in high-income settings.22

Recognising why parents choose to decline cancer treatment is essential to increase paediatric cancer survival. However, no prospective analysis has yet reported of adjusted risk factors for both failure to start treatment and failure to continue childhood cancer treatment. The purpose of this study was to gain an understanding of factors contributing to adherence to treatment, and to determine the cumulative incidence of non-adherence. Over 4 years we prospectively measured the incidence, motives and risk factors for non-adherence among children with cancer at the largest tertiary paediatric oncology centre in Northern Vietnam. Based on previous literature and conclusions from initial qualitative interviews with parents and staff, our hypothesis was that adherence to treatment was associated with poor prognosis, poverty and long travel distance to the hospital, and that adherence to treatment would increase after the initiation of the collaborative programme.

METHODS
Study design and study subjects
We conducted a prospective cohort study of children offered curative cancer treatment at the main referral hospital of paediatric oncology in Northern Vietnam: the National Hospital of Pediatrics (Bệnh viện Nhi Trung Ương) in Hanoi. All 731 consecutive patients younger than 15 years admitted to the department of paediatric oncology from January 2008 to December 2009 were included in the study. Central nervous system (CNS) tumours and retinoblastomas were not represented in this cohort, since they were treated in another department of the hospital. Patients not offered cancer treatment with the intention of cure were excluded from further analysis (figure 1), as were patients curable with surgery-only strategies, not requiring multimodal treatment (ganglioneuroblastoma, localised low-grade gonadoblastoma, mesoblastic nephroma, pheochromocytoma and mature teratoma).

Each patient was followed for a maximum of 2 years from the start of chemotherapy. The date of therapeutic surgery was used as the starting date if surgery was performed before chemotherapy and if malignant diagnosis was available prior to surgery. The date of diagnosis was used as the starting date if the date of first therapeutic treatment was missing. Children were eligible for analysis as long as they were offered curative cancer treatment, and patients were censored at the time of death, at the time of referral to other health facilities or when curative treatment was either completed or no longer offered. The Lund Vietnam Childhood Cancer Program did not support patients and families financially.

Definitions and criteria
The primary outcome was adherence to cancer treatment prescribed with the intention to cure. Non-adherence is more commonly known as treatment abandonment, which is defined by the International Society of Pediatric Oncology as 1. Failure to start prescribed curative cancer treatment, or 2. Failure to continue such treatment, resulting in either premature termination of treatment or a hiatus of four or more weeks in scheduled treatment.25
In this study, we considered abandonment and non-adherence to be identical. The term abandonment has an accusatory connotation in Vietnam, and was avoided. Failure to start treatment occurred per definition on day 0. Failure to continue treatment could occur at any given time from start of treatment to censoring, and this endpoint was therefore connected to a time-to-event. We considered terminally ill children as non-eligible for curative therapy, unable to abandon treatment while in their last week of life.
All continuous covariates were kept linear in the multivariable model, after first ensuring linearity by dividing the range of numerical values into five equal bins, assessing for stepwise monotonic increases in log odds. For the sake of clarity, continuous variables were also dichotomised for stratified display of adherence proportions. Travel distance and regional capture rate were hereby split at the median. Age was split at the age of 6 years, since patients younger than 6 years in Vietnam receive more comprehensive national health insurance.

Decision to continue treatment: A multivariable Cox model established covariate HRs for the time-sensitive binary decision to continue treatment. With 70 events, the model was stable for the inclusion of all six covariates. There were no departures from the proportional hazard assumptions for the model when assessing with supremum test for proportional hazards assumption and martingale residuals (online supplementary appendix C). Time to non-adherence events was also displayed using the Kaplan-Meier method with 95% CIs and log-rank tests.

Alpha was set at 0.05. Statistical software SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA) was used for statistical analyses.

RESULTS
During the study interval, 677 children were eligible for curative cancer treatment. Acute lymphocytic leukaemia (ALL) was the most common diagnosis, affecting 270 (39.9%) of the diagnosed children. Prognosis was defined as ‘favourable’ in about a quarter of all cancer cases (25.4%), and ‘poor’ in over a third (37.7%). More than half of the patients were boys (58.3%).

