An integrated view on assuring quality for multimodal therapy in oncologic care

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8 General discussion and future perspectives

GENERAL DISCUSSION

In most western healthcare systems, over the last decade major efforts have been made to monitor and improve the quality and effectiveness of cancer care. Assuring quality via nationwide clinical audits has proved to be a powerful tool to gain insight in the quality of care and to facilitate quality improvement. In the context of the rapid advancements in new anticancer drugs, the trends in multidisciplinary cancer care and the focus towards patient-centred outcomes, assurance of quality needs to evolve constantly to anticipate to these changes. This thesis aims to investigate how quality could be assured facing these trends in cancer care.

Part I: Assuring quality in multidisciplinary cancer care

Hospital variation in medical oncology

The majority of DICA audits have their focus on the quality of surgical treatment and short-term outcomes of care. Risk-adjusted outcomes like postoperative morbidity and mortality are often used to evaluate hospital performance and give an ultimate insight into the quality of surgical care [1] [2]. However, with a growing number of treatment modalities becoming available for many tumour types, auditing the non-surgical component of multimodality therapy becomes increasingly important.

In gastric cancer treatment, Dutch guidelines recommend perioperative chemo(radio) therapy for patients with resectable gastric cancer who are eligible in terms of physical condition and comorbidity [3]. We have observed considerable hospital variation in the use of adjuvant chemo(radio)therapy in gastric cancer patients, even after random variation and case-mix correction [**this thesis**]. This suggests that the variation is not merely a reflection of age or comorbidity burden, but it may also reflect other (hospital specific) factors.

However, as the DUCA has its focus on the quality of surgical treatment and short-term outcomes of care, detailed information is missing on the adjuvant component and long-term outcome data is not registered. Moreover, hospital-specific quality data in relation to the national average is only fed back to the participating surgeons. Because the underlying cause of the variation could not be further investigated, an in-depth investigation in hospitals was performed with the aim of identifying organizational and process factors associated with the use of multimodality treatment

[4]. A multidisciplinary extension of the DUCA with medical oncologists, radiation oncologists, pathologists and gastroenterologists may offer a better understanding in the decisional process and quality of multimodal treatment from the audit itself and would facilitate such in-depth investigations. All disciplines would then be provided with benchmarked feedback, including oncologists and radiologists who play a major role in the multimodal treatment of gastric cancer patients.
Fortunately, (surgical) DICA audits are slowly transforming to multidisciplinary condition focused audits. The DSCA is converted to the multidisciplinary Dutch ColoRectal Audt (DCRA) as radiotherapists, gastroenterologists, medical oncologist and radiologists joined the audit. In addition to data collection of patient undergoing resections for colorectal cancer, patients with a wait-and-see strategy after initial treatment with (chemo)radiotherapy, with or without surgery, for rectal cancer are now registered.
A true condition focused audit in which multiple treatment strategies are registered by the relevant disciplines has been created for lung cancer: the Dutch Lung Cancer Audit (DLCA), in which radiotherapist, surgeons and pulmonologists participate. In addition, linkage of data from the DUCA and DCRA with long-term survival data from Vektis, a database containing data from all Dutch healthcare insured Dutch citizens, is recently realized.
Although challenging with regards to linkage of databases, privacy issues and registration burden, only such multidisciplinary condition focused audits including survival data would create a better understanding on the quality of multimodal treatment in cancer patients and it's impact on long-term survival. In future, with the increasing population of old and frail cancer patients it would be extremely valuable to track the outcomes of patients who receive palliative treatment or no treatment at all.

Multidisciplinary outcomes
Multidisciplinary tumour boards have become the hallmark for cancer care and have been rooted in everyday practice [5]. In the Netherlands, such multidisciplinary boards have developed evidence-based guidelines on the treatment of many tumour types [3]. In addition, the Dutch federation of oncological societies (SONCOS) has set up multiple multidisciplinary quality standards listing requirements a cancer centre must meet [6]. Although cancer care is increasingly becoming a multidisciplinary undertaking, benchmarked feedback via audits is mainly discussed monodisciplinary in Dutch hospitals. For instance, surgeons only discuss postoperative complications

with their peers. However, adverse outcomes can transcend disciplines [**this thesis**]. We showed that gastric cancer patients with severe postoperative complications had an increased likelihood of adjuvant chemotherapy omission. In hospitals with the lowest administration rate, adjuvant chemotherapy was three times more likely to be omitted compared to the national average. It is unlikely that the omission of chemotherapy can be fully attributed to postoperative complications or frailty of patients. Differences in the expertise of the medical team to recognize and adequately treat complications to ensure patients are fit enough for postoperative chemotherapy might also play a role. The considerable variation might also reflect differences in the culture or communication between surgical and medical departments. It would therefore be valuable to discuss such multidisciplinary quality measures in multidisciplinary team meetings within hospitals on a regular basis. This could stimulate shared accountability and ultimately enhance joint quality initiatives.

