HEALTH SCIENCES DOCTORAL (PHD) SCHOOL

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF PÉCS

New system of complex institutional management of oncological patients supported by OnkoNetwork to improve efficiency of oncological care

Head of PhD School: Prof. József BÓDIS, MD, PhD, DSc

Program leader: Prof. István KISS, MD, PhD, DSc

Supervisor: Dr. med. habil Árpád KOVÁCS, associate professor

Co-supervisor: Prof. Imre REPA, MD, PhD

Doctoral (PhD) thesis

Gábor LUKÁCS MD

Pécs, 2021

1. Introduction

Based on Hungarian public health indicators, malignant oncological diseases are second leading in morbidity and mortality after cardiovascular disorders. More than 70 thousand new tumors are detected annually, which implies a significant challenge and burden on the Hungarian health care system. Based on public health data, Hungary is a leader in international comparisons considering lung, gastrointestinal and breast cancer.

In 2016, 257 deaths per 100 thousand citizens occurred from cancer in the area of the European Union.Of the member states of the European Union, Hungary had the highest cancer death rate standardized by age with 345 deaths per 100 thousand people.The most recent database of the Central Statistical Office states that a total of 81,022 new tumors were reported in Hungary in 2017 (40,349 men and 40,673 women), which decreased a little in 2018 to 78,115 cancers of which 38,732 were men and 39,383 were women. Data indicate nearly 828 patients with cancer per 100 thousand people in 2017, which decreased to 799 in 2018. Based on the data of the National Cancer Registry, 1533 women and 1495 men died from some kind of non-hematological tumor in Somogy county in 2017.

Given the known public health data and facts, Hungary's global leading place in cancer frequency, and markedly poor morbidity and mortality parameters in Somogy county regarding malignant tumors, the management of Somogy County Kaposi Mór Teaching Hospital looked for a solution to renew and improve the complex care of patients with cancer. The institute's management regarded it as a task to change the current practice in the care of patients with cancer, support the work-up, treatment and follow-up of cancer patients, including out-patient, in-patient, chronic and hospice care, as well as all clinical and diagnostic departments of the institute which are in contact with cancer patients.

Following a nearly one-year-long preparation, where oncological care was reimagined, a patient pathway management system called OnkoNetwork was implemented, and has supported the care of oncological patients from November 2015 to this very day. The newly created system has been implemented in a county hospital representing almost the whole clinical spectrum of patient care. The institute is not in a position to be confined to cancer patients as it has to provide polyclinic care for 24 hours a day. In Somogy County Kaposi Mór Teaching Hospital, oncological care has been a priority since 2015, but not at the expense of other patients.

2. Goals

Due to particularly poor morbidity and mortality indicators of malignant tumors in Hungary and Somogy county, and to increase the efficiency of the care of cancer patients, the management of Somogy County Kaposi Mór Teaching Hospital has created a nationally and internationally unique system called OnkoNetwork for the management of oncological diseases in approximately 500,000 citizens.

The system has been implemented with the following goals:

1. To organize the complex oncological care of approx. 500 thousand citizens belonging to Somogy County Kaposi Mór Teaching Hospital and co-institutes based on regional obligation to provide health care services.
2. To establish a uniform, protocol-based, consensus-based patient pathway management system including the whole oncological care (OnkoNetwork).
3. To introduce time factor during complex oncological care.
4. To reduce the number of "missed" patients resulting from the complexity of oncological care and diversity of participating departments and service providers.
5. To provide systematic and complete oncological follow-up for cancer patients.
6. To set up professional responsibility and competency relations.
7. To establish a uniform IT solution ensuring the operation of the system and managing patient data.
8. To implement a uniform, parametric, IT-retrievable basic questionnaire which includes the complete medical history of each and every patient with cancer.
9. To create a valid, uniform and available oncological database of the given population.
10. To assess the efficiency of OnkoNetwork system in the complex care of patients with pancreatic cancer.
11. Literature data have been reviewed to assess the role of time in the management of patients with pancreatic cancer.
12. To compare international data to those acquired at Somogy County Kaposi Mór Teaching Hospital regarding pancreatic cancer.

3. The role of time in the management of cancer patients in the light of international overview

Providing patients with suspected cancer with timely and continuous care poses a major challenge even in countries with the most developed health care systems and sufficient health care professionals. In 2015, the National Cancer Program of Sweden standardized oncological patient pathways and set deadlines for specific time phases, including cases with "well established suspicion", which were determined separately for each type of cancer. The aim of the Swedish initiative was to decrease waiting time, to increase patient satisfaction and to reduce regional disparities in Sweden where cancer survival is typically high compared to other EU member states.

