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Adverse events as a measure of patient safety in cancer care

A study of patient safety in cancer patients using the Global trigger Tool review method to identify adverse events.

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Cover: illustration by Anne-Guri Storjord in memory of her sister who died from cancer.

The tree of life is a symbol of growth and strength. The flowers symbolize love and hope of a good life. The birds and the butterflies are nurses and doctors caring for the patient. The chemotherapy is red, and connected to the hearth, filling it with feelings of hope, anger and fear. Ready to fight and scream in frustration, but also able to find joy and love in the special moments that each day brings. The shoes symbolize her greatest hope; to get back to life the way it was and dance carelessly into the long summer nights…

The past is behind, learn from it.

The future is ahead, prepare for it.

The present is here, live it.

Thomas S. Monson

Acknowledgements

To my parents **Gerd** and **Karl-Erik**[†] for your unconditional love and for always believing in me. Thank you for letting me follow my dreams and teaching me that everything can be achieved with hard work. To my brother **Richard** and my sister-in-law **Ane** for your support and taking part in our lives. To my parents-in-law **Eli** and **Sture** for your support and always helping with the girls.

To my dearest husband **Lars**, thank you for listening to the song of my heart and sing it back to me when I have forgotten the words. You carry me and my world and I love you deeply.
To my super girls, **Hedda**, **Oda** and **Signe** you are my joy and laughter. Thank you for making each day of my life precious.

Finally, thank you to all **my patients** for teaching me that every day is precious, and life is here for us to live and love.

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Summary

"First, do no harm" is a fundamental element of health care and considered indistinguishable from the delivery of quality in health care. While cancer treatment has become more effective, it has also become more complex, consequently increasing the risk for harm. It is no surprise that cancer patients experience treatment related harm, but the extent and severity of treatment related adverse events (AEs) in real world clinical settings is not well investigated.

In the three studies included in this thesis, we have assessed the nature of AEs in hospitalised cancer patients compared to other patients and elucidate how AEs can be used as a clinically relevant measure of quality and safety in cancer care. All three studies are retrospective cohort studies, using the Global Trigger Tool (GTT) to identify AEs in patients hospitalized at three hospitals of Nordland Hospital Trust in Norway.

We find that hospitalised cancer patients more often than other patients experience AEs, but this is due to older age and longer length of stay rather than the cancer itself. Especially medication related harm and healthcare associated infections are safety hazards of concern to cancer patients. Patients dying in hospitals differ in several ways from a general hospitalised population and experience seven times the rate of severe AEs. An AE contributed to death for nearly one in three deceased cancer patients. Despite strong recommendations limiting the use of aggressive anticancer treatments for cancer patients near the end of life, we found that one third of deceased hospitalised cancer patients received some kind of anticancer treatment during the last 30 days of their lives. Anticancer treatment given during the last 30 days of life is associated with a significantly increased rate of AEs with twice the odds of having an AE contributing to death.

Identifying specific AEs in cancer care is clearly warranted and can provide real time measures of quality and safety, enhancing improvement in clinical practice and avoiding overtreatment in end-of-life cancer care. The GTT review of all inpatient deaths provides new valid and reliable measurement of severe AEs contributing to death that otherwise would go undetected. Measuring AEs contributing to death can be a powerful driver of the safety culture and raise awareness for learning and improvement.

Sammendrag (summary in Norwegian)

"Første av alt, ikke skade" er et grunnleggende prinsipp i helsevesenet og anses uatskillelig fra kvalitet og sikkerhet i helsevesenet. Kreftbehandling er blitt mer effektiv, men også mer kompleks som øker risikoen for skader. Det er ingen overraskelse at kreftpasienter opplever behandlingsrelaterte skader, men omfanget og alvorlighetsgraden av disse skadene i klinisk praksis er ikke godt undersøkt.

Formålet med studiene våre var å studere forekomst, alvorlighetsgrad og typer av skader hos innlagte kreftpasienter sammenlignet med andre pasienter, samt å belyse hvordan skader kan brukes som et klinisk relevant mål for kvalitet og pasientsikkerhet i kreftomsorgen. Alle tre studiene er retrospektive kohortstudier, og bruker Global Trigger Tool metoden for å identifisere skader hos pasienter innlagt i Nordlandlandssykehuset.

Vi fant at kreftpasienter oftere enn andre pasienter opplever skader, men at dette skyldes høyere alder og lengre liggetid og ikke kreftsykdommen i seg selv. Spesielt medikamenter og helseassosierte infeksjoner medfører skader hos kreftpasienter. Pasienter som dør på sykehus skiller seg på flere måter fra andre pasienter og opplever syv ganger flere alvorlige skader. For nesten en av tre kreftpasienter som dør på sykehus medvirker en skade til døden.
Selv om det er sterke anbefalinger som begrenser bruken av aggressive kreftbehandlinger nær livets slutt, fant vi at en tredjedel av avdøde sykehusinnlagte kreftpasienter mottok kreftrettetbehandling i løpet av de siste 30 dagene av livet. Kreftbehandling gitt i løpet av de siste 30 dagene av livet er assosiert med en betydelig økt forekomst av skader, med dobbelt så stor risiko for at en skade bidrar til døden.

Å identifisere spesifikke skader hos kreftpasienter er klart berettiget og kan gi mål for kvalitet og pasientsikkerhet som grunnlag for forbedring av klinisk praksis og unngå overbehandling ved livets slutt hos kreftpasienter. Vi finner at en retrospektiv undersøkelse av alle dødsfall på sykehus ved bruk av GTT metoden, gir ny relevant og pålitelig informasjon om alvorlige skader som bidrar til døden og som ellers ikke ville bli oppdaget. Å måle skader som bidrar til død, kan være en sterk pådriver for pasientsikkerhetskulturen og øke bevisstheten om læring og forbedring.

List of Papers

This thesis is based upon three papers, referred to in the text by their Roman numerals (I – III).

I. **Haukland EC**, von Plessen C, Nieder C, Vonen B.
   Adverse events in hospitalised cancer patients; a comparison to a general hospital population.
   Acta Oncologica 2017. doi:10.1080/0284186X.2017.1309063

II. **Haukland EC**, Mevik K, von Plessen C, Nieder C, Vonen B.
   Contribution of adverse events to death of hospitalised patients.
   BMJ Open Quality 2018. doi:10.1136/bmjoq-2018-000377

III. **Haukland EC**, von Plessen, Nieder C, Vonen B.
   Adverse events in deceased hospitalised cancer patients as a measure of quality and safety in end-of life cancer care.
   Under review in BMC Palliative Care.

Abbreviations

ADE	Adverse Drug Event
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society of Clinical Oncology
CI	Confidence Interval
CTCAE	Common Terminology Criteria for AEs
EAPC	European Association for Palliative Care
EHR	Electronic Health Record
ESMO	European Society for Medical Oncology
GTT	Global Trigger Tool
HAI	Healthcare Associated Infections
HMPS	Harvard Medical Practice Study
ICD-10	International Classification of Diseases, version 10
ICPS	International Classification for Patient Safety
IHI	Institute for Healthcare Improvement
IOM	Institute of Medicine
IRR	Incidence Rate Ratio
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NCI	National Cancer Institute
PRO	Patient Reported Outcome
RRR	Retrospective Record Review
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organization

1 Introduction

1.1 Background

Cancer creates great fear and can have devastating consequences for patients and their families. Patients` express their world falls apart and they often think; "Is this it? Am I going to die? " [1]. Being in such an existential life crisis, patients` have no other choice than to trust that healthcare will do the best to cure them if possible. If not possible, then offer the best available care across the whole continuum of cancer care, from diagnosis through end of life. Most of all, patients trust us not to harm them and at the least not to hasten death [1, 2]. *"First, do no harm"* is a fundamental element of healthcare and considered indistinguishable from the delivery of quality.

In 1999, the Institute of Medicine (IOM) published its landmark report, *To Err is Human* [3]. The report created an international sense of urgency to reduce patient harm in healthcare. It recommended healthcare organisations to learn from AEs, mitigate contributing factors, prevent future errors and ultimately make patients safer [4]. Despite progress in the last 15 years, patient safety remains an important public health issue and it is estimated that AEs due to medical error are the third leading cause of death in the USA [5]. Through time, it has become increasingly clear that patient safety is far more complex and AEs far more pervasive than initially anticipated, and to improve we need a system approach that fosters a culture of learning and safety in clinical practice [6, 7]. New treatment and technology constantly becoming available has made cancer treatment more effective, but also more complex, thereby increasing the risk of harm. Moreover, cancer patients are getting older. This addresses important considerations for the treatment of older cancer patients, and how the current healthcare system is prepared to meet the needs of an aging cancer population [8]. Previously under-recognised aspects of safety, such as underutilisation of palliative care and overuse of treatment near end of life are now recognised as important elements of quality and patient safety [6, 9].

It is no surprise that cancer patients experience treatment related toxicities, but the extent and severity of treatment related AEs in clinical practice have not been well researched [10]. To improve patient safety in cancer care we need a thorough understanding of the specific safety problems in oncology. To achieve this, we need good and reliable measurements. The measures themselves cannot determine what is right or wrong, but can enhance discussions about standards of care and encourage improvements. In the three papers included in this thesis, we have assessed the nature of AEs of hospitalised cancer patients in different settings, and investigate how AEs can be used as a clinically relevant measure of quality and safety in cancer care.

1.2 Patient safety

> **Key messages:**
> - Patient safety is the prevention of errors and adverse effects associated with health care.
> - We need standardised definitions and terms to guide our understanding of patient safety.
> - Cancer care is inherently complex, increasing the risk of adverse effects.
> - To improve patient safety of cancer patients we need to look at the whole cancer care continuum from diagnosis to end-of-life care.

The simplest definition of patient safety is the prevention of errors and adverse effects to patients associated with health care [11]. A key step to improve patient safety is establishing a common language that promotes better understanding and a reliable comparison of information [12]. A standardised taxonomy guides the principles of classification and aids the risk manager in understanding why an event happened, how it happened and what impact the event had on patients and providers [13]. With the intention to standardise definitions and terms, WHO developed a conceptual framework to provide a consistent understanding of the domain of patient safety [14]. The International Classification for Patient Safety (ICPS) is designed to facilitate the description, comparison, measurement, monitoring, analysis and interpretation of information to improve patient care [3, 4].

ICPS defines a patient safety incident as an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient. An incident type can be a reportable circumstance, near miss, error or AE. Patient characteristics, incident characteristics and contributing factors are necessary descriptive information that provide context to understand the outcome of the incident. Patient outcome is the impact on a patient, which is wholly or partly attributable to an incident and assessed according to severity of harm. A complex relationship exists between incident type and contributing factors. More than one contributing factor or hazard is typically involved in a single incident and an incident can be a contributing factor to another incident. Incidents can also affect healthcare organisations, e.g. adverse publicity or additional use of resources classified as organisational outcomes. Detection, mitigating factors and ameliorating actions represent detection, prevention, resilience and incident recovery from an incident. The surrounding actions taken are actions aiming to reduce, manage or control any future harm, or probability of harm associated with an incident.

The ICPS framework (Figure 1) illustrates the complexity of improving patient safety and prevention of harm to patients. Healthcare organisations are composed of multiple differentiated and autonomous smaller clinical systems with many tightly coupled and interacting actions [15, 16]. The actions of individuals are interconnected so that the actions of one provider change the context for all the other providers [17]. This makes healthcare complex and unpredictable with an inherent propensity for failure to occur [15]. Safety initiatives should therefore take into account the complete system when investigating an incident and aim to reduce system complexity to improve safety and quality in health care [17, 18].
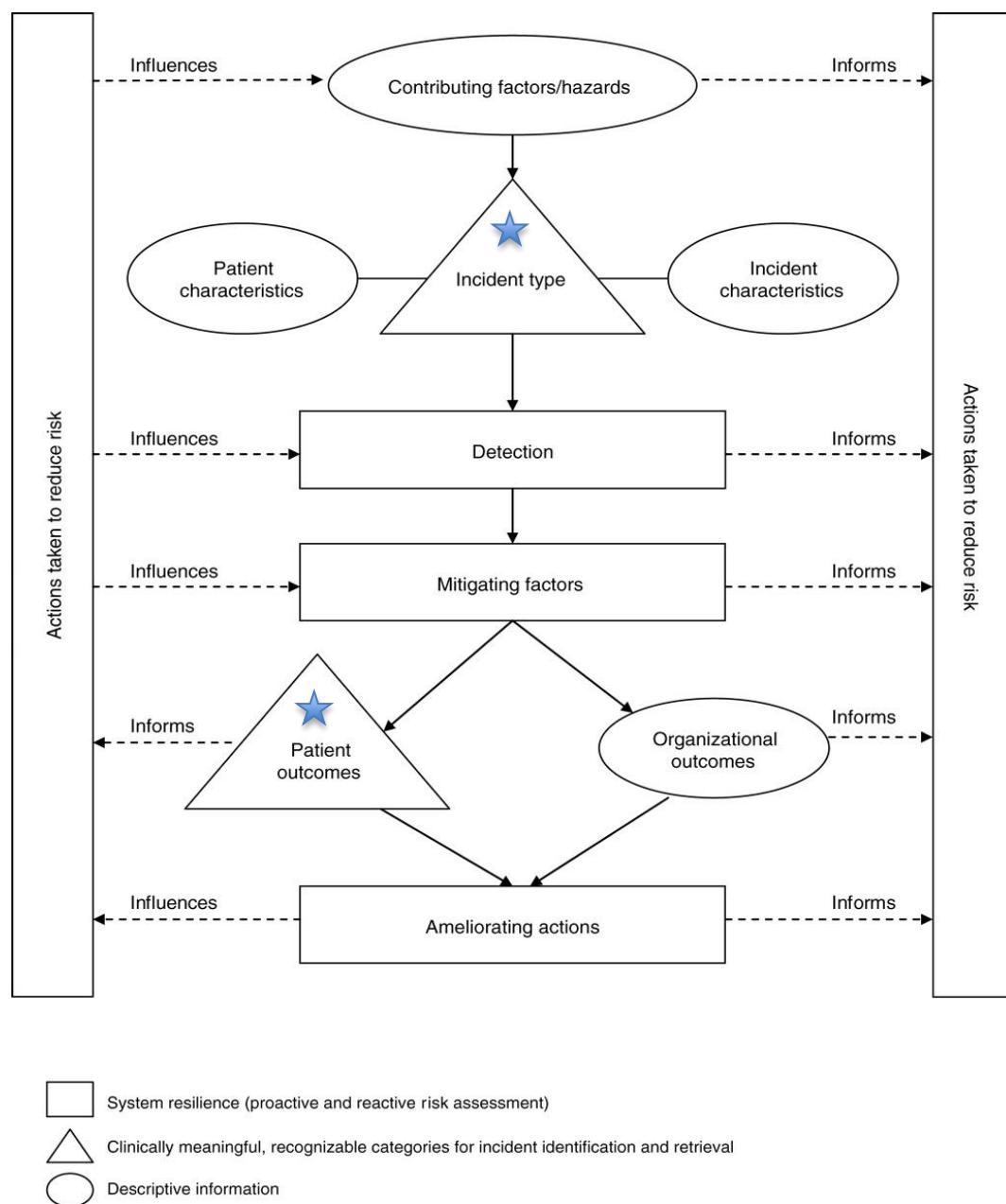
Figure 1 WHO`s Conceptual Framework for the International Classification of Patient Safety