Part II: Assuring quality in precision medicine

Value of registries in medical oncology: appropriate drug use and safety surveillance

The treatment of metastatic melanoma has been revolutionized with the introduction of the BRAF inhibitor vemurafenib and immune checkpoint inhibitor ipilimumab [7]. Since the approval of ipilimumab in 2011 [8] and vemurafenib in 2012 [9] by the European Medicines Agency (EMA), more than seven new drugs are registered for the treatment of metastatic melanoma [10]. These developments indicate the speed with which changes in anticancer therapies are occurring.

The societal challenge is to combine the development and availability of promising new anticancer drugs with the sustainability of our healthcare system. Current checkpoint inhibitors have a list price near 60.000 Euro per year [10]. These promising drugs have also been approved for many other cancers, such as metastatic lung cancer, renal cell cancer, head and neck cancer, bladder cancer, Merkel cell carcinoma, various types of lymphomas, and others will follow soon. As a result of the rapidly evolving treatment landscape of oncologic care together with the aging population and growing number of cancer survivors, the sustainability of cancer services as part of national health systems has become a major challenge. In the Netherlands, the prediction is that around 23 billion euro will be spent on cancer treatment by 2040, over four times as much as in 2015 [11].

In response to this, a special committee of the Dutch Cancer Society (KWF) investigated the accessibility and affordability of expensive anticancer drugs [12]. In their report, they advocate set-ups of registries like the DMTR as it gives insight into real-world cost-effectiveness of treatments and treatment-patterns. First results from the DMTR demonstrate that the new drugs for metastatic melanoma have been safely introduced in the Netherlands with comparable toxicity rates as reported in the pivotal trials [**this thesis**]. This may be attributed to the centralization of advanced melanoma care into fourteen specialized melanoma centres and the obligatory minimum volume standard of 20 melanoma patients yearly [13]. Registries like the DMTR are therefore important to inform policy makers whether interventions work in real world.

Bearing the high costs and potentially life-threatening side effects of the new drugs in mind, defining subgroups of patients who benefit most is of great importance.
This thesis demonstrated that metastatic melanoma patients with a baseline lactate dehydrogenase (LDH) of >2x the upper limit of normal (ULN) who respond to targeted therapy with normalization of LDH have a good chance to get durable response on immunotherapy [**this thesis**]. If LDH remains elevated, immunotherapy does not stand a chance. After a median follow-up of 22 months, we demonstrated that median OS from start of immunotherapy was not reached in the former group while median OS was only 0.9 months in the latter group. This information can be used to determine the optimal sequencing of various drug types in a real-world setting, while the pivotal trials only report on the investigational drug. Although randomized trials are needed to assess the real benefit of sequential treatment strategies, results from the DMTR can be of added value while trial results are yet to be published.

Combining risk factors instead of assessing them separately as has been done in the pivotal trials could be helpful to stratify patients into favourable or poor prognosis groups. Almost 70% of metastatic melanoma patients treated with vemurafenib had multiple risk factors, such as an elevated LDH level, symptomatic brain metastases and poor performance status [**this thesis**]. We demonstrated that survival of BRAF-mutated advanced melanoma patients treated with vemurafenib having >3 risk factors was only a third of the survival of patients without any risk factors (5.4 months *vs* 15.4 months). From a patient and doctor perspective, these data can help in shared

decision making and managing expectations. In patients with multiple risk factors, the drug has a low probability of benefitting the patient and may instead be physically and mentally harmful with wasted costs to the health system. This knowledge can nourish the debate on appropriate drug use.

In response to political and societal pressure, the FDA and EMA have introduced numerous fast-track approval and adaptive pathways for new anticancer drugs since the beginning of the 21st century [14]. Conditional approval may benefit patients by speeding up the availability of 'promising' drugs, but on the other hand are not based on profound evidence of a phase III randomized clinical trial. Such drugs may be studied with smaller patient numbers or in single-arm studies with no comparator [15]. In addition, cancer drug approvals based on surrogate outcomes (e.g. progression free survival) have become more common leading to faster drug access and lower trial costs, but are not always reliable surrogates for improved survival or QoL, in particular in non-curative settings [16]. Together with the fact that trial results are not generalizable to a more heterogeneous patient population in daily practice, great uncertainties regarding clinical benefit and safety remain at time of drug approval.
Real-world registries could complement findings from trials and could provide a better understanding of a drug's real world value after (fast-track) approval [17]. Registry data can hence be helpful to detect approved drugs that fail to demonstrate clinical benefit or harm patients in real world which warrant further investigations or even requires withdrawal from the market.