Median age at diagnosis was 3.62 years (IQR 1.63 to 7.67), and two-thirds (66.0%) of the children were younger than 6 years of age when diagnosed with cancer. Median travel distance between home and hospital was 99.6 km (IQR 47.1 to 164). Patient characteristics are summarised in table 1.

Adherence to treatment was maintained for 369 children (54.5%), while parents declined curative treatment in 238 cases (35.2%), and discontinued commenced treatment in 70 cases (10.3%). Failure to continue treatment was particularly common during the initial phases of treatment, but could happen at any time during the course of treatment (figure 1). Among the patients who failed to continue treatment, the median time to adherence failure was 32 days (IQR 15 to 182) (online supplementary appendix D).

Perceived poor prognosis was the most commonly reported reason not to start (55%) or not to continue (25%) curative cancer treatment, followed by financial difficulties and traditional medicine preference. Travel
Parents and physicians usually had congruent views of prognosis, but 26.1% of the 130 patients who did not start treatment due to disbelief in cure had indeed a favourable or intermediate prognosis (table 2). The adjusted odds of starting treatment increased significantly over the course of the study (OR 1.04 per month (1.01 to 1.07), p=0.002) (table 3). The odds of starting treatment also significantly declined with poorer prognosis (OR 0.51 (0.41 to 0.64), p<0.0001) and increasing travel distance (OR 0.996 per km (0.996 to 0.999), p=0.004) (table 3). The relative influence of non-adherence risk factors varied over the course of treatment (table 3). Girls were less likely than boys to adhere to ongoing curative cancer treatment (log-rank, p=0.028) (figure 1), and had a significantly higher adjusted HR of not continuing treatment (HR 1.69 (1.05 to 2.73), p=0.03) (table 3). Non-adherence per tumour diagnosis is presented in online supplementary appendix E.

**DISCUSSION**

This large prospective cohort study measured incidence, motives and factors associated with adherence to treatment among children with cancer in Northern Vietnam, 2008 to 2009. Almost half the parents chose to decline curative care (45.5%), either before (35.2%) or during (10.3%) the course of treatment. Even when chances of survival were higher, most parents reported perceived poor prognosis as the main reason for non-adherence, followed by financial constraints and traditional medicine preference. Risk factors for non-adherence changed over the course of treatment, and our results support the hypothesis that adherence to started treatment increased throughout the study-period, and that it was independently associated with both prognosis and travel distance to hospital. The results also suggest that adherence to initiated treatment may be significantly higher among boys than girls.

Our study offers the chance to analyse non-adherence over time: how risk factors for not starting treatment were different from risk factors for not continuing treatment. This trend may illustrate how each treatment phase involves its own challenges, but could also reflect how less influential risk factors become increasingly detectable as more influential risk factors have had their effects.

**Adherence rates**

Our finding that non-adherence was a major cause of treatment failure for paediatric cancer is congruent with previous reports from low- and middle-income countries. The wide intervals of published adherence rates reflect vast global disparities in paediatric oncological care, differences in patient populations, geography, health systems and financial support, but also inconsistent definitions. Many previous studies have included only abandonment from commenced treatment, not refusal to start treatment, which in our setting was the considerably larger group. This is well illustrated in a review of Chinese patients diagnosed with ALL: 53.6% refused to start treatment and another 10.8% prematurely discontinued treatment. Most publications present stratified incidence statistics, often based on relatively small samples sizes and select cancer forms. Some studies also survey motives why parents choose not to adhere to treatment, or assess for risk factors among patient characteristics.
Motives
Expert opinions, qualitative studies and semi-structured interviews have acknowledged that multiple medical and socioeconomic factors make parents decline curative cancer treatment for their child. Our finding that non-adherence primarily is due to futility and financial constraints are in line with these previous studies. A well-powered study in Indonesia, that surveyed parents at home after not starting or not continuing ALL treatment, highlighted poverty and perceived poor prognosis as equally important for adherence, followed by treatment side effects, transportation difficulties and that children did not want to be a burden for the family. More than half of the parents had lost their job as a consequence of their child’s disease, many had to sell property such as house and land, and more than half of the families were still indebted years after the child had left the hospital. In a hospital study from Malawi, both direct and indirect costs were of significance for adherence to treatment. More than half of all patients in our study who reported non-adherence due to perceived poor prognosis, had cancer with favourable or intermediate prognosis. Our study is the first to correlate clinical data to given motives, and our results suggest that addressing parental beliefs about cancer, through education and clinical excellence, has the potential to increase adherence.