Denmark suggested a three-part strategy for the timely diagnosis of tumors by urgent referral of patients with cancer-specific symptoms and nonspecific severe symptoms, as well as enabling easy and rapid availability of "yes-no clinics" or multidisciplinary diagnostic centers for patients with frequent and not severe symptoms raising the suspicion of cancer.

The government of the United Kingdom introduced "targeted cancer waiting time" as part of the NHS Cancer Plan in 2000, which prescribes that in case of suspected cancer, the patient should be assessed by a specialist within 14 days, and treatment shall commence within 48 days. Time between referral for suspected cancer and diagnosis and treatment start must not exceed 62 days. Timely detection of cancer in patients with nonspecific symptoms belongs to the top research areas in the UK. The Cancer Taskforce Strategy investigates the establishment of multidisciplinary centers in England, similar to those in Denmark.

The United States introduced the first patient pathway management program in 1990 at Harlem Hospital Center in New York in order to provide free and cheap examinations, mammography screening and patient pathway management to be able to diagnose and treat patients with breast cancer in time. Following the program's start, the rate of patients with breast cancer of stage 3 to 4 at the time of diagnosis decreased from 49% to 21%, whereas 5-year-survival increased from 39% to 70% in the above health center. The program highlighted that the timeliness of cancer management may be limited by significant restrictions presenting on the level of the individual patient, which are in association with social-economical deprivation, as well as by the capacity and rate of organisation of the medical system itself.

There are several facilities in the United States which use patient pathway management systems, however, established evidences on introducing delay cut-offs for each

patient pathway segment in oncological care are frequently debated in literature, and these might vary depending on cancer type. Randomized, controlled studies are rare in this area.

In the frame of the present thesis, data “only” regarding care of patients with pancreatic cancer have been processed.Pancreatic cancer poses only 3% of malignant tumors, however, its frequency continues to increase. Hungary has the 3rd place in Europe regarding incidence (10-15/100,000 citizens/year) and prevalence, mortality is the highest in Central Europe.Despite development in diagnostics and therapy, prognosis is very poor: mean 5-year-survival is the lowest of all cancers, reaching only 6%, which has not changed in the recent 40 years. Poor prognosis is explained by delayed diagnosis and low resection rate. Even in large specialized centers, only 20% of the tumors can be resected. However, most of these patients have recurrence within short time, thus, even curative surgery has a 5-year-survival of only 25%. As surgical resection is the only curative therapy, prognosis could be improved by screening enabling early diagnosis.

This paper summarizes the most recent results regarding pancreatic cancer, highlighting the development in risk factors, diagnosis, prevention and oncological therapy.

4. The establishment of OnkoNetwork, structure and operation of the system

The idea of OnkoNetwork was first brought up in July 2014, when the management of Somogy County Kaposi Mór Teaching Hospital created an interdisciplinary team to explore the background and causes of high cancer mortality in Hungary and Somogy county. The established working group looked for quantitative indicators with high variability, which could be influenced or controlled by the above-mentioned institutes to improve oncological care. Finally, two modifiable and influenceable parameters were identified. On the first hand, diagnostic delay during hospital care (time from the first suspicion of cancer recorded in the medical IT-system of the participating institutes to the tumor board meeting and to the final diagnosis), it exceeded even 6 months in several cases. On the other hand, delay in the start of therapy (time from final diagnosis to the first treatment day) was in many patients also longer than it could be expected optimally. In order to decrease these time windows within the hospital care provision region, a new system was suggested as local initiative to manage and optimize oncological patient pathways. After regular meetings and discussions, the final goal of OnkoNetwork system was defined as follows: *“ensuring timely and equal access to a comprehensive and integrated oncological care by establishing an IT network”.*

On 1 November 2015, after one month of test period, the OnkoNetwork system was officially launched in the Somogy County Kaposi Mór Teaching Hospital and its co-institutes, and its regulation and operation was finalized by instructions of the director general and associated complex provisions were included in the hospital's internal rules.

The target population of OnkoNetwork is adult (≥18 years old) patients with suspected or newly diagnosed solid tumor (ICD code beginning with "C" or "D"), except hematological malignancies and some rare tumors which are managed in specialized centers nationally. One of the basic criteria of the system's efficient operation was the decision of the institute's management that the care of oncological patients has priority in Somogy County Kaposi Mór Teaching Hospital. Management supervised and supported by OnkoNetwork provides priority, individual care pathways and timely access to health care services with quality assurance for included patients from their first appearance in the hospital's IT system.