1.2.1 Patient safety in oncology

Cancer care is highly complex due to diagnostic challenges, multimodal and multispecialty treatment strategies, a narrow therapeutic/toxic ratio for many treatments, long-term and late effects of disease and treatment that contribute to morbidity and mortality [8, 19]. This complexity is driven by the biology of cancer itself, the multiple specialists involved, recognising the correct diagnosis, prognosis and treatment recommendations. In addition, the healthcare system is fragmented and often not prepared to meet the individual needs, preferences, and values of patients who are very ill [8]. Safety and complexity are correlated, where complexity in healthcare increases the risk of harm to the patient [17, 18, 20]. With the introduction of new technology and new systemic anticancer treatments constantly becoming available, the complexity increases persistently. To improve patient safety in cancer care, we need to look at the full cancer care continuum from diagnosis and treatment to maintaining the health of survivors and providing end-of-life care consistent with patients' needs, values and preferences [8].
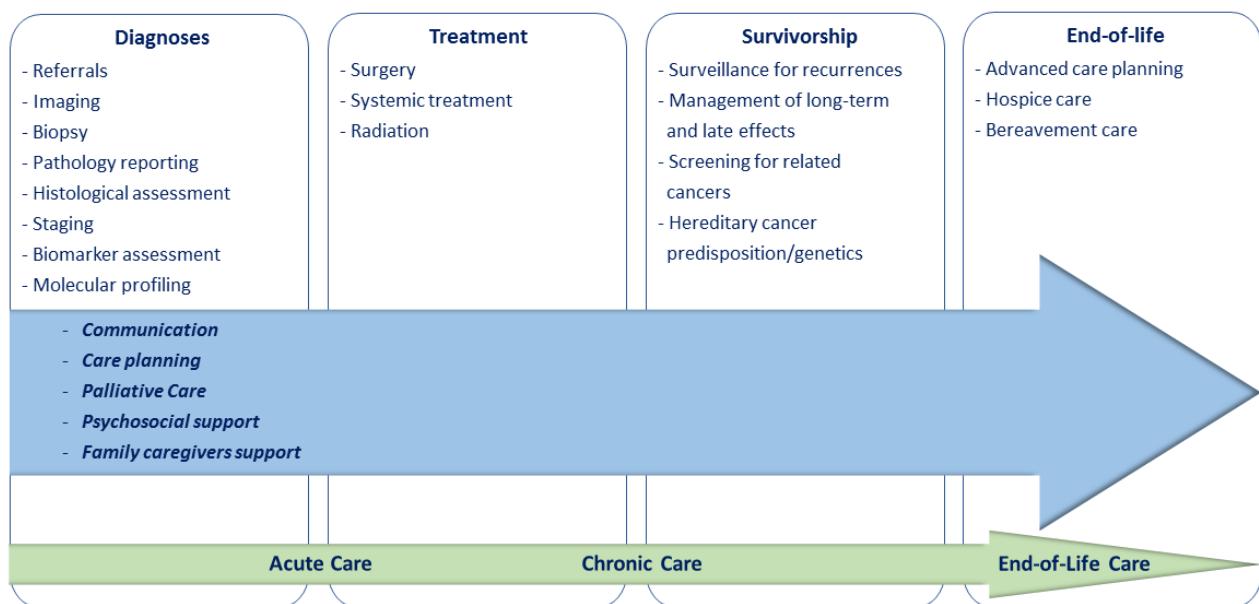
Figure 2 Domains of the cancer care continuum with examples of activities.
The blue arrow identifies components of patient safety that should span the continuum from diagnosis through end-of-life care. The green arrow identifies three overlapping phases of cancer care.
SOURCE: Adapted from Institute of Medicine, Delivering High-Quality Cancer Care [8].

The patient safety focus in oncology has been mainly on the hazards of medication and, in particular, specific risks related to prescribing, dispensing and administration of systemic anticancer treatments [21–23]. A review by Weingart in 2018 found that chemotherapy errors occur at the rate of one to four per 1 000 orders and effect one to three percent of oncology patients [22]. This focuses on any error occurring during the process of medication use, whether the error causes an AE or not. Due to good control systems, most chemotherapy related medication errors are mitigated and do not result in AEs [22]. However, many systemic anticancer treatments have a low therapeutic index (the ratio of the maximally tolerated dose of a medicine to the minimal effective dose), so even when the treatment is given at the correct dosage it may cause an adverse drug reaction (ADE) and AE.

Within patient safety there has been, in terms of AEs, a shift in focus from detecting errors, to focusing on outcome for the patients. This new focus can demonstrate areas of risk and enhance improvements to reduce severe AEs and death occurring as a result of systemic anticancer treatment.

The diagnostic process from recognising symptoms of cancer to a correct diagnosis leads for complex interactions of multiple contributing factors, both at system and individual levels [24]. Diagnostic errors occurring at any stage of this process are considered an important threat to patient safety in cancer care. Diagnostic errors can be defined as a diagnosis that is missed, wrong or delayed [25]. However, while not all misdiagnosis cause harm in patients, for cancer patients a delayed or missed diagnosis can have severe consequences for choice of treatment and prognosis. Delayed cancer diagnosis is claimed to be one of the most harmful and costly types of diagnostic error [26]. Understanding and mitigating diagnostic errors in patients is necessary to improve patient safety in cancer care [27].

An intervention to improve the diagnostic process was implementation of standardised cancer patient pathways for all cancer types in Norway from 2015. A study by Nilssen et al., assessing the waiting time in Norway for the four most common types of cancer from 2007 to 2016, found a gradual improvement with no significant change observed from the time of cancer patient pathway implementation. This may indicate that implementation of the cancer care pathway was just a continuation of an already on-going trend initiated in 2011, when politicians announced a "waiting time guarantee" stating that 80 percent of cancer patients should start their treatment within 20 days of diagnosis [28].

Surgery is the oldest form of cancer treatment, and for many cancer types it provides the best chance of being cured. Surgery also plays a role in diagnosing, staging and supportive cancer treatment. A systematic review by Anderson found that 14 percent of surgical patients experienced at least one AE [29]. This is about the same as a national study in Sweden, identifying that 15 percent of all surgical patients experienced an AE, of which 4.7 percent contributed to permanent harm or death [30]. This identifies surgery as one of the high-risk areas for the occurrence of AEs.

Research asserts that patients are safer and have better short- and long-term survival when their cancer surgery is performed by hospitals and surgeons with sufficient experience [31, 32] This applies especially for some cancer types such as pancreatic, oesophageal, lung and rectal cancer where surgery can be very complex with a higher risk of complications [33]. Not surprisingly, greater hospital volume is associated with both fewer postoperative complications and an 11 percent increase in long-term survival after resection for pancreatic cancer [34]. This has led to a greater centralisation of complex cancer surgery and a longitudinal study by Sheetz et al. indicates that 30-day mortality for three out of four high-risk cancer operations improved over time with high-volume hospitals continuing to have lower complication and mortality rate for all procedures [33]. In another study by Nathan et al. patients who had complex cancer-surgery and experienced serious complications had decreased long-term survival, even if they recovered from their complications. They were also less likely than those with no or mild complications to receive adjuvant chemotherapy [35].

In 2008, WHO introduced the Safe Surgery Checklist as a strategy to improve patient safety and inter-professional teamwork during surgical interventions [36]. The checklist has since proven to contribute to decreasing complications and deaths related to surgical interventions [37][38][39]. Most studies of surgical safety have focused on the operating theatre, neglecting the critical role of post-operative ward care. Anderson et al. found that more than half of AEs were non-operative AEs related to monitoring, medications, anaesthesia and diagnostic procedures, indicating that targeting the entire surgical care pathway is just as important to reducing surgically related AEs [29].

Cancer patients at the end of life are fragile and often require complex care, making them at high risk of safety issues. Consequences may also be greater, since time is limited and valuable. Attention to patient safety is fundamental for good end-of-life care but may require a different approach. Patient preferences and quality of life must balance safety, and overemphasis on patient safety may detract from promoting an end of life consistent with patient values [40]. Many safety issues in end-of-life and palliative care are consistent with recognised safety hazards in patient safety. Examples of common safety issues are falls, pressure ulcers, constipation or delirium after using opioids. Other aspects of end-of-life care should also be considered as safety hazards are poorly controlled pain, underuse of early referral to palliative care, failure of considering prognosis and miscommunication [40–43] Communication is particularly important when it comes to of end-of-life preferences. Lack of communication and miscommunication at the end of life can cause patient harm when patients

consequently accept treatments that are unlikely to benefit them. Up to one out of five cancer patients receives anticancer treatment during the last 30 days of life without the clear benefit of prolonging survival. The treatment also exposes them to the risk of severe negative consequences such as increased toxicity and decreased quality of life [44–46] This emphasises the need to assess symptoms, toxicities and complications of anticancer treatment by systematically measuring AEs in end-of life cancer care.

To limit the extent our research we have focused on AEs contributed to by cancer treatments (surgery, radiation and systemic anticancer treatment) in addition to general care itself, in a treatment- and end-of-life care setting.

1.3 Adverse events

Key messages:
- Definitions of AEs describe an adverse outcome arising from medical care, rather than the patient´s underlying medical condition.
- Most hospital AEs are temporary, but up to 12 percent of AEs contribute to permanent disability or death.
- The overall incidence of AEs varies from one to two per ten patients.
- The incidence depends on setting, review method and sample size.
- Cancer patients experience higher rates of AEs than other hospitalised patients.
- Surgical complications, medication harm and healthcare associated infections are the most common types of AEs.
- Cancer patients experience in addition specific AEs related to systemic anticancer treatment and radiotherapy.

1.3.1 Definition

The ICPS does not provide a specific definition of an AE. Other organisations have published many different definitions. The common denominator for all definitions is that the terms describes an adverse outcome that arises as a result of medical care, rather than from the patient's underlying medical condition.

Table 1 Definitions of adverse events

Institution	Definition adverse event
Agency for Healthcare Research and Quality (AHRQ)	Resulting from exposure to the health care system, likely amenable to prevention by changes to the system [47].
Institute for Healthcare Improvement (IHI)	Unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment, or hospitalisation or that result in death [48].
Harvard Medical Practice Study (HMPS)	An injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalisation, produced a disability at the time of discharge, or both [49].
Office of the Inspector General (IOM)	Harm as a result of medical care or occurring in a health care setting [50].
The National Cancer Institute (NCI)	Any abnormal clinical finding temporally associated with the use of a therapy for cancer; causality is not required [51].

Two other frequently used terms are errors and near misses. Error is a broader term referring to any act of commission (doing something wrong) or omission (failing to do the right thing) that exposes patients to a potentially hazardous situations [52]. Different from AEs, errors may or may not result in harm to the patient, and not all AEs are necessarily a result of errors. A near miss is an unsafe situation that either resolves spontaneously or is neutralised before it develops into an AE. For example, a patient notices that the intravenous chemotherapy does not bear his name on the infusion bag. He alerts the nurse and the wrong treatment is not given. In this situation, an error was committed but the patient did not experience clinical harm and the situation ended up as a near miss.

In our research and for this thesis we have used the IHI definition of an AE:
"Unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment, or hospitalisation, or that results in death."

An important reason for using this definition is that it enhances the patient perspective, arguing that if an AE occurs it is always harm to the patient as long as it was unintended. As an example, being left with a scar after open surgery removing a pancreatic cancer is an expected injury, while leakage of anastomosis is an unintended physical injury even though the expected complication rate is about 5 percent [53]. This also enhances the objectivity of an AE with no need to judge if it was an expected complication or not. Another argument for using this definition is that often there is more than one factor contributing to an AE and direct causality can be hard to determine. This definition only requires that medical care or treatment is a contributing factor.

1.3.2 Severity

Consequences of AEs can range from the very serious to those that have little impact on the patient. Most hospital AEs are temporary harms, but up to 12 percent of AEs contribute to permanent disability or death [54–56]. To determine the impact an AE has on a patient, we need to assess not only the incidence rate but also the severity of the incident. The severity of AEs is assessed in many ways.

In cancer research, the Common Terminology Criteria for AEs (CTCAE) is used as standard practice by clinicians to report toxic effects in trials of cancer treatments. Toxicity is graded from 1- 5 (mild, moderate, severe, life-threatening or death) [51]. These criteria are mainly used in clinical trials to provide standardization and consistency in the definition of treatment-related toxicity but have in recent years also been more commonly used for the management of chemotherapy administration and dosing [57].