Risk factors
Non-adherence to treatment is associated with certain patient characteristics, and identification of these risk factors can also point towards causal mechanisms and facilitate targeted interventions. Confounding effects and collinearity are caveats when interpreting such data. Two studies have previously performed multivariable abandonment assessments, and both excluded patients who refused to begin treatment. In a retrospective study from Honduras, where abandonment from initiated ALL treatment (22.8% of 162 patients) was analysed using time-sensitive multivariable regression, travel time >2 hours and low age were associated with less adherence; prognosis and gender were unrelated to adherence; and there was no information on patient socioeconomic status and to what extent patient costs were covered. In a prospective study from a paediatric oncology centre in El Salvador, abandonment from initiated treatment for all cancers (13% of 612) was analysed without accounting for censoring. All direct patient costs for treatment, travel and housing were covered, and yet family income level and numbers of family members were the only

Table 2 Prognostic classification among patients who stated perceived ‘poor prognosis’ as reason not to adhere to curative cancer treatment

| Prognosis | Total |
|-----------|-------|
|           | n    | %   | n    | %   | n    | %   | P value |
|           |      |     |      |     |      |     |         |
| Not starting treatment |       |     |       |     |       |     |         |
| Due to ‘poor prognosis’ | 12   | 9.2 | 22   | 16.9 | 96   | 73.8 | 130 100 |
| Other causes for non-adherence | 31   | 28.7 | 41   | 38.0 | 36   | 33.3 | 108 100 | <0.0001 |
| Not continuing treatment |       |     |       |     |       |     |         |
| Due to ‘poor prognosis’ | 6 | 37.5 | 5 | 31.3 | 5 | 31.3 | 16 100 |
| Other causes for non-adherence | 25   | 35.7 | 28   | 40.0 | 17   | 24.3 | 70 100 | 0.66   |
Table 3  Adherence to treatment. *Model 1:* Multivariable logistic regression with OR of starting prescribed curative cancer treatment among patients offered curative treatment for childhood cancer (n=677). *Model 2:* Log-rank test and multivariable Cox regression with HR of not continuing treatment among patients starting treatment (n=438)