Considering the data of the last 5 years, every year about 2500-3000 new patients with diagnosed or suspected cancer were included and provided with complex oncological care in our institute.

During the implementation of the system and its IT background, uniform medical history data recording of cancer patients received particular attention. Based on detailed discussions with other specialties, the uniform, reproducible oncological ***Basic questionnaire*** was created which defines the basis for more efficient care. For later retrievability, the whole basic questionnaire was IT parameterized, relevant information can be selected in "opening windows", making them easily accessible from information technological point of view for later assessments. The decreased work-up time window of patients within the OnkoNetwork system did not negatively affect other non-oncological patients' access to diagnostic procedures.Patients' requests are also considered, for example scheduling more diagnostic visits on one day decreases unnecessary multiple travelling and their cost. ***During the first medical visit, the patient receives all referral letters for necessary diagnostic examinations in order to avoid repeated hospital visits just for organizing the next diagnostic procedure.***
The OnkoNetwork system is based on several principles:

- Quality assurance was facilitated by creating and introducing organ-specific, evidence-based clinical protocols.
- Patient monitoring had to be made continuous by an appointed responsible treating physician to avoid "missing" patients.

- Quantitative indicators have been defined: time factor as the tumor board has to issue their final decision on recommended therapy within 30 days of entering the OnkoNetwork system, and therapy shall commence within further 14 days.

Prior to OnkoNetwork system, several ICT (information and communication technological) applications were introduced in the institutes giving place to the system. The aim of OnkoNetwork was not to replace these IT systems but to develop a parallel new IT application tailored to protocol-based care (OncoLogistic) in order to support patient pathway management and documentation, and monitor the efficiency of OnkoNetwork. The greatest challenge of IT development was to establish connections between OncoLogistic and other medical IT systems within the institute. By analyzing deficiencies regarding the program, it appeared that most of the problems could be traced back to connection and alignment issues with the HIS systems. The management regarded it as the most effective and quickest solution to realize patient pathway management by a separate module working as part of the HIS system instead of a separate frame system overlaying the medical IT system. Thus, T-Systems MagyarországZrt. was requested to develop the OnkoNet module for the e-Medsolution patient documentation system which is applied in the institute.

Analyses on efficiency of OnkoNetwork are still ongoing. Five years have elapsed since implementation, which is a milestone even in oncology, therefore, more accurate survival rates can be assessed. Unfortunately, it can be stated that the years 2020-21 significantly modified data due to SARS-CoV-2 (Covid 2019) pandemic, to false positive and false negative directions. Analysis of experiences and data of these two “pandemic years” could be the goal of a separate study on its own.

The OnkoNetwork system was implemented in Somogy County Kaposi Mór Teaching Hospital to provide timely, continuous and quality assured care for patients with confirmed or suspected solid tumors in the health care service provision area of the participating institutes. It can be stated that the OnkoNetwork system is a clearly innovative approach in this context (new professional roles and workflows, supporting, individual IT-network). The model is financially sustainable without receiving financial incentives at macro level for its operation.

5. The role of time factor in the care of patients with pancreatic cancer – international literature review

During international literature review, 5 databases *(PubMed, Scopus, Cochrane Database of Systematic Reviews, LISTA and Library of Congress)* were searched. These databases were reviewed to compare the associations between treatment delay in patients with pancreatic cancer and patients' recovery, in accordance with the principles of *Preferred Reporting Items for Systematic Reviews and Meta-Analyses - PRISMA.* PubMed and Scopus searches included a combination of terms related to pancreatic cancer and delayed care, whereas the search of *Cochrane Database of Systematic Reviews* included all articles related to pancreas.The*LISTA (Library, Information Science & Technology Abstracts)* and *Library of Congress* searches considered all articles related to pancreatic cancer. The search included the period between 2000 and 2017. Duplications in search databases were filtered out, then two independent researchers performed title and abstract filtering with EndNote software, and contradictory opinions were resolved by a leading researcher. All papers after title and abstract filtering were read by two researchers in full text, and their correlation was checked.Inclusion criteria in the phase of full text review listed papers related to pancreatic cancer, which presented data regarding delay in care and at least one conclusion made on delay. Evaluation of identified articles forms an integral part of systematic literature reviews. The possible risk of bias was evaluated with *Cochrane Collaboration Quality Assessment Tool* and *Methodological Index for Non-Randomized Studies - MINORS* used for randomized and controlled trials.