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) in the US developed an index that classifies medication errors according to the severity grading of the outcome [58]. The index considers factors such as whether the error reached the patient and to what degree the patient was harmed. Category A-D reports incidence where no harm occurs to the patient. Category E-I reports on the degree of harm or death to the patient.
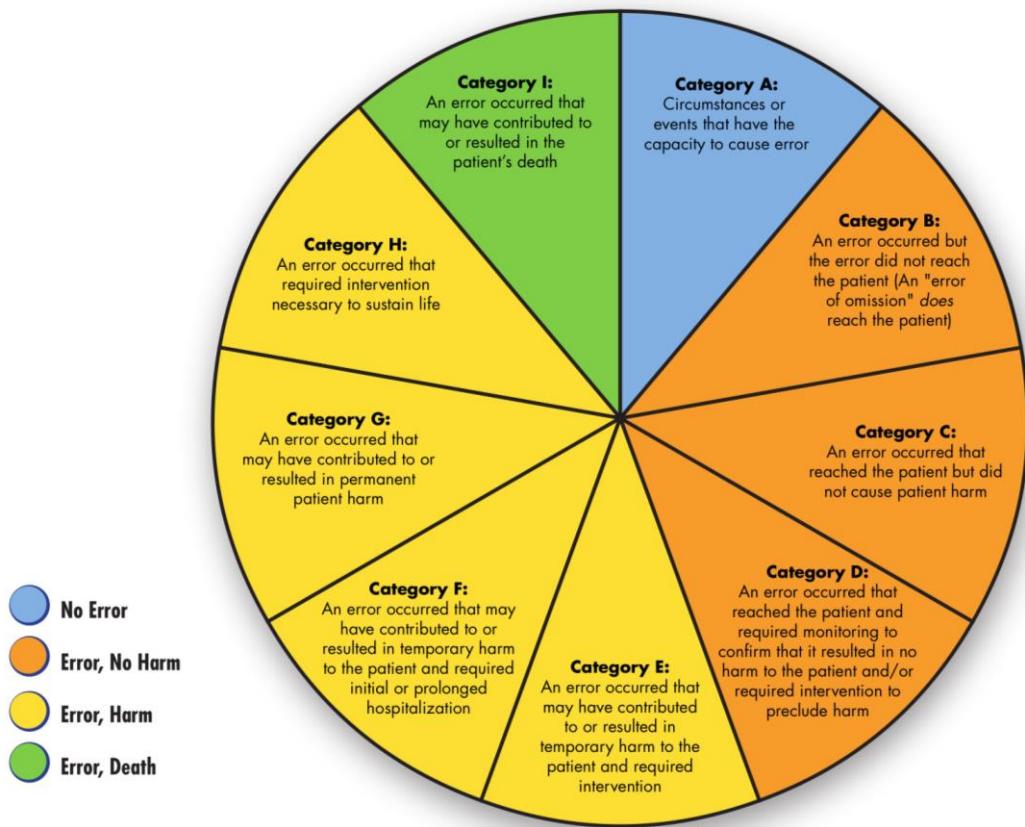
Figure 3 NCC MERP Index for Categorizing Medication Errors

When developing the Global Trigger Tool (GTT) method, IHI adapted the NCP MERP index to categorise the severity of any type of AE in patient safety. Since the GTT method only measures harm to the patient, the adapted classification only includes categories E – I. This classification is commonly used for the grading severity of an AE within patient safety [59, 60]. When referring to the severity of AEs in our papers and thesis we have used this adapted version of the NCC MERP index.

1.3.3 Types

The three most common types of AEs reported are related to surgery, medication and healthcare-associated infections [60, 61]. According to a systematic review undertaken by Swendimann et al. in 2018, surgery related AEs accounts for a median of 40 percent (range 27 - 75 %). Medication related AEs 19 percent (range 4 - 73 %) and healthcare-associated infections 18 percent (range 0.2 - 25 %) of all detected AEs [62].

The intention behind categorising AEs into types is to gain knowledge about healthcare related areas to improve patient care. Since the definition of AE focuses on incidence that occurring through medical care, types of AEs should be grouped into clinical categories according to the aetiology of the incident that led to the outcome for the patient. As an example, bleeding can be a clinical symptom related to bleeding after surgery or a symptom caused by administration of antithrombotic medication. Since they should be categorised according to the aetiology of the incidence, bleeding can be categorised as a complications after surgery or medication harm depending on what medical care contributing to the incident.

To standardise the review process, types of categories should be defined and grouped before the review starts. The original IHI GTT manual does not group AEs into types. In our research, we have categorised types of AEs according to 23 specified types recommended in the Norwegian National GTT manual [63], (Appendix I). When creating categories, the challenge is to find a balance between being specific enough to get an overview and at the same time not include too many subtypes. Heterogeneous categories makes it difficult to compare data and difficult to find interventions for improvement. Monitoring over time can also be difficult since one may not be able to reduce the rate enough to detect the change made. Another measuring challenge with the original 23 categories is that the types are not mutually exclusive, and where relevant one AE could be categorised into more than one category (e.g. postoperative bleeding and a reoperation) [64]. For statistical purposes, we therefore merged the original categories into eight main categories in our research.

- Healthcare associated infections
- Surgical complications
- Bleeding and thrombosis
- Patient fall and fracture
- Medication harm
- Obstetric harm
- Pressure ulcers
- Others

1.3.4   Incidence

WHO states that one out of ten hospitalised patients experience at least one AE and that AEs due to unsafe care is thought to be one of the ten leading causes of death and disability across the world [65]. WHO's statement is based on de Vries' systematic analyses of eight studies between 1991 and 2006 [66]. Later systematic reviews and meta-analyses of overall incidence of AEs in healthcare show considerable variation across studies, with up to 12 percent of the AEs leading to a lethal outcome [55, 56, 60, 67].

A number of methodological differences can account for the variability observed. To study this more closely we made a review of all studies included in these five systematic reviews. From the 209 studies, 79 duplicates were removed and four studies were excluded due to lack of information on percent of admissions with AEs. This left us with 126 studies carried out between 1991 and 2018. Studies from the first decade all indicate an incidence below 20 percent, while studies done after year 2000 report between 10 and 30 percent. See Figure 3. We find an overall average AE rate of 17.7 percent (median 13.5 percent) with a range from 1 to 74 percent.
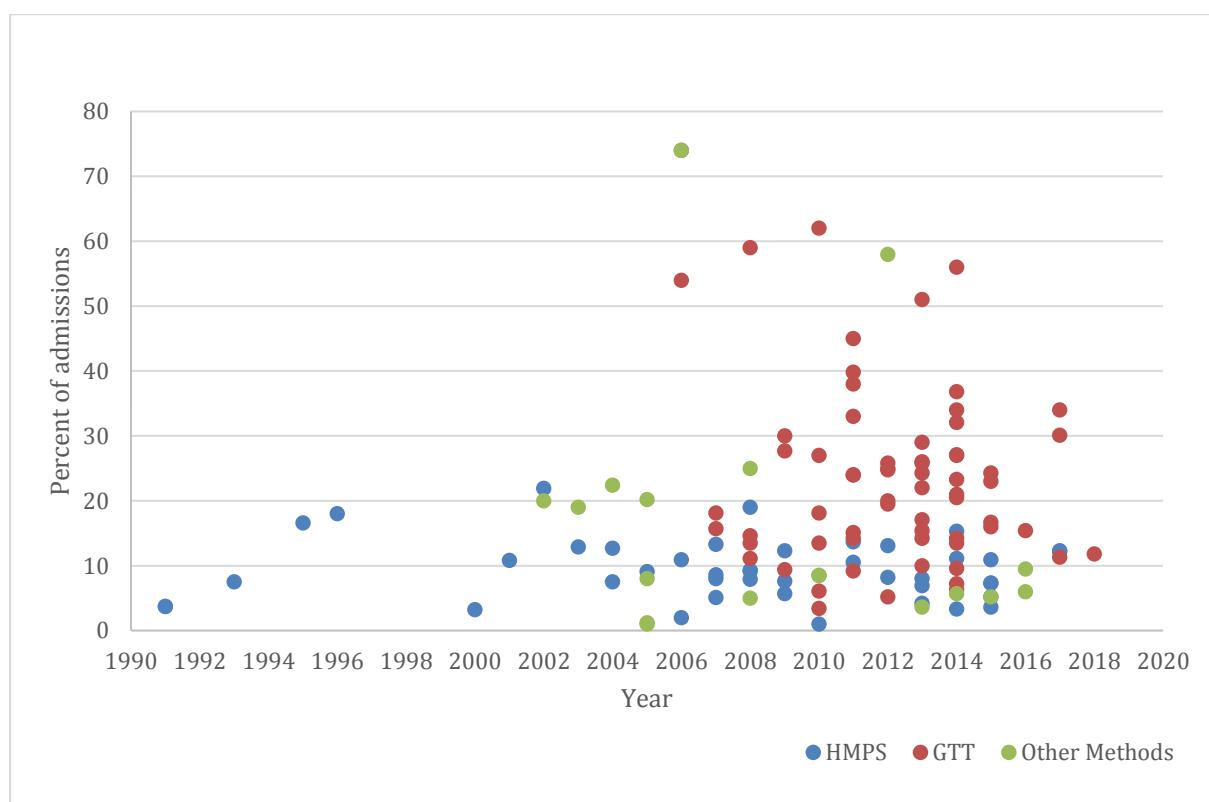
Figure 4 Percentage of hospital admissions with an AE depending on review method used.
Other methods include unstructured retrospective reviews and patient reported data.

Type of review method seems to be an important methodological difference. Studies based on the HMPS review method have an overall lower average of AEs compared to the GTT method, 9.3 vs. 24 percent. The first studies, including de Vries' systematic review, all used the HMPS method, while GTT reviews became more common after 2006. The thresholds for defining an AE and causality differ between these two methods. While the definition of an AE in the GTT method includes all unintended physical injury requiring additional monitoring or treatment, the HMPS method only defines the incident as AE when the patient is hospitalised or gets a prolonged hospitalisation due to the event. This threshold for defining an AE affects the incidence.

Harm rates also depend on the setting included in the studies. Patients admitted to intensive care (39 %), oncology (38 %) and surgery (22 %) experience higher rates of AEs on average compared to patients in obstetrics (5 %) and primary care (11 %). Patients admitted to general hospitals constitute a majority and have a pooled incidence of 14 percent.
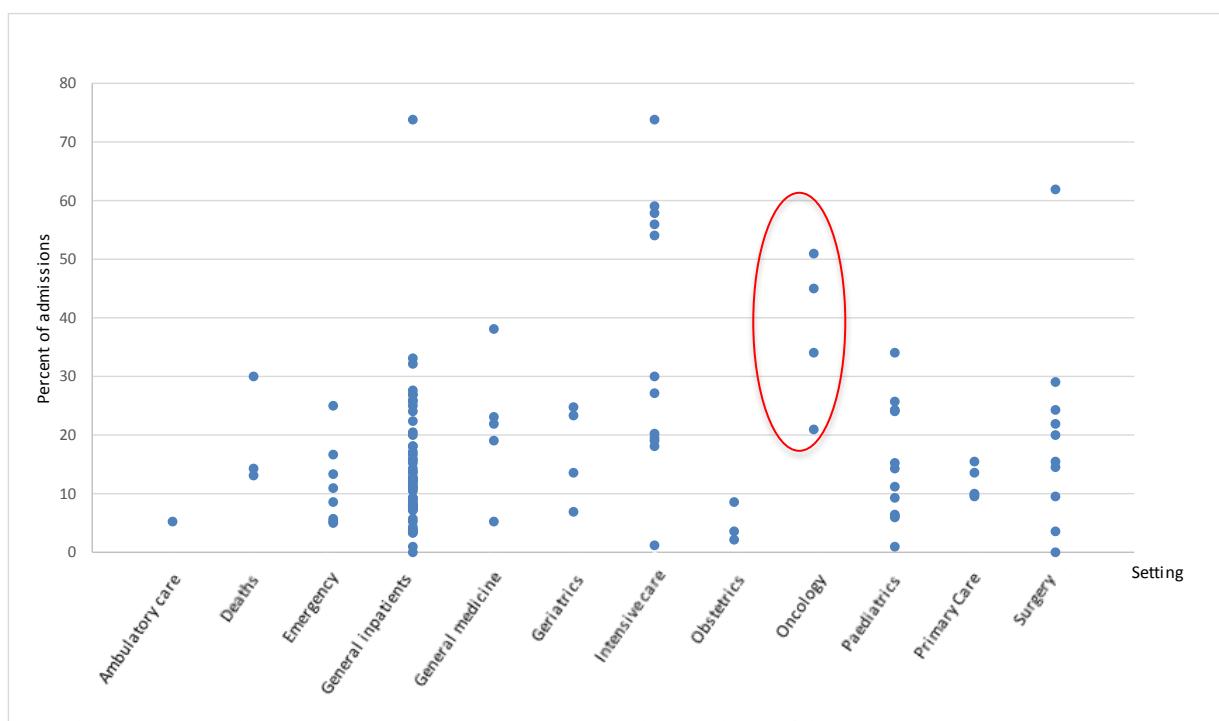
Figure 5 Percentage of admissions with an AE depending on setting.

Other methodological differences reported to affect the incidence are sample size, inclusion of events before or after index admission, the number and types of screening criteria, professional background and the chart reviewers' level of experience [12, 68].

1.4 Adverse events in oncology

Key message
- Medication harm is the most common type of AEs reported in cancer patients.
- Medication harm in cancer patients is related both to systemic anticancer treatment and use of other medications.
- Radiotherapy related AEs are often dose related and can be both short-term and late toxicities.
- The most frequent AEs after cancer surgery are wound problems, genitourinary, cardiovascular and gastrointestinal complications.
- We also need to recognise other safety hazards in cancer care, such as overtreatment near end-of-life and underuse of palliative care.

Cancer treatment often consists of a combination of surgery, radiotherapy and systemic anticancer treatments, which in itself, presents a number of hazards to the patient. The reporting of AEs in oncology has evolved in response to new treatments and modalities. Before the 1980s, retrospective studies provided limited description of AEs, and severity ranking was rare [57]. As clinical trials became more common in the 1980s the National Cancer Institute (NCI) developed the CTCAE system to detect and document AEs commonly encountered in oncology clinical trials. AEs detected through clinical trials do not necessarily reflect clinical practice. AEs can occur throughout the whole continuum of cancer care and patients included in specific clinical trials my fail to reflect sufficiently the actual clinical setting. It should also be recognised that even large phase three trials are often underpowered to accurately assess the risk of low frequency events [69, 70]. Assessing AEs in oncology by using the GTT method provides real world data that can complement and validate AEs reported through clinical trials.

In 2011 Lipczak et al. published one of the first studies looking at specific safety hazards related to cancer care. They found specific AEs related to cancer treatments such as chemotherapy and radiotherapy but also hazards (HAI and surgical complications) similar to those seen in general patient populations [71]. During the last decade there have been multiple studies indicating that cancer patients experience higher rates of AEs than the general population, with an average of nearly 40 percent of admissions with at least one AE [10, 23, 72–74]. It is no surprise that cancer patients experience treatment-related toxicities but the extent and severity of treatment related harm in clinical practice has not been well documented [10].

1.4.1 Medications

Medication harm is the most common type of AEs reported in cancer patients. Adverse drug events related to systemic anticancer treatments are of serious patient safety concern [75]. A study by Damen et al. states that chemotherapy and anticoagulants are the two main medication types responsible for medication-related AEs [76].