DMTR: a blueprint for quality assurance in the era of expensive anticancer drugs?
First results of the DMTR showed the value and feasibility of nationwide registries with new anticancer therapies, as demonstrated by high quality data and nationwide coverage of all patients with metastatic melanoma in the registry within the first year [**this thesis**].
Downside of such a multipurpose registry like the DMTR is the financial and administrative burden. Although detailed data for economic evaluation (informal care, productivity losses) are only collected in selected melanoma centres, the majority of data (clinical, economic, PROMs) are collected for all metastatic melanoma patients. This approach adds a lot to time and costs. One patient record requires 8 hours of registration, including data-entry, validation, data-analyses, reporting and training

of the data managers. Questions could be raised whether this set-up could serve as a blueprint for future registries. For instance, immunotherapies are now approved for lung cancer with over 10.000 eligible patients every year (in contrast to 800 eligible metastatic melanoma patients per year).

To minimize registration burden, a solution may be to use multiple datasets. A small dataset will be collected for all patients to track trivial quality data such as case-mix factors, treatment modality, QoL, mortality and morbidity, whereas additional limited datasets will be collected in a subsample for other purposes like cost-effectiveness. For cost-effectiveness models, cost data of a very small subset can easily be extrapolated because only mean values of costs are required [18].

Second, it needs to be stimulated to evaluate all data items on its added value on a regular basis. Since the landscape of immunotherapy and targeted therapy is evolving rapidly, (detailed) data items of certain treatment modalities can soon be outdated.

Third, data-entry accounts for the majority of the time and costs of the DMTR because data managers manually enter the data by searching though the EHR. Initiatives such as data capture at the point of care (e.g. Registratie aan de Bron) allow registries to obtain (part of) their data directly from EHRs [19]. For instance, head and neck surgeons of Radboudumc have succeeded to reorganize their EHR in such a way that all 150 items required for quality indicators of the Dutch Head and Neck Audit are directly obtained from EHRs. Implementation of such EHR systems could further reduce financial and administrative burden.

Last, a large amount of the dataset of the DMTR is collected to facilitate reimbursement research. In The Netherlands, new expensive drugs can be reimbursement conditionally in order to guarantee early access to promising drugs since 2016. In exchange, it is obliged to gather data on real-world cost-effectiveness. A reassessment of a drug's real-world value after 4 years determines whether additional financing will continue [20]. During this period, a large amount of additional data has to be gathered through the patient registry (e.g. data on hospital resource, non-medical costs).

Assessment of the best time for definite reimbursement decision rather than setting a fixed 4-year period could avoid costly and time-consuming data gathering. Statistical methods have been proposed to calculate the optimal length of registry period based on patient numbers, costs and outcomes. A recent study showed that the observation period to make the definite reimbursement decision on the use of oxaliplatin for

colon cancer could have been stopped after a maximum of 2 years rather than the fixed 4 years [21].

It should also be noted that the costs of multi-purpose quality registries like the DMTR are a fraction of the total costs of the new drugs. The National Health Care institute calculated that less than 1% of the total amount of costs per treated advanced melanoma patient would be required for the set-up and maintenance of the DMTR. It will be important to all stakeholders involved to discuss whether securing a small percentage of the total treatment budget for obtaining quality information for future registries would be acceptable.

Part III: Assuring quality focusing on patient centred outcomes

VBHC auditing– the way forward?

Understanding the effect of treatment on how a patient survives, feels or functions is crucial [22]. Although anticancer treatment has brought major advances in patient survival rates, it is also associated with significant toxicity that can impair quality of life (QoL). The impact on QoL can only be understood by collecting information directly from patients about their physical functioning, adverse events or cancer-related symptoms. Despite growing interest in patient reported outcome (PROs) measures in cancer care, drug developers and physicians do still not systematically collect PROs in pivotal trials or clinical practice [23]. The majority of pivotal trials publish PRO results in separate papers as if it is not important when balancing the risks and benefits of new drugs [24] [25]. This way, true shared decision-making between patients and oncologists is hampered by lack of reliable and acceptable PRO data.

This thesis illustrates the 'blind spot' of collecting merely clinical outcomes. We have demonstrated that benefit of vemurafenib was unlikely in frail advanced melanoma patients with a high disease load in terms of overall survival [**this thesis**]. Since vemurafenib could induce rapid symptom relief in this subgroup of patients [26], the emphasis lies however predominantly on improving quality of life (QoL). Without such information, we are left with an incomplete picture on the properties of this drug. Fortunately, the DMTR is currently collecting QoL data in order to assess the true benefit of the new anti-melanoma drugs in daily practice, which will eventually

lead to better shared decision-making. The importance of collecting PRO data has been acknowledged by other DICA audits of which eight are currently collecting PROMs.