With both quality evaluation tools, one evaluating professional decided on the risk of bias, which was controlled by another evaluator. In addition to the above-mentioned bias evaluation tools, the risks of specific bias described in this research context were assessed.

The risk of bias caused by *wait time paradox* was excluded if the delay period of care was determined randomly. The *lead time bias* reflects the apparent improvement of survival when survival is measured from an earlier point of time from the view of natural science. *Lead time bias* was excluded in survival analyses where the start point of time measurement was not influenced by differences in delay of care. *Length bias* reflects higher mortality in more severe patients, and thereby patients with less aggressive disease becoming more frequent in cohorts with longer delays. *Length bias* was excluded in studies where patients were completely followed-up up to the end of the study.

A total of 18 trials on pancreatic cancer were suitable to be included into the systematic review.Delay periods were described by the authors from the onset of symptoms in 6 studies, from the first specialist consultation in 2 studies, from the first or last cross-sectional imaging in 9 studies, and from the diagnosis of cancer in 1 study.Several studies reported only rates exceeding special delay cut-offs, whereas no unequivocal trend in median delay by time or by countries was detected.

Specifically, *wait time paradox* was not mentioned by either identified study. *Lead time bias* was controlled well in 2 studies, and in these studies survival time was calculated from the onset of symptoms rather than the time of randomization. *Length bias* cannot occur in studies without drop-out, however, many trials excluded patients who did not complete the diagnostic phase or undergo surgery or any other therapy.

Of the 18 affected studies, only 8 reported about multivariate analyses on the relation of delayed care and results. In many of these, alignment with histology, primary location or initial symptom types was not successful. The parameters of the assumed causal relationship were corrected in all but one multivariate analysis, thereby diluting or reducing the association between longer delays in care and poorer prognosis. Based on available data, this is the largest systematic literature review on the connection of care delay and recovery of patients with pancreatic cancer. On the other hand, the most recent systematic review on the delay related to all organ-specific tumors included five and two studies on pancreatic cancer. All of the 18 assessed studies had one or more possible methodological biases. Non-randomized studies avoiding pairing / weighing of compared populations and multivariate analyses are particularly susceptible to bias, thereby providing poor quality of evidence.

The analysis of the subgroup of resection demonstrated that each week of delay in surgery decreased the risk of mortality by 15% if surgery was adapted to interim results (microscopic residual disease and tumor-positive lymph nodes) which were less frequent in the early surgery study. These paradoxical statements unequivocally indicate that the planning of randomized, controlled studies does not guarantee bias-free estimation of effects, and analytic methods to be applied should be thoroughly evaluated. Some non-randomized studies with multivariate analyses (e.g. Tokuda et al, Jooste et al) reported statistically significant paradox connections.

The largest non-randomized study including multivariate analyses was published by Yun et al who analyzed 2309 patients retrospectively, and stated that >31 days of delay between the diagnosis and final treatment, corrected for many co-variants but not for

histology and localization of the tumor within the pancreas, results in ~23% increase in risk of mortality.

Raptis et al only assessed patients with non-periampullary PDAC and concluded that each day of delay in treatment leads to a small but statistically significant increase in the risk of mortality, whereas the time between first referral and treatment did not have a significant relationship with mortality. The authors of the latter article stated that “multivariate analyses excluded that time from referral to treatment would be an independent predictive factor of survival (p=0.108)”, which was a contradictory conclusion on two grounds. Firstly, a statistically non-relevant statement generally does not present evidence against an association, it may result from insufficient statistical power or consideration of interim results (e.g. operability and resecability in this analysis). Secondly, in view of the process, the conclusion that the time before the first medical referral is important and the time afterwards is not important is illogical.Such a conclusion would assume that the behaviour of the tumor changes with the first medical visit. Real associations may be even stronger in these studies due to *wait time paradox, length bias* and alignment to one or more interim results.

The only non-randomized study controlling both *wait time paradox* and *length bias*, and not aligning to interim results in the multivariate analyses was published by Sanjeevi et al.

Recently, Deshwar et al published a relevant study beyond the inclusion period of our systematic literature review. They reviewed the data of 116 patients with ductal pancreatic adenocarcinoma, and assessed the relationship between delay in diagnostics and treatment and the rate of operability.This study did not control *wait time paradox* and excluded all untreated patients; therefore it was exposed to length bias which means that the associations between delays and operability might even be stronger.