Short-term toxicities such as nausea, vomiting and diarrhoea are well known AEs related to anticancer chemotherapy treatment. Current treatments to control these are reasonably effective in most patients, preventing them from developing into severe AEs [77]. On the other hand, neutropenia infection in cancer patients is a feared AE related to chemotherapy treatment. Sepsis and septic shock are leading causes of intensive care unit admission and mortality in cancer patients undergoing intensive cytotoxic chemotherapy [78]. Neutropenia is in itself, an independent risk factor for infection. Additionally, acute leukaemia, prolonged hospital stay, prior surgery, advanced disease, the presence of a central line catheter and treatment with chemotherapy are significantly associated with infection and sepsis in cancer patients with neutropenia [78].

Along with increasing cancer-survival rates, long-term sequels after anticancer chemotherapy have gained more awareness. Peripheral neuropathy is caused by many chemotherapy agents and associated with high morbidity such as depression, ataxia and insomnia [79]. Cisplatin induced nephrotoxicity, higher risk of cardiovascular events, fertility problems, fatigue and cognitive dysfunction are other severe long-term side effects that can appear years after treatment and have significant impacts on patients' lives [77, 80].

New systemic anticancer treatments such as targeted therapies and immunotherapy are now well-established treatments for many cancer types, and their use is continuously expanding. While these agents do not lead to AEs associated with many traditional cytotoxic treatments, they can cause a whole range of other AEs. Many of the AEs caused by targeted therapies are short-lived or reversible when stopping therapy and are often not associated with long-term AEs [80]. Unlike conventional chemotherapy, immune checkpoint inhibitors boost the immune system and can lead to a unique constellation of inflammatory toxicities known as immune-related AEs. Symptoms occur as inflammations in different organs and can sometimes be challenging to identify. If not recognized and treated at an early stage immune related AEs can be life threatening. The rate of severe immune related AEs requiring immunosuppression and withdrawal of immunotherapy is estimated to be 0.5–13% [81]. Introduction of new treatments has improved the outcome for many patients with advanced cancer. However, their introduction is also associated with unique new AEs that we need to identify with real-world data from the clinical setting.

Studies have also shown that other medications causing AEs are at least as common as chemotherapy Narcotic agents such as opioids, sedatives and steroids are high-risk medications often used for

palliative care and frequently cause AEs in cancer patients [23, 43, 82, 83]. Systemic anticancer treatment has a potentially increased risk of interaction with other medications, in particular warfarin, antihypertensive medications, corticosteroids and anticonvulsants [84]. This emphasises the importance of medication reconciliation and close collaboration between oncologists and other physicians during a course of treatment.

1.4.2   Radiation

Radiotherapy is a highly effective treatment option for palliation and has a substantial role in the treatment of 40 percent of patients cured of their cancer [85]. The process of radiotherapy is complex and rapidly evolving with new equipment and technology as well as changes to clinical guidelines. There is a long history of documenting incidents and AEs related to system failures in technology and the radiotherapy treatment process. In radiotherapy, toxicity is dose related and AEs are to some extent expected, but not very often measured in a clinical setting. A systematic review by Shafiq et al. summarises that mild to moderate harm occurs to patients in 1500 per million-treatment courses and of them about 1.4 percent of patients were reported to have died due to radiation toxicity [86]. Nausea, diarrhoea, mucositis, dermatitis and fatigue are common temporary short-term AEs. Radiotherapy can also induce chronic changes in non-proliferating normal tissues, with fibrosis being the typical example. The potential late toxicities depend upon anatomic region, volume of tissue irradiated, dose and use of concurrent chemotherapy. Examples of frequently occurring long-term AEs are cognitive dysfunction, lung fibrosis, bowel dysfunction, incontinence and hypothyroidism increasing morbidity in cancer patients. Modern techniques such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy and proton therapy can reduce the incidence and severity of both short term and late toxicities [80].

1.4.3 Cancer surgery

In a Swedish national study, hospital acquired infections and surgical/other invasive procedures were the most common AEs in surgical care, accounting for more than half of the admissions with AEs [30]. Post-operative wound infections were the most common hospital acquired infection. Among specific surgical AEs, reoperation was the most common (32 %), followed by organ laceration (18 %), postoperative haemorrhage or hematoma not requiring reoperation (16 %). More than 60 percent of all surgical AEs were considered preventable [87]. Anderson et al. found that the overall most frequent AEs after cancer surgery were wound problems, genitourinary, cardiovascular and gastrointestinal complications [29].

1.4.4 Other safety hazards

A single-minded focus on cancer treatment toxicities may fail to recognise other AEs related to the diagnostic process, general care and palliative care that can occur throughout the continuum of cancer care.

Deaths occurring within 30 days of chemotherapy are increasingly recognised as an indicator of quality in cancer care [88]. In general, anticancer treatment given in this late phase of the disease rarely benefits the patient, and may even hasten death [89–91]. A systematic review of the efficacy and safety of anticancer treatment compared to palliative care found no difference in overall survival and significantly more severe AEs among patients with an estimated survival of less than 6 months [92]. Patients receiving anticancer treatment had significantly higher incidence of severe levels of fatigue, nausea/vomiting, mucositis, neuropathy and myalgia leading to poor quality of life. Early integration of specialised palliative care alongside traditional cancer treatment has been shown to contribute to better oncology care for patients and families, in terms of better symptom management, quality of life, satisfaction with care and less psychological distress [93]. Based on this, the underuse of palliative care, may in it self represent a failure to provide the best standards of care for cancer patients with advanced disease.

1.5 Measurement of adverse events

Key messages:
- Good and reliable measurements are the foundation from which to advance quality improvement.
- Different measurement methods identify different AEs and each method has its strengths and limitations.
- The Global Trigger Tool provides an easy-to-use method for identifying AEs and measuring the rate of AEs.
- The GTT method is not specific enough for cancer patients, raising a need for a more

After nearly two decades, accurate and reliable measurements of AEs remain a major challenge for the patient safety field [6, 7, 94]. Measuring AEs is more difficult than measuring many other health care processes or outcomes. This is partly because AEs needs to be understood in the context of the complex systems within which they occur. An AE is usually the result of numerous latent system factors in addition to more manifest clinical factors affecting the process of treatment and care of a patient. Latent system factors such as, for example poor patient flow and inadequate staffing, are difficult to measure because they occur over a broad time frame and space, and may exist for long

periods before they lead to a more apparent AE directly related to patient care. Active clinical factors can be omission or commission affecting processes related to treatment or care of the patient (such as administration of the wrong dose of a medication) and are easier to measure because they are limited in time and space [95]. Different measuring methods vary in their precision, accuracy and ability to detect latent and active failures resulting in harm to patients. A comprehensive monitoring system for patient safety might include combinations of methods measuring both latent and active failures [95].

1.5.1 Different methods to measure adverse events

Many methods have been developed to detect AEs. A relatively easy way to is to utilise already available administrative data. Storesund et al. found that using ICD-10 codes to identify AEs in surgical patients overestimated the rate of AEs compared to rates found by the GTT method [96]. Another widely used method to measure AEs in healthcare is voluntary reporting. Incidence reporting systems detect only 2-8 percent of AEs detected using the GTT method and only 5 percent of the AEs detected by the GTT method were reported to a national repository for sentinel events [97]. A study from Denmark on patients with lung cancer compared safety information reported to national database with AEs found using the GTT method. Both methods had an equally good identification of specific surgical complications, but the GTT covers a broader spectrum of safety issues related to infections, other procedures, pain management and care in general than the national database [98]. Another study by Lipczak et al. comparing three different methods of measuring AEs in cancer patients finds that the methods complement each other and find different types of AEs. Healthcare personnel report treatment-related (chemotherapy, surgery, procedures and radiotherapy) AEs to the national registry. The GTT method uncovers mainly HAI and complications related to procedures and surgery, while patients report mainly on the clinical process related to diagnosis/assessment and communication [71]. The incidence of AEs varies markedly depending on the method used and no method seems to provide complete detection of AEs [99, 100]. Different methods identify different AEs and each method has its strengths and limitations, as seen in the overview provided in Table 2. It is therefore important to consider these strengths and limitations when choosing a method and often a combination of methods is recommended to obtain complete detection of AEs [6, 101].

Table 2 Strength and limitations of different methods to measure AEs

Measurement Method	Type of failure detected	Strengths	Limitations
Administrative data - *ICD-10 codes* - *Length of stay* - *Readmissions*	Mainly active failures	Utilizes readily available data, inexpensive. Routinely collected. Can screen big populations. Integrates multiple data sources.	Incomplete and inaccurate data. No clinical context.
Incidence reporting - *Local and national databases*	Latent system failures and active clinical failures	Part of routine. Provide multiple detailed perspective over time. Can identify rare AEs.	Underreporting. Reporting and hindsight bias. Difficult to generalise. Timeliness.
Malpractice claims	Latent system failures and active clinical failures	Provide multiple perspectives.	Reporting and hindsight bias. Non-standardised data.
Patient reported outcome measures (PROMs)	Latent system failures and active clinical failures	Patient experience, different perspective	Reporting and hindsight bias. Need of standardised and relevant instruments to measure.
Retrospective Record Review - *Full chart review* - *HMPS*	Mainly active clinical failures	Quicker, cheaper and easier than prospective studies.	Information bias in medical records and hindsight bias. Reliability concerns. Resource extensive. Risk of selection bias. Subject to confounding factors.
Trigger tools - *GTT*	Mainly active clinical failures	Regular update on data.	Information bias in medical records and hindsight bias. Reliability concerns. Excludes omission and preventability. Limited review time.
Observation of patient care - *Direct observation* - *Filming*	Active clinical failures	Potentially accurate and precise. Provides data otherwise unavailable. Detailed information. Prospective.	Difficult to train observers. Observation modifies behaviour. Expensive. Confidentiality concern. Not good for detecting latent system failures.
Clinical surveillance - *Clinical registry data*	Active clinical failures	Potentially accurate and precise for rates of AEs. Prospective. Timely feedback.	Incomplete and inaccurate data. Expensive. Latency in data reporting. Not good for detecting latent system failures.

1.5.2 Retrospective record review using triggers

The retrospective record review (RRR) obtains data from patient journals to answer clinical queries. It is a commonly used methodology in healthcare research and quality assessment of AEs. Yet, performing a full retrospective record review of all information included in a patient journal can be very cumbersome, time consuming and costly. RRR using triggers provides a structured approach to identify AEs and involves the application of different criteria or triggers to guide the medical record review process. A trigger can be defined as a "clue" or "flag" that "triggers" further investigation to determine the presence or absence of an AE. Trigger tools potentially enable the review process to be more efficient than a full chart review. The two most widely used structured RRR methods using criteria or triggers to identify AEs are the Harvard Medical Practice study (HMPS) and the IHI GTT method. While the HMPS was designed as a RRR method for researchers, the GTT method was primarily designed as a quality improvement tool to be used in clinical practice. An analysis by Hogen et al. comparing seven methods of measuring AEs indicates that RRR has the potential to identify the largest number of AEs and provides the richest source of information concerning such incidents [55, 102].

1.5.3 The Global Trigger Tool

In 2003 The Institute for Healthcare Improvement developed the Global Trigger Tool (IHI GTT) to provide an easy-to-use method for accurately identifying AEs and measuring the rate of AEs over time [103]. The GTT method is a two-stage manual retrospective review of a random sample of inpatient hospital records using 54 triggers to identify AEs. A time frame of 20 minutes is set for the review of each patient record. With this limited time, it is unlikely that all AEs will be identified in larger records and the intent of the method was not to identify every single AE. Rather, it should allow for sufficient safety improvement in the hospital. Severity of the AEs is categorised according to an adapted version of the NCC MERP index.

The Norwegian version is identical to the IHI GTT, except for minor changes to three triggers (Appendix II) [63, 104]. Figure 6 illustrates the review process of the Norwegian GTT method used in our research.

Table 3 GTT review process to detect AEs in patient journals
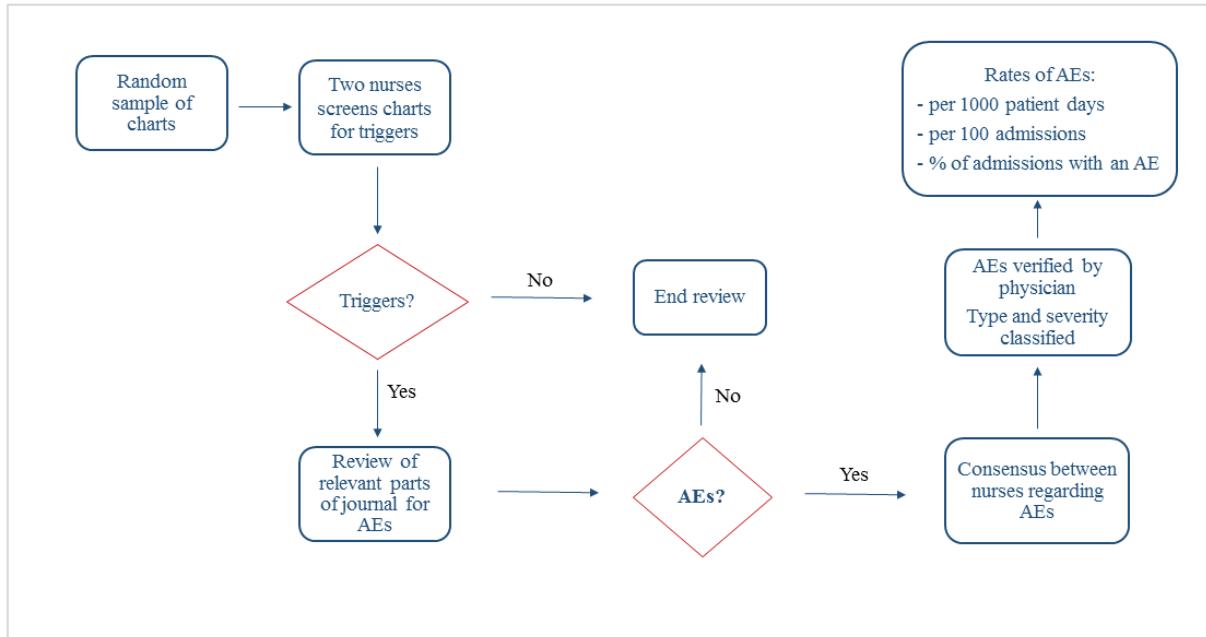
If it is uncertain whether an AE has occurred, the method recommends taking the viewpoint of the patient and asking; "Would I be happy if this happened to me?" This stresses that the patients` perspective should be emphasised when deciding whether the incident is an AE or not.