Many tumour types can increasingly be seen as a chronic disease. In The Netherlands, the 5-year overall survival of cancer patients is almost doubled in the past 50 years (Figure 1), where traditional outcome measures such progression-free and overall survival are less relevant, and quality of life and functional outcomes will be more valued. As a result of having had cancer and its treatment, cancer patients and survivors are affected by gastrointestinal problems, sexual dysfunction, pain, lymphedema, chronic fatigue, depression, and so on. A wider recognition of cancer care as a chronic disease is required in quality assessment programmes.
This has been acknowledged by the International Consortium for Health Outcomes Measurement (ICHOM) that recently launched a patient-centred outcomes set for patients with colorectal cancer and breast cancer [**this thesis**]. The ICHOM standard sets encompass the entire care spectrum, from diagnosis, treatment, short- and long-term outcomes to end-of-life care. Patient-reported outcomes are included in every standard set to capture symptom burden, functional status and health-related quality of life. The ICHOM breast and colorectal standard set comprises fourteen patient-centred outcomes of which the majority (70%) is patient-reported (Figure 2). DICA has started to synchronize its datasets with the ICHOM standard sets, including the incorporation of PROMs recommended by ICHOM. Such monitoring and comparison of patient-centered outcomes can identify opportunities for improvement and ideally, lead to a sharing of best practices within the full range of cancer care. Moreover, international comparison with other (nationwide) registries can be achieved.

Although the VBHC principle has been embraced in multiple countries, there are also reasons to be cautious.
In contrast to existing surgical audits where short-term outcomes like anastomic leakage after colorectal surgery are clearly linked to interventions [1], patient-centred outcomes like fatigue or sexual functioning after breast cancer treatment are likely to be multifactorial. It is harder to accurately assess case-mix variables as these outcomes can also be influenced by other factors than patient- and tumour characteristics such

as societal and financial characteristic or supportive therapies such as psychological treatment.
Secondly, ICHOM standard sets only focus on outcomes, while process measures like waiting times or completeness of pathology report are not included. These measures are however important to identify the critical steps in a process that lead to a particular outcome (quality assessment). This way care providers accountable for these steps can be determined. In order to set-up quality improvement initiatives, negative outcomes as defined by the ICHOM standard set must be distilled to its essence by identifying these steps.
Moreover, patient-reported experience measures (PREMs), which capture a patient's view of what happened during the care process, were not included in the ICHOM standard sets. Cancer care nowadays has become an integral part of the lives of most cancer patients and survivors, and experience measures such as autonomy, choice, communication and support (access to family and community support networks) are increasingly be seen as important measures of the effectiveness of healthcare [27]. This was also demonstrated by the results of the patient validation survey of the ICHOM breast and colorectal standard sets. In both sets, 20% of patients believed additional outcomes on experience measures had to be included [**this thesis**]. The ultimate model might be a hybrid model where the most important process measures (clinical and PREMs) and (long-term) patient-centred outcomes (clinical and PROMs) are collected.

Although PROMS data has proved to be highly wanted for assuring quality in cancer care [28], more research is needed on the feasibility of collecting PROMs in daily practice. For instance, since 2013 Santeon, a Dutch network of seven hospitals, collects PROs systematically for prostate cancer and lung cancer but compliance rates of only 20-25% have been reported [29].
One explanation might be the significant patient burden of the questionnaires. The majority of existing questionnaires are primarily designed for clinical trials resulting in lengthy, static and old-fashioned surveys. For instance, the ICHOM dataset on breast cancer recommends the collection of (part of) multiple PROMS ranging from 59-82 questions [**this thesis**], which could be discouraging. Multiple organizations focusing on PROM development are currently developing computerized adaptive testing (CAT) versions, which should reduce respondent burden [30]. On the

other hand, previous studies showed that the number of questions is not the primary reason for non-compliance [31]. Problem areas are more related to implementation practices, such as reminder issues or user-unfriendly PRO design. The use of modern technology for data capture may reduce the frequency of these issues, such as completion of electronic PROs (ePROs) via tablets, cell phones and computers including online reminders [32]. Moreover, staff commitment and education with regards to integration of PRO collection efficiently in daily practice is crucial for successful data collection.
Another issue might be that PROs are mostly used for scientific purpose and results are not fed back to the patients. If PROs are used to detect symptom worsening and would alert physicians during consultations, patients are more willing to complete the (lengthy) questionnaires [33]. A recent trial even found a survival benefit of 5 months with symptom-monitoring via ePROs including feedback compared with usual care in patients with metastatic cancer [34].