| Covariates                        | Starting treatment (model 1) | Continuing treatment (model 2) |  |  |  | Log-rank HR (95% CI) | P value |
|-----------------------------------|-------------------------------|-------------------------------|-------------------|-------------------|-------------------|-----------------|----------|
|                                   | n    | %     | OR (CI) | P value | n    | 1 week | 1 month | 1 year | 2 years | P value |
| Overall                           | 677  | 64.8% |         |         | 438  | 97.1%  | 90.8%  | 80.1%  | 75.0%  |         |
| Age                               |      |       |         |         |      |         |         |         |         |         |
| <6 years                          | 479  | 66.0% |         |         | 316  | 96.4%  | 89.5%  | 79.2%  | 71.9%  |         |
| ≥6 years                          | 198  | 62.1% |         |         | 123  | 99.0%  | 94.4%  | 82.7%  | 82.7%  | 0.06    |
| Per year                          |      |       | 0.98 (0.94 to 1.02) | 0.43 |      | 0.94 (0.87 to 1.01) | 0.08 |
| Gender                            |      |       |         |         |      |         |         |         |         |         |
| Male gender (ref)                 | 395  | 64.8% |         |         | 256  | 98.2%  | 94.3%  | 84.4%  | 78.1%  |         |
| Female gender                     | 282  | 64.9% | 0.98 (0.69 to 1.38) | 0.90 | 183  | 95.5%  | 86.1%  | 74.2%  | 71.1%  | 0.03    |
| Prognosis                         |      |       |         |         |      |         |         |         |         |         |
| Favourable (ref)                  | 172  | 75.0% |         |         | 129  | 98.3%  | 96.5%  | 78.1%  | 72.3%  |         |
| Moderate (ref)                    | 250  | 74.8% |         |         | 187  | 96.5%  | 96.5%  | 83.5%  | 77.8%  |         |
| Poor                              | 255  | 48.2% | 0.51 (0.41 to 0.64) | <0.0001 | 123  | 96.6%  | 91.7%  | 77.2%  | 77.2%  | 0.62    |
| Progress over time                |      |       |         |         |      |         |         |         |         |         |
| 2008                              | 345  | 59.7% |         |         | 206  | 97.8%  | 91.1%  | 77.7%  | 71.6%  |         |
| 2009                              | 332  | 70.2% |         |         | 233  | 96.3%  | 90.6%  | 82.6%  | 78.5%  | 0.42    |
| Per month                         |      |       | 1.04 (1.01 to 1.06) | 0.002 |      | 0.99 (0.95 to 1.02) | 0.41 |
| Travel                            |      |       |         |         |      |         |         |         |         |         |
| Short distance                    | 340  | 70.6% |         |         | 240  | 98.4%  | 92.2%  | 82.1%  | 75.1%  |         |
| Long distance                     | 337  | 59.1% |         |         | 199  | 95.6%  | 89.3%  | 78.1%  | 75.2%  | 0.50    |
| Per km                            |      |       | 0.998 (0.996 to 0.999) | 0.004 |      | 1.00 (1.00 to 1.00) | 0.10 |
| Regional capture rate             |      |       |         |         |      |         |         |         |         |         |
| High capture                      | 345  | 60.6% |         |         | 209  | 96.7%  | 91.5%  | 81.2%  | 74.9%  |         |
| Low capture                       | 332  | 69.3% |         |         | 230  | 97.3%  | 90.0%  | 78.8%  | 74.9%  | 0.77    |
| Per %                             | 3.66 (0.67 to 19.9) | 0.13 |      | 1.03 (0.09 to 11.8) | 0.98 |

km, kilometre.
factors associated with abandonment. Gender and protocol length were not correlated with adherence, and prognosis and travel distance were not controlled for.\textsuperscript{30} The results from these two publications differ from ours, where only female gender seemed to be a risk factor for failure to continue treatment, particularly during the first months of treatment.

Previous studies have highlighted somewhat conflicting evidence on univariate associations between abandonment and prognosis,\textsuperscript{18, 20, 32, 43–45} travel distance/time,\textsuperscript{18, 20, 30, 32, 46–47} age,\textsuperscript{18, 20, 20, 30, 35, 45, 48} gender,\textsuperscript{20, 30, 32, 35, 45, 47} cost,\textsuperscript{18, 20, 30, 33, 36, 47–49, 50} side effects,\textsuperscript{24, 32, 33, 38, 39} patient–doctor interaction,\textsuperscript{18, 24, 36} twinning programmes,\textsuperscript{12, 37} local protocols,\textsuperscript{18} socioeconomic status,\textsuperscript{18, 24, 30, 32, 33, 46, 48, 53} social support networks,\textsuperscript{32} traditional medicine,\textsuperscript{33} religion\textsuperscript{46} and delays in surgical treatment.\textsuperscript{54} The array of risk factors and effect measure variability is a natural consequence of treatment abandonment not being a fixed or biology-driven risk factor, but contextual and modifiable. Yet, few studies have previously analysed factors influencing the decision to start cancer treatment by controlling for multiple factors simultaneously. We identified that the decision to start treatment depended on prognosis, travel distance and quality improvement, when adjusting also for age, gender and regional capture rate.

Our data are limited to the major referral hospital in Northern Vietnam, but it seems as if the capacity of regional hospitals to detect and refer patients with suspected cancer constitutes an important barrier for many children with cancer in Northern Vietnam. Capacity at regional hospitals for basic maintenance treatment and supportive care has been suggested to increase adherence to treatment in other settings,\textsuperscript{20, 30} and we hypothesised that regional capture rate could reflect such a general regional capacity for paediatric oncology, but found nothing to support its influence on adherence.