Overall, only text review and synthesis were performed as heterogeneity of definitions and populations, and methodological limitations prevent quantitative metaanalysis of the trials. Despite the fact that none of the studies reported statistically sufficiently “strong” calculations, and 7 out of 8 studies were affected by other biases which drove statements to negative and paradoxical results, 5 out of 8 studies showed statistically significant relationship between delayed care of pancreatic cancer and negative clinical consequences, particularly in patients with potentially curable disease. It is important that all studies tested the “superiority” of shorter delays with the null hypothesis that shorter delays would lead to better results.

In these “superiority” trials, lack of statistically significant results should be interpreted that there are no evidences on rejecting the null hypothesis.

However, this and similar statements do not provide sufficient evidence against the assessed associations, that is they do not exclude that a shorter delay would lead to better results; they simply do not provide enough evidence to conclude on this. This is particularly true for studies with small sample size and low statistical power. Statistical power calculations were not included in either of the studies, therefore, the risk of low research evidential value cannot be excluded. Instead of “superiority” analyses, other types of statistical methods such as “noninferiority” and “equivalence” analyses would be justified to exclude the clinical benefits of earlier diagnoses and treatment with high probability, based on predefined equivalence zones.However, none of the identified trials reported corresponding analyses which test the hypothesis if care with longer delay would lead to poorer or equal result than care with shorter delay. Equivalence or “noninferiority” type conclusions are unequivocally inadequate based on non-significant results of “superiority” assessments.

It follows from the above considerations that for suspected pancreatic cancer, continuous efforts for timely management of patients are supported by empirical evidence, whereas opposite statements / recommendations have no valid scientific rationale.

Notably, all studies focused on clinical results, e.g. stage distribution, resectability and overall survival, despite the fact that the patients’ experiences and availability of health care resources are also important aspects in the health care procedure, which shall be considered in health political decisions within the Triple Goals of health care. This is a critical lack of evidence: program aiming to improve timeliness of care for pancreatic cancer cannot be evaluated reliably from health economic point of view without these considerations.Given that early diagnosis and treatment are associated with longer patient survival, randomized, controlled studies on the effects of longer delays in the treatment of pancreatic cancer would hardly be ethically acceptable. Therefore, observational studies play an important role in demonstrating evidences despite their methodological limitations. The included observational studies had several sources of potential bias, mostly making those susceptible to negative or paradoxical conclusions, and heterogeneous definitions were applied to define delay and results, which prevented quantitative integration of conclusions between studies. However, the systematic review methodology was well-established, unique and comprehensive, and considered possible sources of methodological bias during targeted synthesis.

6. Analysis of cases with pancreatic cancer at Somogy County Kaposi Mór Teaching Hospital – Patient data, methods, results

The research plan and necessary annexes were assessed and approved by the Institutional Ethics Committee of Somogy County Kaposi Mór Teaching Hospital (TUKEB, IG/03901-000/2016).

The efficiency of OnkoNetwork as patient management system and its added value to clinical outcome were assessed. The system was launched in November 2015, following 1 month of test period.The database included data of 545 patients diagnosed with ICD code pancreatic cancer.Two cohorts were created, which included 296 patients prior to OnkoNetwork (control group) and 250 patients managed within the frame, and supported by OnkoNetwork (program group). The assessed periods were 2010 to September 2015 and November 2015 to December 2019, during which the hospital's e-MedSol medical IT-system, and available text documentation of patients were individually reviewed. To enable the most accurate comparability, inclusion criteria were restricted to the histological type of pancreatic ductal adenocarcinoma exclusively in order to avoid differences in outcome resulting from therapeutic (mainly chemotherapeutic) variability. The created "raw database" was checked by 2 independent investigators many times based on detailed patient documentation and, if available, pathological reports, thereby gradually restricting the final patient population. In several cases, coding was incorrect (false ICD code recording).

All patients with the diagnosis of chronic pancreatitis, biliary adenocarcinoma, cholangiocellular carcinoma, Klatskin's tumor etc. at the end of investigations were excluded.9 patients diagnosed during the one-month-test period of OnkoNetwork program were also excluded from the final data analysis. To create the database forming the basis of final statistical analysis, the existing cohorts were further narrowed and refined.

The two-arm retrospective trial analyzed the benefits of "belonging" to the OnkoNetwork period. A so-called *propensity score* analysis was carried out enabling that the two patient groups would be the most "similar" to each other. First of all, it was determined with a logistic regression analysis which patient features characterize belonging to the OnkoNetwork period; then a score was created for each patient (propensity score - PS), and patients in the control cohort were considered after correction with weighing by these scores. The main reason for this was that in the OnkoNetwork patient group, the time between the first symptom and the first medical visit was significantly shorter than in the control group.