FUTURE PERSPECTIVES

Clinical auditing outside the traditional boundaries of medical specialties and hospitals
Although clinical auditing is increasingly shifting from monodisciplinary to multidisciplinary and condition-focused audits, most audits are set-up within the boundaries of medical specialties. However, the role of nurse specialists and allied healthcare professionals such as psychologists, physiotherapists, and dietitians in cancer care has increased. These disciplines are likely to contribute to patient outcomes, in particular on QoL and functional aspects. For instance, the Dutch guideline on breast cancer recommends physiotherapeutic treatment in patients who have undergone axillary treatment as it could have beneficial effects on functional complaints and lymphedema [35]. Dietary issues and management by a dietician were considered highly important by colorectal cancer patients who were involved in the development of the ICHOM colorectal cancer standard set [**this thesis**].
The Dutch Head and Neck Audit is the first DICA audit that gathers quality indicators from the perspective of allied health professionals in addition to the perspective of the medical specialties and patients. First results showed it is challenging but feasible to create quality indicators and collect data from allied health professionals [36].

Complementing quality data of the standard medical therapies with data of supporting therapies will give us insight in the quality of all aspects of cancer care. This way, we could assess the impact of supporting therapies, learn from other disciplines and motivate collaboration even more.

The ICHOM breast and colorectal standard sets created a focus towards cancer survivorship with the inclusion of long-term clinical and PRO data. However, these data is solely collected during or in between outpatient visits within a hospital setting. In the Netherlands, substitution of (cancer) care is high on the political agenda in order to keep care affordable. One main goal is the transition of follow-up visits of cancer survivors that are not required at a high level of care, to primary care practices [37]. Transitioning care for low-risk cancer survivors from oncologists to primary care physicians is found to be safe and cost-effective in other countries [38]. This transition would be a major influence on the organization of cancer care and it would be important to track and understand the impact on patient outcomes, such as QoL, emergency visits, hospital admissions, recurrence and survival outcomes.
Quality measurement is not new for primary care in The Netherlands. Several quality indicators exist for patients with chronic illness, such as diabetes and COPD for internal and external use [39] [40]. One of the aims is to assess whether the coordination of diabetes and COPD care into coordinated multidisciplinary care groups in primary care has helped improving the quality and has lowered the costs [41].
Measuring quality of care in primary care practices could help justify such changes and transitions and could guide further improvement and collaboration between care providers in hospitals and primary care practices.

Big data technologies to assure quality
Several efforts have been made in order to enhance data quality and to reduce registration burden for physicians. Some hospitals have reorganized their EHRs in such a way that required data for clinical auditing could be automatically extracted. Moreover, existing databases are connected to clinical audits to obtain relevant data once, such as the linkage of PALGA, the national database of pathology results, with the DCRA so that pathology data can directly be entered into the DCRA. However, database linkage is not possible for all data items and different IT systems across hospitals make it difficult to introduce automated data subtraction on a national level.

Furthermore, IT systems are primarily build to support daily practice and don't have an (financial) incentive to make it as effective for quality purposes. These barriers could hinder expansion to condition-specific audits in the future.
Although uniform data collection for multiple purposes needs to be stimulated, rapid advances in health information technology (HIT) have created opportunities to collect, aggregate and analyze large amounts of real-world data in unconnected servers, unstructured notes in EHRs and other sources such as claims databases [42]. This could help overcome the wide variation that exists between EHR data standards. Rapid-learning systems could examine all available information on patient characteristics, genetics, treatments, outcomes and costs. It could serve a variety of purposes, ranging from quality improvement to data driven guidelines and clinical decision support tools based on a vast amount of observational data. Rapid-learning systems in different forms already exist within oncology, such as CancerLinQ created by ASCO [43]. Although the published literature on the practicality and results of such systems remain quite preliminary [44] and privacy and juridical issues have to be managed, the potential impact of big data in assuring quality is evident.

END CONCLUSIONS

This thesis showed that the multi-purpose design of the DMTR could be used as a blueprint for future quality initiatives in the era of rapid advancements in immunotherapy and targeted therapy. It could complement findings from trials, as it provides information on long-term (functional) outcomes and optimal sequencing of drugs in a heterogeneous patient population that are normally excluded from trials. The new drugs are becoming a larger part in medical oncology as the number of immunotherapies and targeted therapies increases for a growing number of tumour types. Together with the rise of early access programmes of new expensive drugs, registries like the DMTR are highly needed for cost-effectiveness analyses and to accurately assess the safety and real-world benefit of these drugs.
Notwithstanding, efforts should be made to minimize registration and financial burden to such a level that the balance between practical feasibility and data quality and reliability is optimal.

Furthermore, this thesis showed that important quality outcomes could transcend disciplines. The expansion from monodisciplinary to condition-focused audits is therefore a welcoming development and hopefully, this will stimulate discussions of benchmarked feedback in a multidisciplinary setting within hospitals and facilitate joint quality initiatives.

The breast and colorectal cancer standard sets of ICHOM incorporate outcomes of almost a full cycle of care, from diagnosis to treatment and long-term survivorship, with an emphasis on patient-reported outcomes. While these sets stretch the capabilities of most hospitals, the integration of PROs in daily practice with direct feedback to the patient during outpatient visits may improve the experience, efficiency and outcomes of care. The sets are intended to facilitate international comparisons and research on quality of care outcomes. Monitoring and comparison of outcomes can identify opportunities for improvement and ideally, lead to a sharing of best practices and improvement in patient outcomes.