The GTT method is widely used in numerous healthcare organisations and countries all over the world [54, 55, 105]. The sensitivity and specificity of the method has proven very high compared with other methods for detecting AEs using an RRR approach [99, 106, 107]. While the original GTT method was developed for adult inpatients, it has since been modified for use in many different hospital specialties, deceased inpatients, primary care, nursing homes and even dental practices [55, 108]. This illustrates the adaptability of the method and that using the methodology in specific fields of healthcare can provide a more accurate and detailed information on AEs to use in further quality improvement.

1.5.4   Considerations using the Global Trigger Tool method

The IHI method has received criticism because it underestimates the true burden of harm because it does not detect diagnostic errors and errors of omission, or judge preventability. The IHI definition of an AE focuses only on those AEs related to active delivery of care (commission) and excludes issues related to substandard care (omission). The reason for not including omission of care, is that determining if substandard of care leads to an AE can requires detailed information on up to date best practice, and subjective judgment of this can affect the reliability of the measurement [103]. The problem with excluding omission is that it may not be possible from the level of detail in the medical

records to determine whether the AE was commission or omission. AEs associated with omission are noted as an important source of learning for improvement and should therefore perhaps be included [66].

The IHI definition also includes all AEs whether preventable or not, arguing that if an AE occurs it is always harmful to the patient. The GTT protocol states that there should be no attempt to measure preventability, as AEs which are unpreventable are only an innovation away from being preventable. IHI argues that if the definition of AEs constantly changes depending on what is deemed preventable, any measure over time would become meaningless [103]. Studies of preventability show large variations, and there are great challenges associated with subjective judgment of preventability and variations in how this is measured [54, 109, 110].

It must be acknowledged that retrospective record review methodology using triggers is also at risk of bias that could lead to over- or underestimation of AEs. Contextual factors within healthcare systems, such as variation in the quality and methods of medical and patient record documentation across countries and hospitals, might be a key information bias leading to variation in AE detection. Most hospitals in high- and middle-income countries now use electronic patient records to document medical practice, but the quality and structure of the documentation may vary considerably. It is only possible to review what has been documented and lack of documentation may pose a limitation. Hindsight bias is another limitation using RRR methodology. Hindsight bias is the influence of knowing the outcome and its severity on the judgement of causation [111]. This can be present in all types of retrospective record review, but especially if the outcome in known to be severe or result in death, a hindsight bias may result in a more critical review leading to overestimation of AEs.

1.5.5 Trigger Tools in oncology

Lipczak et al. published one of the first studies using the GTT method to search a disease specific knowledge in cancer care. They found the GTT method not specific enough for cancer patients, where hazards are related to specific treatments such as chemotherapy and radiotherapy in addition to general hazards [98]. The IHI GTT includes 31 triggers unrelated to oncology and 11 that could possibly be adapted to the field [23]. The use of the GTT to monitor patient safety in cancer care is also limited by the fact that it is a generic tool specifically focusing on hospitalised patients, while most cancer treatments are delivered in an outpatient setting [71].

As part of the 1000 lives campaign in Wales, Velindre Cancer Centre developed an oncology specific addition to the UK Global trigger Tool. They added 17 cancer specific triggers with the aim of achieving a more specific identification of AEs experienced by patients treated for cancer. [112]. Each of the 17 triggers had a definition with the relevant CTCAE grading system included to differentiate what was considered an AE. Examples of specific cancer-related triggers are mucositis, constipation, aspiration, neutropenia and extravasation.

Mattsson et al. evaluated the additional value by adding this oncology module to the general IHI GTT and found no significant difference between the review methods [113]. Most likely this is explained by the measurement properties of the method and moderate inter-rater agreement between the review teams. They found the same total number of AEs but only one-third of these were identical events. The oncology module identified AEs related to dysphagia, diarrhoea and constipation not identified by the general module, indicating that oncology triggers may identify specific types of AEs related to oncology treatment not identified by general triggers.

Hébert et al. developed another oncology specific trigger tool measuring ADEs guided by flowcharts and standardised grades of harm. An expert panel constructed the flowcharts using international guidelines, good clinical practices and local recommendations [23]. They ended up with a total of 25 triggers, where each trigger had its own ADE analysis flowchart describing the criteria needed to confirm or reject ADE occurrence. This reduced the inter-rater variability and produced a robust oncology medication focused trigger tool, which on testing yielded a high rate of ADEs.

Recently Lipitz-Snyderman et al. developed a cancer specific trigger tool that identifies AEs occurring in ambulatory and inpatient settings during the whole continuum of cancer care [114][115]. The final modified trigger tool includes 49 triggers or readily identifiable clinical indications of potential harm. The overall positive predictive value of the triggers was 0.48, with great differences in performance between the triggers. The sensitivity of the medical record review using this tool was estimated to be 92 percent compared with the gold standard of combining confirmed AEs from medical record reviews and incidents reported to the local reporting database. The ultimate objective is to optimise the tool`s efficiency by creating automated real-time AE detection and mitigation algorithms [115, 116].

2 Aims of the thesis

The overall aims of this thesis are to determine the rates, severity and types of AEs in hospitalised cancer patients compared to other patients and to elucidate how AEs can be used as a clinically relevant measure of quality and safety in cancer care.

The specific objectives are:

Paper I

To investigate whether cancer patients have a higher risk of AEs compared to a general hospital population as documented by the IHI Global Trigger Tool.

Paper II

To investigate the contribution of severe AEs to death in hospitalised patients and clarify methodological challenges using the Global Trigger Tool method on all inpatient deaths compared to a sample of general hospitalised patients.

Paper III

To investigate the association between anticancer treatment given during the last 30 days of life and AEs contributing to death and elucidate how AEs can be used as a clinically relevant measure of quality and safety in end-of-life cancer care.

3 Material and methods

Key messages:
- Since 2010, it has been mandatory for all Norwegian hospitals to review AEs using the GTT method.
- All our studies are retrospective cohort studies using the GTT method to assess rates, severity and types of AEs.
- In addition to systematic bias, other causes of variation such as case mix, use of denominators, sampling and sample size should be considered explaining differences in rates of AEs.
- Poisson regression or Negative binominal regression was applied to compare rates of AEs, severity level and types of AEs

3.1 Setting

All three studies were conducted at Nordland Hospital Trust in Northern Norway. The trust has three somatic hospitals: one central hospital and two smaller district general hospitals with 524 beds in total and provides healthcare to a population of approximately 136 000 inhabitants. Cancer patients are treated and hospitalised in all three hospitals and accounted for a stable rate of 11 percent of admissions during the study period between 2010 and 2013. Only the central hospital has a separate oncology-, haematology department and specialised unit for palliative care. All three hospitals provide ambulatory chemotherapy, while palliative radiotherapy and most cancer surgery is performed at the central hospital. None of the hospitals has a separate oncological inpatient unit. Accordingly, specialists in fields other than oncology retain the everyday medical responsibility for cancer patients when they are admitted to hospital.

3.2 Study design

All three studies are observational. We collected data retrospectively on different cohorts of hospitalised patients to observe the incidence rate of adverse events. An advantage with cohort studies is that they can examine various outcome variables and permit calculation of the effect of each variable on the probability of developing the outcome of interest [117]. The major disadvantage of cohort studies is the impossibility of controlling for all confounding factors that might differ between the groups [117].

Observational studies are often used to investigate the cause of diseases, but also have a role in healthcare research looking into the benefits and harms of medical treatment [118]. Observational studies can be carried out either prospectively (from the present time into the future) or retrospectively (look to the past to examine outcomes). Prospective design has been ranked higher in the hierarchy of evidence than a retrospective design [119]. The advantage of a prospective cohort study is the accuracy of data collection with regard to exposures, confounders, and outcome. However, prospective studies are often expensive and time-consuming because of a usually long follow-up period. They also have a potential failure with follow up. Retrospective cohorts, on the other hand, are often cheaper and quicker as the data are already collected, but there is a risk of missing relevant information since the data was collected for other reasons [120].

A study by Michel et al. comparing three observational methods' (cross sectional, prospective cohort and retrospective cohort) ability to identify AEs found similar rates of AEs by means of the prospective and retrospective cohort, while the point prevalence obtained by the cross sectional method was about one third of the two other methods [121]. This equal ability to identify rates of AEs indicates that the use of retrospective cohort studies is suitable to assessing rates of AEs in healthcare research in a cost and time effective manner.

Practicality and feasibility inherent in the study design typically dictate whether a cohort study or a case-control study is appropriate [122]. All our studies are retrospective cohort studies since we at the start of the studies did not know the outcome status (rate of AEs) of the different subjects included. Figure 7 illustrates the study design for retrospective cohort studies used to investigate rates of AEs. Since retrospective cohort studies are often influenced by different confounding factors the aim is to evaluate associations and not causality between outcome and exposures. Even so, using Beverly Hills criteria of causation can provide an epidemiological approach to imputing causality in quality improvement initiatives and research [123].
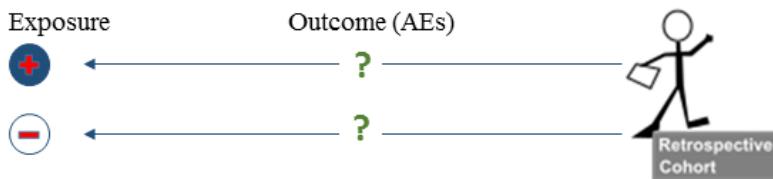
Figure 6 Illustration of retrospective cohort study design used to investigate rates of AEs.

To ensure high-quality methodological rigor many journals recommend using STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) in reporting the results of observational studies [118, 124]. The STROBE guidelines provide a checklist for observational studies and are also recommended for retrospective record reviewing studies to ensure high quality [125]. The STROBE guidelines where followed in writing all three papers.

3.3 Method

In 2010, The Norwegian Ministry of Health and Care Services mandated all hospitals to review a minimum of 20 randomly selected medical records per month using the Norwegian version of the IHI GTT [104]. This initiative was part of a planned national safety campaign aimed at reducing harmful events to patients and increasing the focus on patient safety in hospitals.

To achieve more accurate measurement and better support for local improvement initiatives, Nordland Hospital Trust chose from the start to review 140 records monthly [68]. The first three years this was done as a standard manual review of the electronic health record. By 2013, the health trust developed and implemented a modified GTT method where triggers are automatically identified and only records with triggers are reviewed manually to determine if the triggers represent an AE [126]. The review of all three studies was done manually and conducted according to the Norwegian version of the IHI GTT [63].

At the time of our research, the UK Global Trigger Tool was the only oncology-specific trigger tool developed and we used a modified version of this reviewing cancer patients in Papers II and III [112]. In our modified version, we ended up with 21 oncology specific triggers. In addition to the triggers included by Velindre Cancer Centre, we added another 4 triggers; hyperkalaemia, neuropathy, allergic- and anaphylactic reaction. These triggers are included in the general UK GTT but not in the IHI GTT. They were added since we found them relevant to oncology. An overview of all triggers is presented in Appendix III.

For the oncology triggers we used the CTCAE definitions and classifications to identify if harm had occurred to the patient before we assessed the severity of the AE using the adapted NCC MERP index. When combining the use of these two reporting systems we see that CTCAE grade 3-5, is always consistent with AEs according to the NCC MERP index. The intention in using the CTCAE grading as part of the assessment was to standardise the process and what was considered an AE.

Table 4 Example of oncology trigger "O4 Diarrhea"

Diarrhea	Grade 1	Grade 2 Severity E	Grade 3 Severity F	Grade 4 Severity H	Grade 5 Severity I
A disorder characterised by an increase in frequency and/or loose or watery bowel movements.	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

In Paper I, seven different teams in the health trust made the retrospective review of records routinely. Patients under the age of 18 years, admitted for less than 24 hours and admitted for rehabilitation or psychiatric care were excluded, since triggers are not developed for these areas. For our study, we gathered these data into a complete database of 6720 reviews performed between January 1st 2010 and December 31st 2013. Cancer patients were reviewed together with the other patients and separated afterwards for the study.
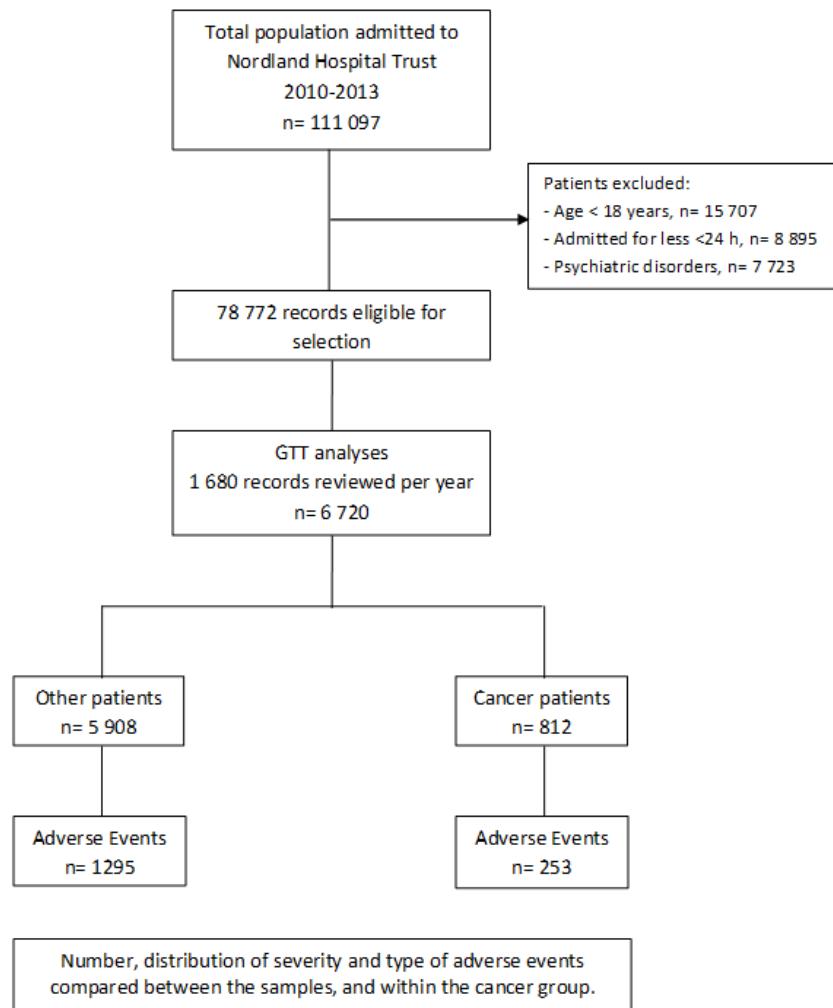
Figure 7 Flowchart of study design and population in Paper I