During data collection, each patient's documentation was reviewed to identify references and accurate dates which would tell what was the first sign or symptom indicating pancreatic cancer, such as sonography for abdominal pain detecting tumor, or a radiological report referring to cancer. Given that the main research goal was the efficiency of the OnkoNetwork system and its effect on clinical outcomes, the above mentioned differences and subsequent bias had to be excluded.

To decrease bias resulting from the so-called composition of OnkoNetwork and control groups, the patients were assessed by subgroups, during which it could have been stratified based on the observed variables, then the effect of "belonging" to OnkoNetwork could have been compared in each subgroup. If stratification had been carried out by al covariants, there would have been to many subgroups, and estimates would have been inaccurate due to low patient number, thus making the comparison unfeasible. This fragmentation could be avoided by *propensity score* based weighing.

Descriptive comparison of the weighted data of the assessed cohorts was performed with the following parameters. Necessary data were gained from the coded files in the hospital system and the patients' available text documentation. During descriptive analyses, categorical variables were assessed with chi-squared test, whereas two-sample t-test was applied to age and tumor stage. Assessed parameters included percentage of presentation to Tumor Board, and in the two cohorts it was evaluated whether OnkoNetwork and its regulation system was able to improve the rate of commenced therapies, and the time to presenting examinations within the targeted deadline (time from the first medical visit to the decision of the Tumor Board shall not exceed 30 days) and the patients' documentation to the Tumor Board. The study also included the treated patients' ECOG status. The prognosis of patients with pancreatic cancer is generally influenced by the stage of the disease, the TNM stage was therefore also taken into account, with particular consideration to so-called early stages (Ia-Ib and IIa), and the percentage rate of these cases. When OnkoNetwork system was implemented, it was important that after investigations, patients are treated according to the Tumor Boards decision as soon as possible (within 40 days after inclusion into OnkoNetwork). Accordingly, it was assessed how many patients had their radio- and/or chemotherapy started, or surgery performed within the above time interval.

Cancers of the pancreatic head cause biliary congestion by occluding the biliary duct, leading to jaundice and pruritus. In most of the operable cases, stage cT1-3cN0cM0 tumors may cause so-called obstructive jaundice even at early stage, making diagnosis quite straightforward. Therefore, jaundice was given special attention as first symptom.

One of the cardinal components of OnkoNetwork's operation is timeliness. For all patients, the date of first symptom indicating tumor (jaundice, belt-like abdominal pain), and of the first radiological study to describe tumor (mainly abdominal sonography requested by GP), as well as the date of the first oncological ICD code were noted by reviewing medical history. Times to the Tumor Board decision, and to the start of treatment from the date of first oncological code in the hospital's medical IT system were also analyzed.

In the case of certain clinical parameters, the frequency of occurrence over time was determinedusing weighted data generated by *propensity score* methodology. Based on available data, it was determined what is the frequency of the event associated to the assessed parameter for all patients in both cohorts. For this, a "survival type" graph was created with R software, which presents the frequency of cumulative occurrence of each event versus time. The occurrence rate reaches the maximum value, in ideal case 1, if the event occurs in all patients in the study cohorts (e.g. Tumor Board presentation). One event was only presented once for each patient in this analysis. If the assessed event did not occur for all patients, the maximum value was less than 1.

Survival of patients in the two study cohorts was determined based on available data. Kaplan-Meier curves were drawn for interventional and control arms.

Kaplan-Meier curves were determined regarding weighted data created with propensity score matching methodology. Starting date of survival analysis (T0) was the date of the first appearance of tumor code in the hospital's documentation.

As most members of the OnkoNetwork patient group are still alive, classic survival differences of the two cohorts cannot yet be calculated. The end of patient monitoring period was defined as the date of death or of the patient's last appearance in the hospital's system, thus "missed" patients are statistically censored from the given date. In order to be able to evaluate the effect of OnkoNetwork system independent of patients' condition and treatment, a multivariate Cox-regression analysis was performed. Multivariate models either included all baseline parameters (because weighted data were analyzed), or considered all post-baseline variables as the latter can also be regarded as interim endpoints and thus potential explanatory variables. During the analysis, non significant variables were not excluded from the final models. Following the previously mentioned *propensity scoring*, non-weighted potential significant differences "disappeared" as expected. As mentioned above, significant difference was observed between the two patient groups regarding time from the first documented symptoms to the first medical visit, and the first appearance of an oncological code in non-weighted data.