FIGURES

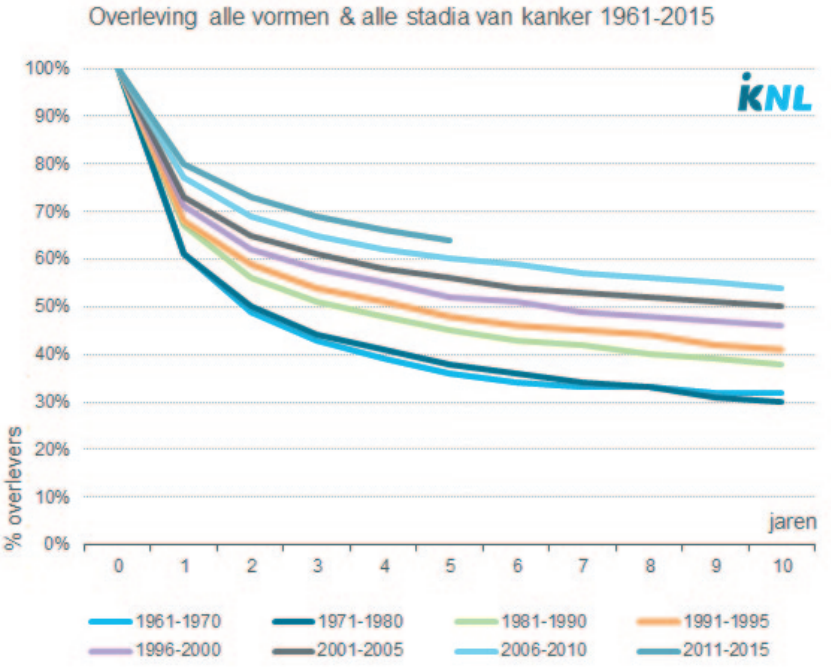
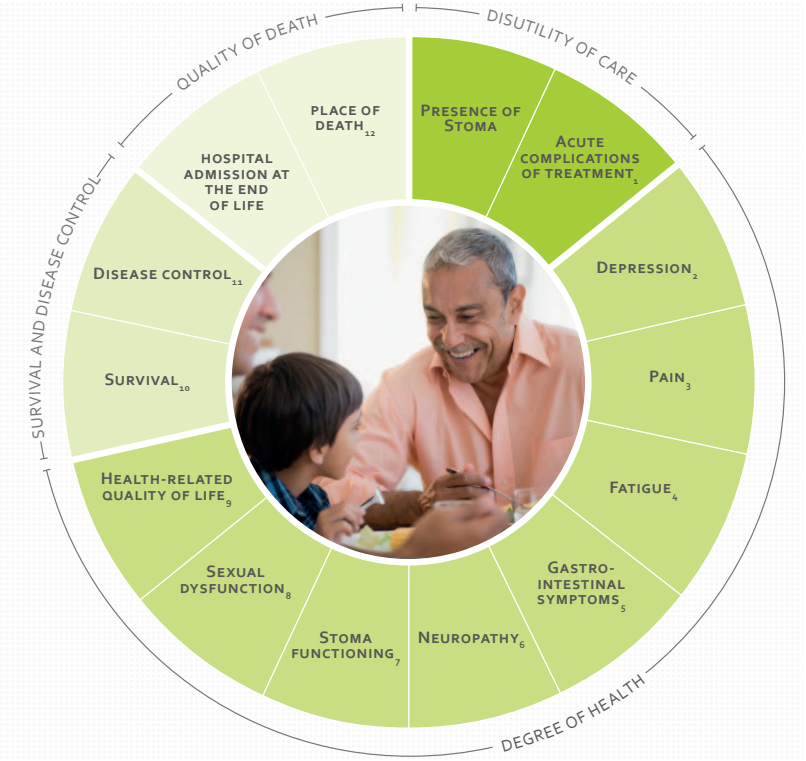


Figure 1. Overall survival of all tumour types in The Netherlands (1961-2015). Source: IKNL



(a)

Figure 2. The ICHOM standard set outcomes wheels for colorectal cancer (a) and breast cancer (b), detailing the outcome domains within the Standard Set.