In Paper II, the retrospective review of the 1 680 general patient records was done as in Paper I. All 377 patients who died in our three hospitals during 2013 were included in the inpatient death sample. An independent team consisting of two nurses and one physician did the review during six months in 2015. The review was done in the same way as the general sample, but the physician reached consensus together with the nurses. To validate the results, we added another step to the process, where two other physicians independently re-reviewed the records of AEs contributing to death, and agreed/disagreed on the AE, severity and type of harm. Finally, the physician from the primary review team and the verifying physicians discussed the findings and reached consensus.
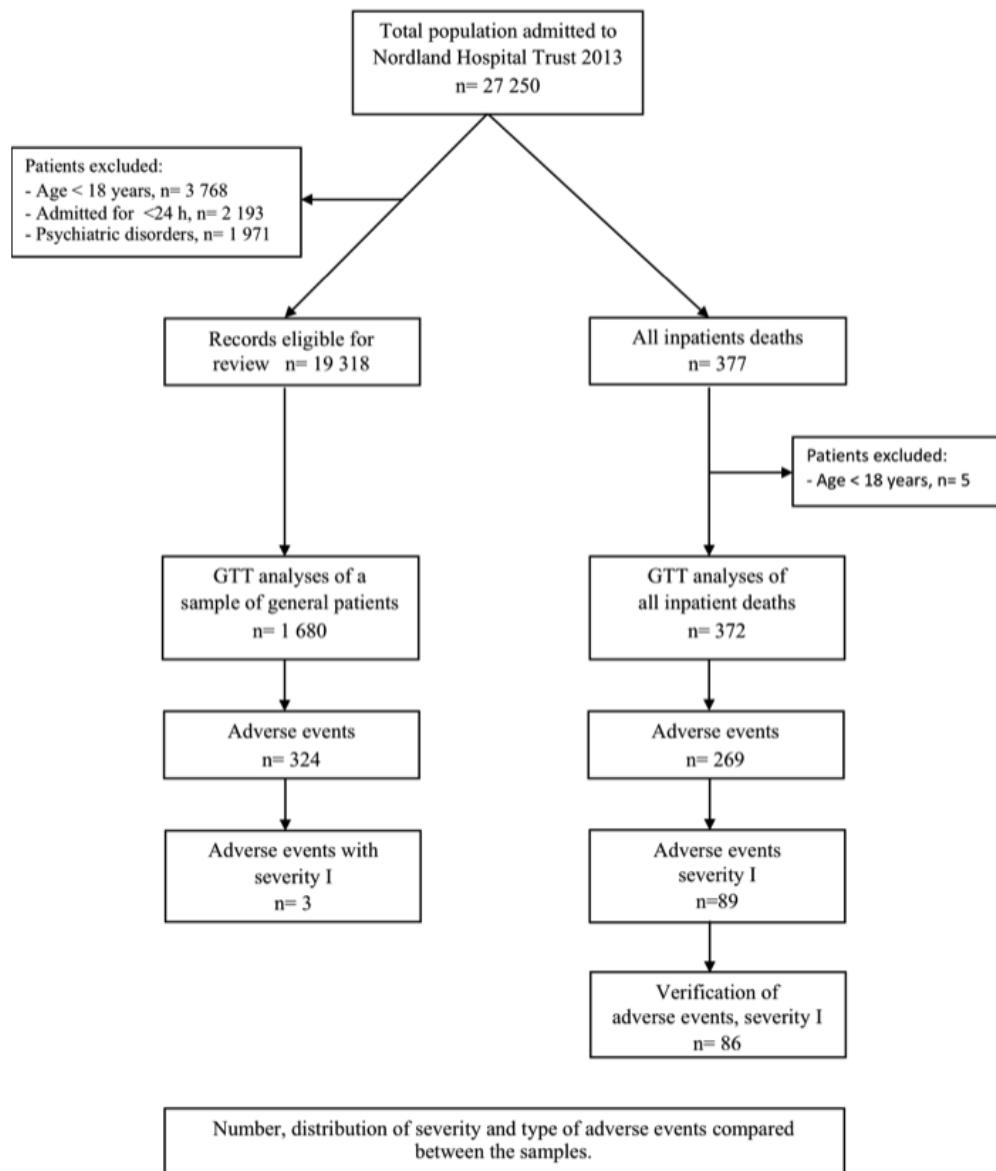
Figure 8 Flowchart of study design and population in Paper II

Paper III includes 247 cancer patients who died during hospitalisation in 2012 and 2013 at our three hospitals. Two oncology nurses and one oncologist did the review during six months in 2015. All cancer patients were reviewed together before they were divided into two groups; one group that had received any kind of anticancer treatment during the last 30 days of life and a second group that had not received any treatment. Also, in this study, we added a last step to the process to validate our results, where two different physicians independently re-reviewed the records of AEs contributing to death and confirmed/rejected the AE, severity and type of harm.
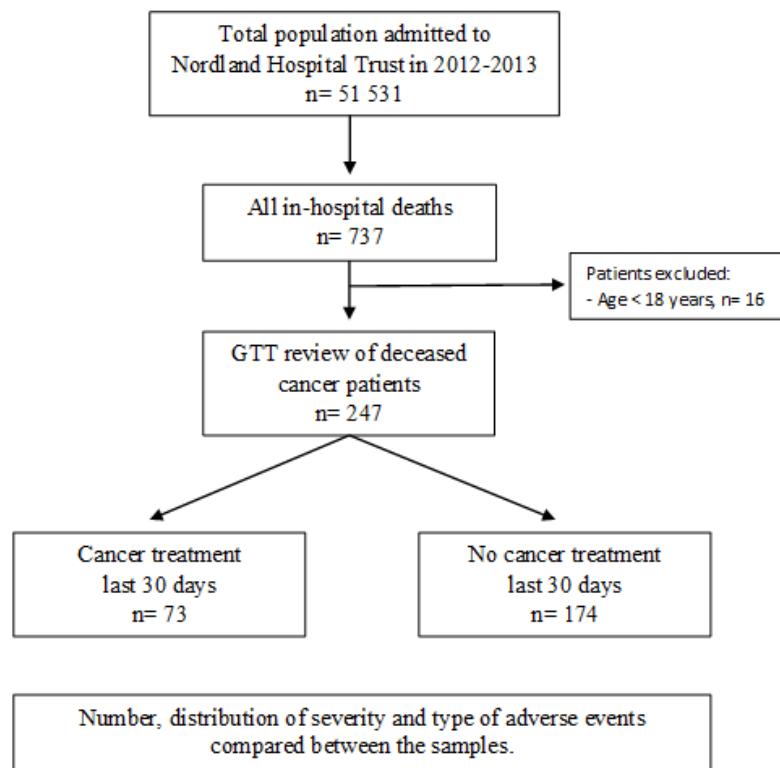
Figure 9 Flowchart of study design and population in Paper III

3.4 Methodological considerations

All measurements may be subject to some degree of systematic measurement error and therefore result in the introduction of bias into the study. Bias related to retrospective record reviewing and use of the trigger tool referred to in 1.5.1 could be present in all three studies. Especially, information bias may occur in all three papers since the identification of AEs relies on what is documented in the patient records. In Paper I seven different teams did the review, the subjective judgment of what is considered an AE, and the severity is more likely to vary both individually and between the teams. In Papers II and III hindsight bias is more likely to occur since the reviewers knew the outcome, i.e. death for the deceased patients. In addition to systematic bias, other causes of variation such as case-mix adjustments, sampling, sample size, the validity and reliability must be considered in explaining differences in rates of AEs.

3.4.1 Case mix adjustment

Patient characteristics such as age, co-morbidities or disease severity are independently associated with incidence of AEs [100]. Differences in specialities, complexity of procedures and services provided at different healthcare institutions also affect the incidence of AEs [55, 127, 128]. When characteristics differ between the groups it may result in different rates of AEs related to the exposure. This can cause over- or under-estimation of the true association and may even change the direction of the effect. The GTT method is a measurement tool for quality improvement and does not recommend case-mix adjustment. When using this method for research, confounding factors must be adjusted for before looking at the outcome-exposure relationship between different groups of patients. Case-mix adjustment is also essential when comparing rates of AEs across healthcare organisations with different patient populations.

Therefore, in our statistical analyses, we included and adjusted for generally acknowledged case-mix variables in patient safety and cancer care (age, gender, length of stay, hospital, department, type of admission, primary malignancy and setting in cancer care). A limitation in all our studies is minimal adjustment for comorbidities. We only adjusted for other diseases using primary and secondary diagnosis on discharge instead of a more thoroughly assessment using the Charlson comorbidity index.

3.4.2 Denominators

Rates, ratios and percentages are used to present and compare data in a meaningful way. The choice of denominator used in the calculation of rates will have a substantial impact on the outcome of such analyses be it admissions, bed days or particular healthcare processes. The rate of AEs will vary depending on the denominator chosen [129]. The GTT methodology recommends three ways to present data on AEs:

- % of admissions with an AE
- % rate of AEs per admission
- Rate of AEs per 1 000 patient days

The two first present AEs as the percentage of patients admitted to the hospital during a defined period and being at risk of AEs. This also tells us what patients and healthcare personnel experience and provides a more easily understood representation of AEs. Percentage of admissions with an AE diminishes the number of events because some patients may have more than one AE during a hospital stay. It is therefore less sensitive to change than the two other rate measurements (IHI GTT). Major disadvantages using proportion/percentage are that it ignores variations of interest among patients, such as age, length of stay, severity of conditions and comorbidity. AEs per 1 000 patient days is the traditional measure and is the recommended measure to track the rate of AEs over time. Length of stay can be extracted automatically from administrative data and is a recognised indicator for efficiency in healthcare [130, 131]. There is a risk of underestimating length of stay using automatic extraction from administrative data, since many systems register transfer between hospitals as separate admissions. From a patient perspective, length of stay should include all bed days from first admission to discharge, regardless of transfer between departments or hospitals. If not all patient days are included the denominator decreases and the rate of AE as a whole will increase, presenting a false high number of AEs per 1 000 patient days.

To make sure we used the correct number of days as a denominator we did a manual check of length of stay in Papers II and III. In Paper II we found 551 days difference between manual check and automatic extraction in the inpatient death sample, 3 504 days vs. 2 953 days. Calculating unadjusted rate of AEs per 1 000 patient days for all inpatient deaths we find a significant difference in rates of AEs between automatic extraction and manual check, 91.1 vs. 76.7 (p=0.04, RR 0.84, CI 95 % 0.712 – 0.998). In Paper III we find the same significant difference in rates of AEs per 1 000 patient days, automatic extraction 78.6 and manual extraction 64.8 (p=0.05, RR 0.82, CI 95 % 0.677- 1.00). This illustrates the importance of collecting the correct number of days when using length of stay as a denominator to avoid presenting false high numbers of AEs.

3.4.3 Classification by ICD-10

In Papers I and III cancer patients were identified by matching the patient ID number in the sample to primary or secondary C-diagnosis as classified by ICD-10 in the discharge lists of the hospitals. Cancer patients' accounted for a stable annual rate of 11 percent of admissions in the health trust during the study period. In Paper I, approximately 12 percent of the records included are cancer patients suggesting that this is a representative sample of the population of interest.

In Norway, it has been mandatory since 1999 for clinicians to code diseases on discharge according to the ICD system. Studies and administrative audits of coding in Norway have reported variable coding quality raising concern about the accuracy using this type of data extraction for research [132, 133]. Due to variation in coding practices, there is a risk of misclassification bias. This may lead to incorrect associations of the outcome and may either increase or decrease an observed association [134].

In Paper I we were not able to check the accuracy of coding practices for cancer diagnoses on discharge. In Papers II and III all records of deceased patients were checked, and we only found one patient in Paper II who was incorrectly categorised with cancer and all cancer patients were coded with a cancer diagnosis on discharge. Notification of new cancer diagnosis to the national cancer registry is mandatory in Norway. Whenever a clinician code a patient on discharge with a new C-diagnosis using the ICD-10, a notification is sent to the cancer registry. The registry also sends reminders to the clinicians three times a year to fill in this report [135]. This practice prevents misuse of the C-diagnosis and increases the accuracy of coding practices for cancer. We therefore argue that identification of cancer patients based on primary and secondary C-diagnosis by the ICD-10 system in our papers is reliable and accurate with a low probability of misclassification bias.

3.4.4 Sampling

Normally, it would be impractical to collect all data on whole populations, so sampling is a method that allows researchers to get information about a population based on results from a subset of the chosen population. It is important that the individuals selected are representative of the whole population of interest. The IHI GTT method recommends random sampling of 10 patient records every two weeks from the entire population of discharged adult patients. Data from such small samples may show wide variation from sample to sample [68], and the intent of the method is not to measure all types of AEs, but to provide useful information about trends and special cause variation in AEs in an organisation and enhance improvement [103].

In Paper I, stratified random sampling was used to select records for review. Since improvement efforts to reduce harm require focused efforts in specific areas, our health care trust decided to stratify the information gathered by seven functional units (surgery, orthopaedics, internal medicine, gynaecology/obstetrics, neurology/others and the district hospitals of Lofoten and Vesterålen). A systematic random sample of 10 patient records every two week was included from the discharge list of these seven units in the health trust. This ensures that the sample contains approximately the same proportion of the specified criterion as in the study population. At the same time, it should be acknowledged that random sampling might miss rare AEs.

In Papera II and III we included all deceased patients and deceased cancer patients in our three hospitals over a set period of time. Including all patients avoids the sampling bias of excluding certain individuals. Even if we were able to select data on a whole study population, it is important to keep in mind that the study population may still be inherently different from the target population. For example, cancer patients who die in hospitals are not necessarily representative of all cancer patients dying in this region or the country. There may be differences in the severity of the cancer disease or demographics of the patients depending on the type of health care facility, region or country. Hence, it is not advisable to generalise the results from a single hospital-based study to all patients, a region or country [136].