With regard to the final clinical outcome, this might have significant effect, however, this difference had to be eliminated as it could severely distort the evaluation of the system's efficiency. This difference is well demonstrated on the data of *"from first symptom to first code"* quartiles. The rate of patients getting to a physician within 0-2 days was 12% and 38.9% in the control group and in the OnkoNetwork group, respectively. With regard to the basic data, the differences of the two arms could be compensated with PS values, which is well demonstrated by Rubin R and Rubin B indicators (Rubin B value 112.509 in the non-weighted patient group versus 0.045 in the weighted population). When considering coefficients of variation, it is shown that Rubin R value was 1.576 prior to weighing, and 1.008 after weighing.

As for stages, chi-squared test was carried out (for all "abbreviated" stages, St. I, St. II, St. III, St. IV). Significant difference was not shown for any of the stages between the two patient groups.

Weighted data demonstrated that there was marked significant difference between the two patient groups in the presentation to Tumor Board (94.1 % vs 99.5 %, p= 0.00523458). Furthermore, marked significant difference was shown between the patients in the OnkoNetwork program and in the control group with regard to commencing therapy (64.6 % vs 85.9 %, p= 0.00047052). ECOG statuses (p= 0.04962195) also differed significantly (p> 0.05). For both patient groups, reports of thorax-abdomen CT and, if available, liver-pancreas MRI studies performed as part of the work-up were separately reviewed to determine accurate 0-staging cTNM stage, and results showed that significant difference was also seen in 0-staging lymph node stages (cN) (p= 0.03597479).

The review of the complete documentation of the two patient groups demonstrated that for most of the patients therapy was initiated based on, and following Tumor Board decision, whereas in some cases in both patient groups, the patient's treating physician requested approval by institutional Tumor Board after commencing chemotherapy. Censored data showed significant advantage for the OnkoNetwork patient group for both non-weighted and weighted results. The effect of OnkoNetwork on survival in weighted and non-weighted patient groups was assessed with univariate and multivariate Cox regression models. The Kaplan-Meier analysis detected significant difference in favour of OnkoNetwork patient group. Based on the results of the multivariate weighted Cox regression analysis of overall survival, patients' survival was significantly worse in case of ECOG performance status of 2 or higher (reference: ECOG 0), and stage III or IV tumor (reference: stage I), whereas it improved significantly if the patient also underwent surgery.

Radiotherapy also had beneficial effect, however, this has not shown statistical significance. Aligned to all these factors and the effect of chemotherapy, belonging to the OnkoNetwork cohort had a further independent, statistically significant benefit (HR 0.68, 95%CI 0.48-0.99, p = 0.0427).

Further research is warranted to investigate the beneficial effects of OnkoNetwork system in more detail.

7. Conclusions

In the introduction of the thesis it was described that Hungary is among the leaders in the European Union with regard to the frequency of cancer and cancer mortality. Given the fact that European and Hungarian citizens are gradually ageing, the above process is assuming worrying dimensions. Somogy County Kaposi Mór Teaching Hospital, taking available advantages, attempts to do something efficiently against it by modifying factors that can be influenced by the hospital. Thanks to the individual and unique OnkoNetwork system, which had been implemented in the institute, significant improvement was achieved in the treatment of diseases (pancreatic and lung cancer) assessed so long.

Naturally, the evaluation of the system's efficiency has not yet ended with this. There are several further tumors where the benefit of time factor during care is unequivocal with regard to clinical outcomes (e.g. melanoma malignum, gastric, gall bladder and biliary duct, bowel tumors, brain tumors, gynecological and urological cancers), whereas it is possible that for some tumors (e.g. hormone-receptor-positive breast cancer, prostate cancer) belonging to the OnkoNetwork system does not necessarily mean survival benefit. Of course, further research and analyses are needed to confirm these assumptions. It is important to state that in addition to the time factor defined during the implementation on OnkoNetwork, the application of the system had another very important result, namely, oncological care has become much more organised than before. The numerous check-points in the patient pathway management system, although unable to avoid completely, significantly decreases the number of "missed" patients who would otherwise be deprived of the possibility of final recovery. The efficiency of OnkoNetwork and care process could be optimized further if GP network belonging to the care provision area of the oncological center, and oncological screening program sites would also participants of the system, thus malignant tumors could be actively investigated at an even earlier stage. As a result, times from the first symptom to the end of investigations and to therapy could be further reduced.