SURVIVAL AND DISEASE CONTROL
DISUTILITY OF CARE
DEGREE OF HEALTH
RECURRENCE FREE SURVIVAL
SURVIVAL 13
REOPERATION DUE TO POSTIVE MARGINS
ACUTE COMPLICATIONS OF TREATMENT 1
DEPRESSION 2
PAIN 3
FATIGUE 4
BODY IMAGE 5
ARM AND BREAST SYMPTOMS 6
VASOMOTOR SYMPTOMS 7
NEUROPATHY 8
ARTHRALGIA 9
FINANCIAL IMPACT 10
SEXUAL DYSFUNCTION 11
HEALTH-RELATED QUALITY OF LIFE 12

(b)

REFERENCES

1. Snijders HS, Henneman D, Leersum NL Van, Berge M, Fiocco M, Karsten TM, et al. Anastomotic leakage as an outcome measure for quality of colorectal cancer surgery. BMJ Qual Saf. 2013 Sep;22(9):759–67. doi:10.1136/bmjqs-2012-001644.
2. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, Henneman D, van Grieken NCT, Wouters MWJM, et al. Early outcomes from the Dutch upper gastrointestinal cancer audit. Br J Surg 2016;103:1855–63. doi:10.1002/bjs.10486.
3. Dutch guideline for gastric cancer. www.oncoline.nl (accessed November 5, 2018).
4. Beck N, Busweiler LAD, Schouwenburg MG. Factors contributing to variation in the use of multimodality treatment in patients with gastric cancer: A Dutch population based study. Eur J Surg Oncol 2018 Feb;44(2):260–7. doi:10.1016/j.ejso.2017.11.023.
5. Borras M, Albreht T, Audisio R, Briers E, et al. Policy statement on multidisciplinary cancer care. Eur J Cancer 2014 Feb;50(3):475–80.
6. https://www.soncos.org/ (accessed November 5, 2018)
7. Luke JJ, Hodi FS. Ipilimumab, vemurafenib, dabrafenib, and trametinib: synergistic competitors in the clinical management of BRAF mutant malignant melanoma. Oncologist 2013;18: 717–25. doi:10.1634/theoncologist.2011-S1-71.
8. Hodi FS, O 'Day SJ, Mcdermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 2010;3638363: 711–23. doi:10.1056/NEJMoa1003466.
9. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation for the BRIM-3 Study Group. N Engl J Med 2011;364:2507–16. doi:10.1056/NEJMoa1103782.
10. https://www.horizonscangeneesmiddelen.nl/geneesmiddelen (accessed November 5, 2018)
11. https://www.vtv2018.nl/zorguitgaven (accessed November 5, 2018)
12. Kanker S, Kankerbestrijding KWF. Toegankelijkheid van dure kankergeneesmiddelen Nu en in de toekomst. Available at: https://www.kwf.nl/sitecollectiondocuments/sck%20rapport%20toegankelijkheid%20van%20dure%20kankergeneesmiddelen.pdf (accessed November 5, 2018)
13. SONCOS. (Foundation of Oncological Cooperation) Multidisciplinary standards for oncological care in the Netherlands. Available at: http://nvog-documenten.nl/uploaded/docs/11Normering_Rapport_SONCOS_Februari_2014[1].pdf (accessed November 5, 2018).
14. Banzi R, Gerardi C, Bertele V, Garattini S. European Journal of Internal Medicine Approvals of drugs with uncertain benefit–risk profiles in Europe. Eur J Intern Med 2015;26:572–84. doi: 10.1016/j.ejim.2015.08.008.
15. Gonsalves G, Haven N, Zuckerman D. Commentary: Will 20th century patient safeguards be reversed in the 21st century? BMJ 2015 Mar 25;350;1500:9–10. doi:10.1136/bmj.h1500.
16. Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from

anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann oncol 2015 Aug; 26(8):1547–73. doi:10.1093/annonc/mdv249.
17. Groot CAU. A Practical Guide for Using Registry Data to Inform Decisions About the Cost Effectiveness of New Cancer Drugs: Lessons Learned from the PHAROS Registry. Pharmacoeconomics 2015;33:551–60. doi:10.1007/s40273-015-0260-4.
18. Gils CWM Van, Groot S De. Real-World Cost-Effectiveness of Oxaliplatin in Stage III Colon Cancer: A Synthesis of Clinical Trial and Daily Practice Evidence. Pharmacoeconomics 2013 Aug;31(8):703–18. doi:10.1007/s40273-013-0061-6.
19. https://www.registratieaandebron.nl/ (accessed November 5, 2018)
20. https://www.zorginstituutnederland.nl/ (accessed November 5, 2018)
21. Mohseninejad L, Gils C Van, Groot CAU, Buskens E, Feenstra T. Evaluation of Patient Registries Supporting Reimbursement Decisions: The Case of Oxaliplatin for Treatment of Stage III Colon Cancer. Value Heal 2015;18:84–90. doi:10.1016/j.jval.2014.10.008.
22. Guideline on the evaluation of anticancer medicinal products in man. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf. [Accessed November 5, 2018]
23. Basch E. Patient-reported outcomes: an essential component of oncology drug development and regulatory review. Lancet Oncol 2018 May;19(5):595–7.
24. Long G V, Atkinson V, Ascierto PA, Robert C. Effect of nivolumab on health-related quality of life in patients with treatment-naive advanced melanoma: results from the phase III checkMate 066 study. Ann Oncol 2016;27. doi:10.1093/annonc/mdw265.
25. Robert C, Maio M, Mortier L, Hassel JC, Rutkowski P, Ph D, et al. Nivolumab in Previously Untreated Melanoma without. N Engl J Med 2015. doi:10.1056/NEJMoa1412082.
26. Hassel JC, Lee SB, Meiss F, Meier F, Dimitrakopoulou-strauss A, Dirk J, et al. Vemurafenib and ipilimumab: A promising combination? Results of a case series. Oncoimmunology 2015 Oct 29; 5(4). doi:10.1080/2162402X.2015.1101207.
27. Earle BCC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying Potential Indicators of the Quality of End-of-Life Cancer Care From Administrative Data. J Clin Oncol 2003Mar 15; 21(6):1133–8. doi:10.1200/JCO.2003.03.059.
28. Kotronoulas G, Kearney N, Maguire R, Harrow A, Domenico D Di, Croy S. What Is the Value of the Routine Use of Patient-Reported Outcome Measures Toward Improvement of Patient Outcomes , Processes of Care , and Health Service Outcomes in Cancer Care? A Systematic Review of Controlled Trials. J Clin Oncol 2014;22. doi:10.1200/JCO.2013.53.5948.
29. Zorg voor Uitkomst 2016. Available at: https://www.santeon.nl/uitkomstenboek2016.pdf (accessed November 5, 2018)
30. http://qol.eortc.org/projectqol/eortc-cat/ (accessed November 5, 2018)
31. Atherton PJ, Burger KN, Pederson LD, Kaggal S, Sloan JA. Patient-reported outcomes questionnaire compliance in Cancer Cooperative Group Trials (Alliance N0992) . Clin Trials 2016 Dec;13:612–20. doi:10.1177/1740774516655101.

32. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial . J Clin Oncol 2016 Feb 20;34(6):557-65. doi:10.1200/JCO.2015.63.0830.
33. Boyce MB, Browne JP. Does providing feedback on patient-reported outcomes to healthcare professionals result in better outcomes for patients? A systematic review. Qual Life Res 2013 Nov;22(9)2265–78. doi:10.1007/s11136-013-0390-0.
34. Basch E. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatmen. JAMA 2017;318:197–8.
35. Dutch guideline for breast cancer. http://www.oncoline.nl/borstkanker (accessed October 30, 2018).
36. Dutch Institute for Clinical Auditing. Annual report 2017. Available at: https://dica.nl/jaarrapportage-2017 (accessed November 5, 2018)
37. Korevaar J, Jong J De. NIVEL - Naar een toekomstbestendige nazorg bij kanker: is er ruimte voor een grotere rol van de eerste lijn? Available at: https://www.nivel.nl/sites/default/files/bestanden/Kennissynthese_nazorg_bij_kanker.pdf. (accessed November 5, 2018)
38. Rossi S De, Earle CC, Grunfeld E, Zwicker V. Examination of Health System Resources and Costs Associated With Transitioning Cancer Survivors to Primary Care: A Propensity-Score – Matched Cohort Study. J Oncol Pract 2018. doi:10.1200/JOP.18.00275.
39. NHG: Overzicht en definitie van diabetesindicatoren huisartsenzorg. Versie 1.5c. Available at: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/ha-diabetesindicatoren-v1.5c-2april14.pdf. (accessed November 5, 2018)
40. NHG: Overzicht en definitie van indicatoren voor COPD in de huisartsenzorg. versie 1.5. Available at: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/ha-copdindicatoren-v1.5-10feb15.pdf (accessed November 5, 2018)
41. Struijs JN, Til JTDJ, Lemmens LC, Drewes HW, Bruin SR De, Baan CA. Drie jaar integrale bekostiging van diabeteszorg. RIVM rapport. 2012. Available at: https://rivm.openrepository.com/rivm/bitstream/10029/257271/3/260224003.pdf. (accessed November 5, 2018)
42. American Society of Clinical Oncology: Shaping the future of oncology: Envisioning cancer care in 2030. Outcomes of the ASCO Board of Directors strategc planning and visioning process, 2011-2012. Available at: http://www.asco.org/sites/default/files/shapingfuture-lowres.pdf. (accessed November 5, 2018)
43. Shah A, Stewart AK, Kolacevski A, Michels D, Miller R. Building a Rapid Learning Health Care System for Oncology: Why CancerLinQ Collects Identifiable Health Information to Achieve Its Vision. J Clin Oncol 2016 Mar 1;34(7):756-63. doi:10.1200/JCO.2015.65.0598.
44. Rubinstein SM, Warner JL. CancerLinQ: Origins,Implementation,and Future Directions. JCO Clin Cancer Informatics 2018;2:1–7.