3.4.5 Sample size

A sample must be of a certain size in order to have the required degree of accuracy in the results and identify any significant differences or association that can be present in the study population. A power analysis is often used to determine the sample size. Power refers to the probability that our review will detect a real effect if it is present and is normally set to at least 80 percent. For all our papers, the null hypothesis is that there is no difference in rates of AEs between the mean of the two cohorts, and the aim of the studies is to reject this null hypothesis. If we think there is a difference, when in fact it is just due to chance sampling variation, we have false positive result or Type I error. Type I errors are controlled by choosing the significance level, normally 5 percent. Conversely, if we fail to find a true difference, we have a false negative result known as a Type II error. Controlling Type II errors is more difficult as it depends on difference between the means of the groups, the variation among included patients (SD) and the sample size. Studies with larger samples have greater power, but also differences in the mean of the outcome is important [137–139].

For Paper I, the review of 6720 patient records (5908 general patients and 812 cancer patients) was already performed routinely during 2010-2013 and available to be included in the analyses. Previously published GTT studies indicate incidence of AE rates of 15 percent for general patients and studies of cancer patients indicate incidence rates of AEs of 20 percent [98, 113]. The significance level was set to 0.05. This gives the study a good power of 94.3 percent ability to detect a difference between the two groups.

In Paper II, we made a sample size estimation based on previous studies indicating that general hospitalised patients experience 15 percent incidence rates of AEs and deceased patients seem to experience AEs twice as often (30 percent) [140]. The significance level was set to 0.05 and the power was set to 90 percent. The enrolment ratio was set to 0.2 since the standard GTT includes 140 patient records per month and 30 patients' died in the hospitals every month on average. The minimum number of patient records to be included was estimated to be 459 general records and 92 deceased patients. Since the patient records in the general sample already were reviewed, and we had the resources and time, we decided to increase the sample size to include all 1680 records reviewed during one year in the general sample and all deceased patients during the same year, approximately 360 patients.

In Paper III, we found no previous studies indicating incidence rates of AEs contributing to death in cancer patients receiving active cancer treatment during the last 30 days of life. For a pilot study, calculating sample size a priori to the study is challenging. We therefore did a consecutive sampling of all cancer patients who died in the three hospitals between January 1st 2012 and December 31st 2013, and ended up with 247 deceased cancer patients in total. During this period, 73 patients received active cancer treatment and 174 patients did not receive any cancer treatment during last 30 days of life. The study revealed an incidence of 33 vs. 18 percent in the two groups. With a significance level set to 0.05 a post-hoc analysis, identified a power of 71.8 percent. This means that the study has a 28 percent risk of not detecting a difference between the groups when a difference actually exists. This is lower than the desirable power of 80 percent. To achieve 80 percent, we would have needed to increase the sample size by 59 patients, to 306 patients in total. As an alternative to post-hoc power, analysis of the width and magnitude of the 95 percent confidence interval (95% CI) may be a more appropriate method of determining statistical power.

3.4.6 Validity

Measurements should be both precise (free of random measurement error) and accurate (free of systematic measurement error). Precise or consistent can be used as synonyms for reliable, and accurate as a synonym for valid. Reliability and validity are closely related [141]. Figure 11 illustrates the correlation between reliability and validity as measurement properties.
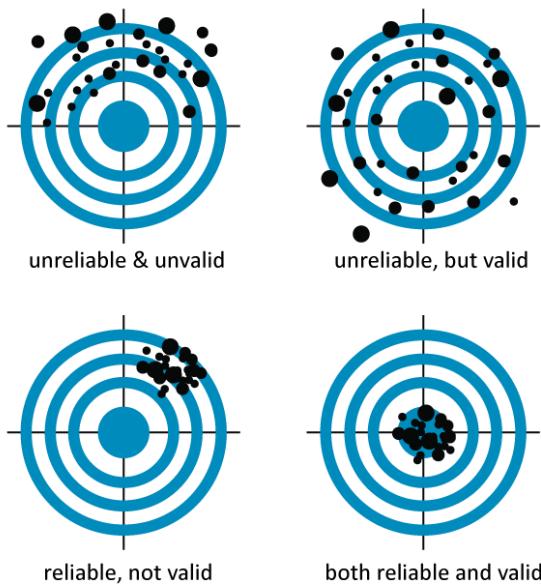
Figure 10 Correlation between reliability and validity as measurement properties.

Validity refers to the accuracy of a measurement, the extent to which the method measures what it is supposed to measure [141]. If research has high validity it means it produces results that reflect the real situation. There are four categories of validity that need to be considered in measuring AEs; face-, construct-, content- and criterion validity.

Table 5 Assessing the validity of the GTT method

Type of validity	What does it assess?	Validity of the GTT method
Face	The acceptability amongst users and experts that the method is an adequate reflection of the AEs to be measured.	The GTT method is the most common method used all over the world to measure AEs [54, 56, 67] and promoted as the best available single method to determine rates of AEs in health care settings [142, 143].
Construct	The degree to which a method measures what it is supposed to measure.	The method has high sensitivity of 94.9 % in detecting at least one AE and a specificity of 100 % to detect no AEs [100].
Content	The extent to which the measurement covers all aspects of AEs.	Concerns are raised about the ability of the general GTT method to detect all types of AEs in certain specialties (cancer, intensive care, paediatrics) [113, 144]. More specific trigger tools have therefore been developed for some specialties [108, 115, 145].
Criterion	The extent the results of the measure correspond to other valid measures of AEs.	Different methods identify different AEs c.f. 1.5.1. Compared to the GTT method ICD-coding overestimates AEs [96], incidence reporting and malpractice claims identify fewer AEs [97, 99, 146], registry data covers a different spectrum of AEs [71], observational studies identify incidence of AEs [147].

The validity of a study is determinedl largely by the research design, and to assess the validity we need to consider internal validity and external validity. Internal validity refers to the degree of confidence that the exposure - outcome relationship being tested is trustworthy and not influenced by other factors or variables. To ensure internal validity in our three papers measuring AEs we found the GTT method the most appropriate. An important consideration in choosing this method is the definition of an AE emphasising the patient's perspective. The definition for harm includes all physical injury contributed to by medical care, even if it just required monitoring or treatment, and gives the method greater construct validity than other available review methods requiring harm to prolong hospitalisation. The method has high face validity and is the mandatory recommended method to use in identifying AEs in Norwegian hospitals. Compared to other available methods, the GTT method is regarded as the best single method of determining rates of AEs in hospitalised patients [142]. It is thoroughly researched

regarding strengths and limitations and having these in mind when constructing our studies, we were confident that choosing the GTT method would provide us with reasonable internal validity measuring AEs in hospitalised patients.

External validity refers to the extent to which results from a study can be generalised to other situations or groups of patients. To produce valid generalisable results in our three studies we had to ensure enough participants and that they were representative of the population we wanted to study. As described in 3.3.5, sample size and power estimates where undertaken for all three papers. Papers II and III, include the whole population at risk since we included all deceased patients/cancer patients. All cancer patients, solid tumours and haematological malignancies were included to increase generalisability to all types of hospitalised cancer patients. By including all three available hospitals in a region of 136 000 inhabitants the generalisability of the papers is increased even further to all hospitalised cancer patients in Norway, in contrast to a single hospital study.

3.4.7 Reliability

Reliability refers to the consistency of a measurement and the extent to which the result can be reproduced using the same method under the same circumstances [148]. Reliability is a major consideration in studies of quality, where much depends on judgment of standards of care. There are three types of reliability: test-retest, inter-rater and internal consistency.

Table 6 Assessing the reliability of the GTT method

Type of reliability	What does it assess?	Reliability of the GTT method
Test-retest	The consistency of a measure across time. Do you get the same results when you repeat the measurement?	Innovation and improving standards of care alter conceptions of what is considered an AE and may change over time. Warning about using the method for benchmarking and comparison between departments and hospitals [149, 150].
Inter-rater (IRR)	The consistency of a measure across raters or observers. Do you get the same results when different people conduct the same measurement?	Criticised for limited agreement between review teams regarding what is considered an AE and severity level [149, 151, 152]. A systematic review indicates moderate to substantial IRR with a pooled $\kappa=0.65$ [56]. IRR increases when using small groups of reviewers, consistency in teams, experience in reviewing, training and a structured review process [56, 68, 99, 109, 152].
Internal	The consistency of the measurement itself. Do you get the same results from different parts of a test that are designed to measure the same thing?	Not relevant for the GTT method since it is a single-item test only measuring AEs and no other variable.

In Paper II we were able to assess the inter-rater reliability between the samples, since 33 patients in the deceased sample were already reviewed in the general sample. The review of general patients by seven different teams found eight AEs, where three of them contributed to death. Review of the inpatient death sample found 26 AEs, where 12 of them contributed to death. Using Cohen`s kappa to determining the inter-rater reliability in rates of AEs between the general sample and the inpatient death sample there was fair agreement between the reviewers' judgements, $\kappa = .231$ (p=0.07). For the three matching AEs contributing to death, the agreement is in reality only one. One of the deceased patients died after discharge and was not included in the inpatient death sample. One other AE was not considered to contribute to death in the inpatient review sample. A majority of the disagreements are identified at the district hospitals in Lofoten and Vesterålen. It seems as if this fair inter-rater agreement is due to underreporting of AEs in the general sample, reviewed by seven different teams. This is similar to findings from other studies identifying that consistency between teams is considerably more difficult to ensure when the review process is decentralised into local clinical areas across the institution [153]. An increase in the number of reviewers has also been shown to reduce the consistency in utilisation of the definition of an AE. In addition, the definition seems to mitigate through time with a tendency to change according to the focus areas and experience of the review team. This enhances the importance of a good standardised training process, and consistency when team members change [154]. It also emphasises the need for quality assurance by a centralised, experienced reviewer when the review process is decentralised into local clinics across an institution

To ensure higher levels of reliability in our papers we have made a number of adjustments. To increase the consistency of the assessment, all team members had received the same training using the GTT method. The training included theory, identical practical review exercises and debrief sessions as recommended by IHI [103]. To ensure consistent use of the method a standardised GTT manual and reporting sheets were used to guide the review process. For the oncology triggers used in Paper II and III additional guidelines using CTCAE classification were used to identify and grade the severity of an AE. In Papers II and III, we used a small team of three reviewers with clinical experience in oncology. The review process was slightly altered in Papers II and III to include discussion between all reviewers before reaching agreement on AEs and level of severity. This was done since collaboration and discussion between reviewers have proven to significantly improve the agreement between teams [151, 155]. When a team works together closely for a long time, there is a risk of overestimation in their ratings. To control for this possible bias we added another step to the review process of Papers II and III, where two independent physicians reviewed and discussed the most severe AEs contributing to death once more before consensus was reached. Consistent agreement in this step supports that our results in deceased patients in Papers II and III are reliable. Making these adjustments to the GTT method, we argue that we have increased both the validity and reliability of the method and our results.

3.5 Statistical analyses

Poisson regression or Negative binominal regression in Generalised linear models was applied to compare rates of AEs, severity level and types of AEs expressed as counts between the different samples. Which one of these was most appropriate depends on whether the counts follow a Poisson distribution, where the mean and the variance of the counts are equal. In Paper I, we had an unbalanced group size (general patients 88 percent and cancer patients 12 percent) and an excess of zero AEs resulting in overdispersion, where the variance is greater than the mean. For overdispersed data, we chose to use Negative Binominal distribution since it has an additional parameter that models for the variance [156, 157]. In Paper II and III the samples sizes are more balanced and the incidence of AEs is higher resulting in approximately equal values of the mean and variance, and the data fulfilled all five assumptions using Poisson regression. Logarithm of patient days was used as offset variable to compare rates per 1 000 patient days. For admissions with AEs the offset variable was set to a fixed value of zero. Adjustment for demographic variables was done by including them as covariates. Incidence rate ratio (IRR) was obtained as a relative measure of the effect and approximated the relative risk or the odds ratio if the occurrences are rare.

In Paper III we used Binary logistic regression to analyse whether AEs were significantly associated with use of anticancer treatment during the last 30 days of life. AEs contributing to death were set as the dependent variable (dichotomous yes/no) and treatment given during last 30 days was set as a categorical independent variable. Based on previous knowledge about confounding factors for AEs and by assessing which variables were a potential confounder we build a model included length of stay, age, gender and primary malignancies as covariates. Both unadjusted and adjusted odds ratio (OR) were obtained as a measure of the effect treatment during the last 30 days of life had on AEs contributing to death.

Demographic variables were summarised using descriptive statistics. Statistical association between samples for non-parametric continuous variables was compared using the Mann-Whitney U, since data were not normally distributed and could not be transformed. Categorical variables were compared using Chi square, Fisher`s exact or Linear-by-Linear test, depending on the number of counts and type of outcome. For all analyses, we used two-sided tests and the significance level was set at 5 percent, reporting 95 % CI when relevant. The statistical analyses were performed using the IBM SPSS statistical package, version 23.0 - 25.0.

When performing statistical a test there is always a chance of committing a Type I error. It is also known as "false positive" and is the error of accepting the alternate hypothesis when the results can be attributed to chance. Type I error is generally reported as the p-value (significance level) and is traditionally set to 0.05 or 0.01 to minimize the possibility that the variation seen is due to chance.

When performing multiple testing, the chance of a rare event increases and the risk of committing Type I errors also increases. To reduce the probability of Type I errors the number of hypotheses tested together should be limited and the significance level can be reduced proportionally to the number of tests (Bonferroni correction) [158]. This was taken into considerations when performing the Binominal logistic regression in Paper III. Regardless of significance level, adjustment for other variables (age, length of stay etc.) increases the validity of our results.

3.6 Ethical consideration

The studies were performed in accordance with the Helsinki Declaration of 1975. The project proposal was submitted to the Regional Committee for Medical and Health Research Ethics in Norway (Protocol ID: 2013/1823). They categorised the purpose of the project as quality assurance, and therefore not requiring approval by the committee cf. The Health Research Act §9 and The Research Ethics Act § 4 [159].

The main argument from the committee is that the project does not generate new knowledge about health and disease. They refer to the guidelines for The Health Research Act chapter 2.4 where "quality assurance is defined as projects, investigations or evaluations with the purpose to control that diagnostics and treatment gives the intended results. Quality improvement work must be based on systematic documentation." Neither research nor quality assurance are unambiguous concepts and it can be difficult to determine what a project should be classified as [160]. There is great variation in the interpretation of research issues related to patient safety and WHO recommend that when in doubt, all projects should be submitted to the ethic committees to determine if approval is needed [161].

The project was approved by the Data Protection Office at Nordland Hospital Trust in 2013 in accordance with the Personal Data Act of April 2000 no. 31, allowing the Data Protection Office to approve research of limited scope. The information from the patient records was anonymised after extraction and included in databases. The databases and all other research material were hosted within an encrypted environment with restricted access granted only to involved research personnel.