The structure and resource demand of OnkoNetwork system completely optimize its implementation in oncological centers. Results so far show that its wider introduction should be considered at national health political level, taking public health aspects into accounts.

8. New scientific statements of the thesis

With regard to morbidity and mortality rates of malignant tumors in Hungary and Somogy county, to improve efficiency of oncological care, the management of Somogy County Kaposi Mór Teaching Hospital has implemented a nationally and internationally unique patient pathway management system called OnkoNetwork.

The system's implementation achieved the following goals:

1. As a result of introduced deadlines and their monitoring, complex work-up, treatment and care of patients has become more efficient at Somogy County Kaposi Mór Teaching Hospital and co-institutes.
2. Given the system's structure, the number of "missed" patients, who would have access to successful and efficient treatment with lower chance, could be reduced significantly.
3. The created database and its retrievable, analysable form enable participation in national and international tenders.
4. A unique database including data on care and medical history of oncological patients was created which enables comprehensive retrospective analyses of different tumor types, including the process and efficiency of patients' diagnostic, therapeutic and oncological follow-up procedures.
5. Through the operation of OnkoNetwork, integrating oncological screenings into the system would pose a major improvement in complex and more successful oncological management.
6. With regard to clinical outcomes, the relevance of time factor was confirmed in complex oncological care of patients with pancreatic cancer.

9. Scientific activity

Publication in association with the topic of the thesis

János, György Pitter ✉ **; Gábor, Lukács** ; Marcell, Csanádi ; Zoltán, Vokó
Clinical impact of treatment delay in pancreatic cancer patients revisited
INTERNATIONAL JOURNAL OF CANCER 142 : 12 pp. 2621-2622. , 2 p. (2018)
DOI WoS Scopus PubMed
IF: 5.145

Lukacs, Gábor ; Tóth, Zoltán ; Sipos, D ; Csima, Melinda ; Hadjiev, J ; Bajzik, G ; Cselik, Zs ; Semjen, D ; Repa, I ; Kovacs, A
Longterm follow-up results of concomitant chemoradiotherapy followed by adjuvant temozolomide therapy for glioblastoma multiforme patients. The importance of MRI information in survival: Single-center experience
IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 71 : 3-4 pp. 95-103. , 9 p. (2018)
DOI REAL-J WoS Scopus PubMed
IF: 0.327

Lukács, Gábor ; Kovács, Árpád ; Csanádi, Marcell ; Moizs, Mariann ; Repa, Imre ; Kaló, Zoltán ; Vokó, Zoltán ; Pitter, János György ✉
Benefits of timely care in pancreatic cancer: A systematic review to navigate through the contradictory evidence
CANCER MANAGEMENT AND RESEARCH 11 pp. 9849-9861. , 13 p. (2019)
DOI WoS Scopus PubMed Other URL
IF: 2.886

Pitter, János G. ✉ ; Csanádi, Marcell ; Szigeti, Annamária ; **Lukács, Gábor** ; Kovács, Árpád ; Moizs, Mariann ; Repa, Imre ; Zemplényi, Antal ; Czypionka, Thomas ; Kraus, Markusetal.
Planning, implementation and operation of a personalized patient management system for subjects with first suspect of cancer (OnkoNetwork): system description based on a qualitative study
BMC HEALTH SERVICES RESEARCH 19 : 1 Paper: 131 (2019)
DOI WoS Scopus PubMed Other URL
IF: 1.987

Abstracts serving as basis for this thesis

Lukács, Gábor ; Tóth, Zoltán ; Cselik, Zsolt ; Bajzik, Gábor ; Toller, Gábor ; Ruzsa, Ágnes ; Moizs, Mariann ; Repa, Imre ; Kovács, Árpád
Daganatos betegek komplex, intézményi ellátásának OnkoNetwork által támogatott új rendszere, az ellátás hatékonyságának növelése céljából [New system of complexinstitutionalcare of cancerpatientssupportedbyOnkoNetworktoimproveefficiency of care]
KLINIKAI ONKOLÓGIA 3 : KlszPaper: 017 , 1 p. (2016)

Lukács Gábor, Moizs Mariann, Repa Imre, Pitter János
A prevención túl: onkológiai betegút-szervezés [Beyondprevention: oncologicalpatientpathwayorganisation]
10th anniversary of Prevention and Health Promotion Office Scientific meeting
Somogy County Kaposi Mór Teaching Hospital, 15/11/2018