Limitations
By not including socioeconomic status variables in our model, we remain ignorant of its influence and may have reduced our explanatory power for analysing other covariates. Income level and number of children per household have previously been shown to independently correlate with event-free childhood cancer survival in developing countries,\textsuperscript{24} and in our study almost 20\% of parents reported financial reasons for not adhering to treatment. Insurance level was indirectly included in our analysis: healthcare expenditure of children below 6 years is covered by a national health insurance, while children above 6 years are subject to a certain family co-payment, and we found no sign of this threshold being correlated with adherence to treatment.

Another concern relates to the challenges of maintaining and validating a prospective database in a developing country with limited human resources, an over-crowded ward and language barriers. It was particularly difficult to be certain about the point in time when doctors no longer prescribed cancer treatment with the intention of cure (after which non-adherence per definition no longer can occur). Some patients may have been prescribed curative treatment to a point where discontinuation would be a more rational choice. Though generally complying with the end-points indicated in the registry, we did consider 31 terminally ill patients, who declined treatment in their last week of life, as ineligible for non-adherence, and instead recoded them as censored for mortality. There may have been additional terminally ill patients, registered as non-adherence, for which such an early death date remained unknown to us. This represents a grey area between curative and palliative care, where also the most developed countries would struggle with the terminology. Our intention was not to depart from the international definition of abandonment,\textsuperscript{25} but to comply with it to the best of our abilities.

Finally, our results on parental motives must be interpreted in the context of a 90.8\% response rate among those not starting treatment, and 62.9\% among those not continuing treatment. We acknowledge the potential for selection bias, and that in-depth home-visit interviews would have been more informative, reliable and possibly preventive. Such home-visits would also have enabled the measurement of abandonment-related mortality.

Clinical implications
Childhood cancer is fatal without proper treatment,\textsuperscript{25, 32, 33, 55} and our findings imply that fatalism and non-adherence to treatment remain a major cause of mortality in childhood cancer in Northern Vietnam. Adherence failure should be explicitly included as an adverse event in reports on event-free-survival,\textsuperscript{25, 45} and each centre and country must assess and address the setting-specific relative contribution of different abandonment risk factors in their community. Interventions that specifically address adherence to treatment – such as targeting public perception of childhood cancer as a curable condition,\textsuperscript{45} tailoring treatment intensity according to local and individual circumstances, strengthening of paediatric oncology capacity at regional hospitals,\textsuperscript{20, 30} and improving transportation services and guest houses – may have substantial effect on clinical outcomes, at relatively low cost. Through such multidisciplinary collaboration, two recent studies indicate that adherence rates at in Vietnam have increased to approximately 85\%.\textsuperscript{22, 36}

If we assume a baseline survival rate of 70\% among fully treated children, then treatment success must increase to impossible 100\% to match a rise in treatment adherence from current 54.5\% to 77.9\%. In other words, the clinical impact of non-medical interventions that increase adherence can surpass what is possible to achieve by medical care improvement alone. The same effect would be achieved if we intervened even further upstreams, and improved detection and referral of children with cancer at regional hospitals. Balancing well-measured costs and effectiveness of paediatric oncology is certainly relevant for all countries with limited funds for health, but it is
seems particularly important that resources in low- and middle-income countries are deployed wisely.

Future directions

Non-adherence to lifesaving treatment tends to elicit questions, and we suggest that constructive criticism is redirected from the parents to the particular circumstances under which they are victims. Non-adherence exposes the tragedy of poverty and exemplifies the health effects of non-comprehensive healthcare systems.

Paediatric oncology has long realised the need to differentiate treatments according to needs and risk factors of individual patients, to avoid the dire consequences of over- treatment and under-treatment. This is equally true in developing countries, but here also other risk factors are at play. Very intensive, modern therapy might not be the best option, due to increased risk of treatment related mortality, but also due to decreased adherence. Paediatric oncology can show the way towards strengthening the national healthcare system in low- and middle-income countries – for sustainable diagnostics, referrals and effectiveness of treatment. If built into the national healthcare system, the solutions that work for children with cancer may also be valuable for referral level paediatric care in general, and for children with other non-communicable diseases.

CONCLUSION

Our study prospectively measured adherence to paediatric oncology treatment in the major referral hospital in Northern Vietnam, and quantified motives and risk factors for non-adherence. Almost half of the parents chose to decline curative care (45.5%), either before (35.2%), or during the course of treatment (10.3%). Most parents reported perceived poor prognosis as the main reason for non-adherence, followed by financial constraints, even in instances when prognosis was favourable and financial treatment support was at hand. The odds of starting treatment increased throughout the study-period, and was independently associated with both prognosis and travel distance. The design of the healthcare system and the economic power of the affected families seem to determine the overall prognosis of children with cancer in the low- and middle-income countries. Measures for diagnostic capacity and increasing adherence will have a substantial impact on childhood cancer survival.

Acknowledgements
We acknowledge the hard work and contribution of all the colleagues and data manager Ms Tuyet at the Department of Pediatric Oncology at the National Hospital of Pediatrics, Hanoi, Vietnam. We would also like to acknowledge professor Nguyen Thanh Liem, former hospital director of the Vietnam National Children’s Hospital (VNOH), Hanoi (now with the Vinmec Institute of Stem cell research and technology), Drs Cristina Siesing and Kristina Persson who performed the initial qualitative interviews with patients and parents, and Drs Louise Olsson and Johanna Tunlid for their valuable literature review.

Contributors
BNL contributed with registry formation, data acquisition and critical revision of the manuscript. AC contributed with study conception and design, registry formation, data interpretation and critical revision of the manuscript. TW contributed with registry formation, study design and critical revision of the manuscript. JT contributed with registry formation, study design and critical revision of the manuscript. OM contributed with study conception and design, registry formation and critical revision of the manuscript. LH contributed with study conception and design, data analysis and interpretation and drafting of the manuscript.

Funding
The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests
None declared.

Patient consent for publication
Not required.

Ethics approval
Biomedical Research Ethics Committee of the National Hospital of Pediatrics (NHP) and the Research Institute of Child Health (RICH), Hanoi, Vietnam (Reference number NPH-RICH-13-003).

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
In order to fully protect our patients integrity, we would like to refrain from open access of the full data set.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES
1. Farmer P, Frenk J, Knaul FM, et al. Expansion of cancer care and control in countries of low and middle income: a call to action. Lancet 2010;376:1186–93.
2. Knaul FM, Atun R, Farmer P, et al. Seizing the opportunity to close the cancer divide. Lancet 2013;381:2238–9.
3. Sullivan R, Atalisa CI, Anderson BO, et al. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. Lancet Oncol 2015;16:1193–224.
4. The Lancet Oncology Commission on Sustainable Paediatric Cancer Care. 2018 https://www.thelancet.com/campaigns/cancer/paediatric-cancer/code=lancet-site.
5. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol 2017;18:718–31.
6. United Nations DoEaSA, Population Division (2017). World Population Prospects: The 2017 Revision, DVD Edition, 2017.
7. Rodriguez-Galindo C, Friedrich P, Morrissey L, et al. Global challenges in pediatric oncology. Curr Opin Pediatr 2013;25:3–15.
8. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197–223.
9. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151–61.
10. Magrath I, Steliarova-Foucher E, Epelbaum S, et al. Paediatric cancer in low-income and middle-income countries. Lancet Oncol 2013;14:e104–e116.
11. Wagner HP, Antic V. The problem of pediatric malignancies in the developing world. Ann N Y Acad Sci 1997;824:193–204.
12. Kellie SJ, Howard SC. Global child health priorities: what role for paediatric oncologists? Eur J Cancer 2008;44:2388–96.
13. Gapminder. 2018 https://www.gapminder.org/tools/ (Accessed 12 May 2018).
14. Ribeiro RC, Steliarova-Foucher E, Magrath I, et al. Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: a descriptive study. Lancet Oncol 2008;9:721–9.
15. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010;28:2625–34.
16. Ellison LF, Pogany L, Mery LS. Childhood and adolescent cancer survival: a period analysis of data from the Canadian Cancer Registry. Eur J Cancer 2007;43:1967–75.
17. Gatta G, Zigoen G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995–2002. Eur J Cancer 2009;45:1002–1005.
18. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. Pediatr Blood Cancer 2007;49:941–6.