Quality assurance work is mandatory according to the requirements of the Norwegian Health Specialised Service Act § 3-4 a, and in the Hospital Trust health information can be obtained from patient records without consent for such purpose in accordance with The Health Personnel Act § 26. Baker et al. suggests three guiding criteria to justify waiver of consent in quality improvement research [162]. First, the quality research must be of minimal risk and the disadvantages of not being informed are considered minimal. Confidentiality and safeguarding of sensitive data are also required. Secondly, collecting data should be part of the quality assurance work of the health trust. Thirdly, collecting informed consent from patients or relatives of deceased patients would be costly, time

consuming and might even be a burden or inconvenience for the patients/relatives. We regard that all these criteria were met in all three studies.

Since the purpose of our research is ultimately to improve patient safety, the results of our research have been reported back to the hospital leadership so that appropriate actions can be taken at the system level [161]. It has also been an ethical obligation towards the health trust to inform the leadership about the results before they were published, since they potentially could reveal sensitive information about the safety level of the institution.

4 Results

Key messages
- Cancer patients experience 39 percent more AEs compared to general patients.
- Length of stay and age are the main risk factor for experiencing an AE.
- Higher rates of AEs are identified in deceased patients.
- Patients receiving anticancer treatment during the last 30 days of life experienced nearly double the rate of AEs contributing to death compared to patients not receiving such treatment.
- Healthcare associated infections, surgical complications and medication harm are the most common AEs.

In this thesis, we examine differences in rates, severity and types of AEs in cancer care measured by the GTT method. Since the three papers are strongly connected, the results are presented by theme rather than separately for each paper. This also allows to more easily compare results across the three papers.

4.1 Patient characteristics

Patient characteristic in Papers I and II are almost the same, while deceased cancer patients included in Paper III have a longer length of stay, are older and more often male. Demographic variables for the 9 019 patients included in all three papers are presented in Table 7.

Table 7 Demographic variables

	Paper I	Paper II	Paper III
	n= 6 720	n= 2 052	n= 247
Mean length of stay, days (SD)	6.4 (7.4)	6.1 (7.5)	12.5 (12.7)
Mean age, years (SD)	61 (21.0)	62 (21.3)	73 (12.5)
Gender n (%)			
Female	4006 (60%)	1175 (57%)	96 (39%)
Male	2714 (40%)	877 (43%)	151 (61%)
Hospital n (%)			
Bodø	4800 (72%)	1427 (70%)	156 (63%)
Lofoten	960 (14%)	296 (14%)	33 (13%)
Vesterålen	960 (14%)	327 (16%)	58 (25%)
Department n (%)			
Internal medicine	1925 (29%)	744 (36%)	120 (49%)
Surgery	2747 (41%)	773 (38%)	116 (47%)
Gyn/Obst	1099 (16%)	276 (13%)	0 (0%)
Neurology	639 (9%)	168 (8%)	2 (0.5%)
Others	309 (5%)	90 (5%)	9 (3.5%)
Cancer patients n (%)	812 (12%)	311 (15%)	247 (100%)

Patient characteristics such as age, gender and length of stay are similar, except that deceased cancer patients included in Paper III have a longer length of stay. Cancer patients included in Papers I and II more often have surgery and are in a curative setting, while deceased cancer patients in Paper III are mainly in a palliative setting. Deceased cancer patients in Paper III received more systemic anticancer treatment. Comparison of characteristics for the 1 370 cancer patients included in all three papers is presented in Table 8.

Table 8 Characteristics of cancer patients

	Paper I n= 812	Paper II* n= 311	Paper III n= 247
Mean length of stay, days (SD)	8.4 (9.6)	8.1 (8.3)	12.5 (12.7)
Mean age, years (SD)	70 (13.0)	69 (13.1)	73 (12.5)
Gender n (%)			
Female	364 (45%)	136 (44%)	96 (39%)
Male	448 (55%)	175 (56%)	151 (61%)
Cancer categories n (%)			
Gastrointestinal	210 (26%)	99 (31%)	69 (28%)
Urinary and male genitalia	208 (26%)	51 (17%)	29 (12%)
Respiratory	95 (12%)	49 (16%)	60 (24%)
Lymphoma and hematology	85 (11%)	35 (11%)	39 (16%)
Breast and gyneacology	146 (18%)	35 (11%)	18 (7%)
Unknown origin and others	98 (12%)	42 (14%)	32 (13%)
Setting n (%)			
Diagnostic			40 (16%)
Curable	281 (35%)	80 (26%)	5 (2%)
Palliative	531 (65%)	231 (74%)	202 (82%)
Treatment n (%)			
Surgery	281 (35%)	75 (24%)	12 (5%)
Systemic anticancer	77 (9%)	58 (19%)	116 (47%)
Radiation	40 (5%)	21 (7%)	19 (8%)
None	414 (51%)	157 (50%)	100 (40%)

* Extracted afterwards for the thesis

4.2 Incidence of adverse events

The incidence of AEs in all three papers is presented in Table 9. Incidence is presented as unadjusted percentage of admissions with one or more AEs and unadjusted rates of AEs per 1 000 patient days.

Table 9 Incidence of AEs in all three papers

		Admissions with AEs		AEs per 1 000 patient days	
		Percent	CI 95%	Rate	CI 95 %
General patients	Paper I	17.4 %	16.3 - 18.6	36.0	34.1 - 38.0
	Paper II	16.3 %	14.4 - 18.3	36.5	32.7 - 40.7
Cancer patients	Paper I	24.2 %	20.7 - 28.2	37.1	32.8 - 42.0
	Paper II*	29.9 %	24.4 - 36.6	52.6	44.0 - 62.4
Deceased patients	Paper II	46.0 %	39.6 - 53.5	76.7	68.1 - 86.4
Deceased cancer patients	Paper III*	50.6 %	44.4 - 56.8	64.8	56.1 - 74.4
Deceased cancer patients treatment <30 days	Paper III	69.9 %	59.3 - 80.5	81.9	64.6 - 99.2
Deceased cancer patients treatment >30 days	Paper III	42.5 %	35.1 - 49.9	55.9	45.7 - 66.2

* Calculated afterwards for the thesis

We find that hospitalised cancer patients experience more admissions with AEs compared to general patients in both Papers I and II. In Paper I, cancer patients have a 39 percent greater risk of experiencing an AE compared to general patients (p<0.00, 95 % CI 1.19-1.62). Estimating the rate per 1 000 patient days, cancer patients have no higher rate of AEs than general patients, 37 vs. 36 (p=0.65, 95 % CI 0.90-1.18). Adjusted for demographic variables we still find no significant difference between the groups, but the incidence rate of AEs decreased, 24 vs. 26. Length of stay and age are the main risk factor for experiencing an AE, increasing the risk by 5.1 percent for each day spent in hospital and 1.3 percent for every year increase in age.

We identify significantly higher rates of AEs for deceased patients compared to both general and cancer patients included in Papers I and II. Since the confidence intervals comparing admissions with AEs and rates of AE per 1 000 patient days are overlapping, we can also conclude that there is no significant difference in rates of AEs between deceased general patients in Paper II and deceased cancer patients in Paper III. Deceased patients experience nearly three times as many admissions with one or more AEs compared to that identified in the general sample (p<0.001, 95 % CI 2.34-3.43). Deceased patients have twice the rate of AEs per 1 000 patient days compared to the general sample, 76.7 vs. 36.5 (p<0.001, 95 % CI 1.79-2.47).

Deceased cancer patients are a high-risk population for occurrence of AEs and in Paper III we investigated if anticancer treatment given during the last 30 days of life affected this risk. We found that patients receiving anticancer treatment during the last 30 days of life had 46 percent more AEs than cancer patients not receiving such treatment during the last 30 days of life, 82 vs. 56 AEs per 1 000 patient days (p<0.01, CI 95% 1.10 – 1.94). In addition, patients receiving anticancer treatment during the last 30 days of life experienced nearly double the rate of AEs contributing to death compared to patients not treated during the last month of life, 33 vs. 18 percent (p=0.03, adjusted OR 2.10, CI 95 % 1.09 – 4.01). Receiving follow up by specialist palliative care reduced the rate of AEs per 1 000 patient days in both groups by 29 percent (p= 0.02, IRR 0.71, CI 95% 0.53 – 0.96). The variability of the individuals is small, so the wider confidence intervals seen in Paper III mainly reflect the small sample size.

4.3 Severity of adverse events

Regardless of the type of patients included in the three papers, the majority of AEs identified were temporary harms, severity E and F (range 61-95 %). Considerably higher proportions of severe AEs contributing to death (severity I) were identified in deceased patients compared to other samples of patients (27-32 % vs. 0.9 – 1.2 %). Percentage and number of AEs per patient identified for each severity for all three papers are presented in Table 10.

Table 10 Distribution and number of AEs per patient identified for each severity level

| | | Severity level AE (%) | | | | | | | | |
| | | E | | F | | G | | H | | I | |
		AE/n	(%)	AE/n	(%)	AE/n	(%)	AE/n	(%)	AE/n	(%)
General patients	Paper I	0.12	(55)	0.09	(39)	0.008	(3.6)	0.002	(0.8)	0.003	(1.2)
	Paper II	0.10	(54)	0.08	(41)	0.007	(3.7)	0.001	(0.6)	0.002	(0.9)
Cancer patients	Paper I	0.10	(53)	0.08	(41)	0.007	(2.4)	0.001	(2.3)	0.002	(1.2)
Deceased patients	Paper II	0.24	(33)	0.20	(28)	0.03	(4.5)	0.01	(1.9)	0.23	(32)
Deceased cancer patients	Paper III	0.28	(35)	0.24	(31)	0.02	(3.0)	0.03	(4.0)	0.22	(28)
Deceased cancer patients treatment <30 days	Paper III	0.40	(34)	0.37	(31)	0.02	(2.3)	0.03	(4.7)	0.33	(28)
Deceased cancer patients treatment >30 days	Paper III	0.24	(36)	0.20	(30)	0.02	(3.5)	0.02	(3.5)	0.18	(27)

Comparison of severity level

In Paper I, we found no difference in severity level of AEs between cancer patients and general patients. In Paper II we identified considerably higher rates of severe AEs contributing to death (Severity I) in deceased patients compared to that found in general and cancer patients in Paper I. There was however, no difference between deceased patients and general patients in rates of temporary AE per 1 000 patient days. This great difference between deceased patients and the general sample of patients is also confirmed when comparing deceased cancer patients in Paper III to general hospitalised cancer patients in Paper I. In Paper III, patients receiving treatment during the last 30 days of life experienced both higher rates of temporary AEs and AEs contributing to death.

4.4 Adverse events contribute to death

In Paper II, an AE contributed to the death of 86 patients, accounting for 32 percent of all deceased hospitalised patients. Lower respiratory infections (48 %) and medication AEs (20 %) were the most common types of AEs contributing to death. For medication related AEs contributing to deaths, 70 percent of the patients had cancer and half of the AEs were lethal complications after chemotherapy.

In Paper III, an AE contributed to the death of 55 patients, accounting for 22 % of all deceased hospitalised cancer patients. AEs contributing to death were mainly healthcare associated infections and medication related AEs. Systemic anticancer treatment contributed to death in 11 percent of patients receiving systemic anticancer treatment, all given during the last 30 days of life (Figure 11).
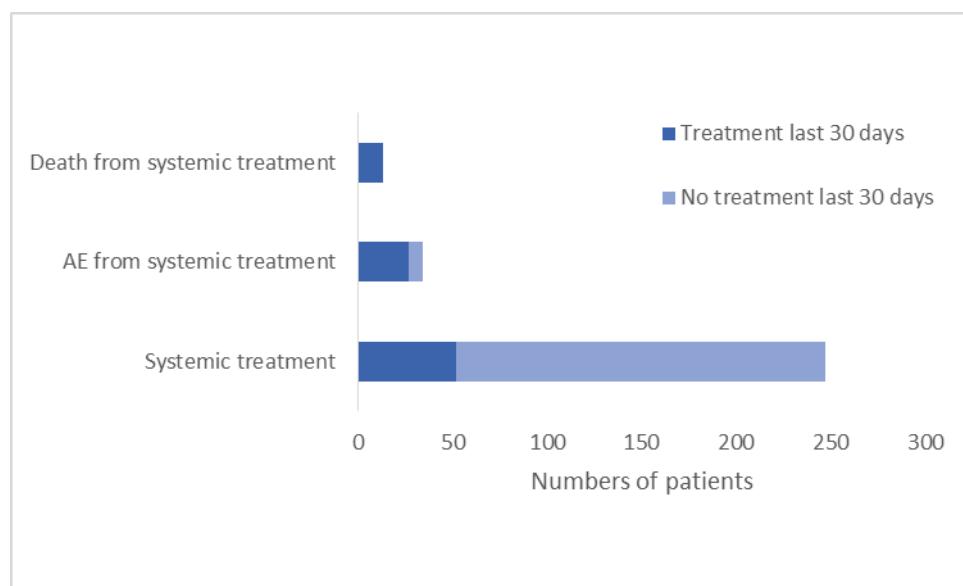
Figure 11 AEs and death due to systemic treatment in deceased cancer patients

Patients receiving anticancer treatment during the last 30 days of life experienced nearly twice the rate of AEs contributing to death compared to patients not being treated during the last month of life, 33 vs. 18 percent (p=0.03, adjusted OR 2.10, CI 95 % 1.09 – 4.01). For cancer patients not receiving treatment during the last 30 days of life, healthcare acquired infections contributed to death in 58 percent of the patients. An AE contributed to death more commonly in patients with lymphoma and haematological malignancies (S_{res} 2.1).

4.5 Types of adverse events

Healthcare associated infections, medication harm and surgical complications are the most common types of AEs identified in all three papers. These types of AEs are also the most common types of AEs found in cancer patients (Figure 12). Adjusted for length of stay and other demographic variables in Paper I, medication related AEs are the only type of AEs cancer patients have higher rates of compared to general patients, 2.6 vs. 1.6 (p=0.045, RR 1.58, 95 % CI 1.01-2.46). In Paper II we found that most of the medication AEs in cancer patients were related to systemic anticancer treatment. In Paper III we investigated this more in depth and found that 24 percent of deceased cancer patients receiving systemic anticancer treatment had an AE related to the treatment. Patients receiving anticancer treatment during the last 30 days of life had more than twice the rate of medication related AEs, 21 vs. 9 AEs per 1 000 patient days (p<0.001, RR 2.35, CI 95 % 1.55-3.58).
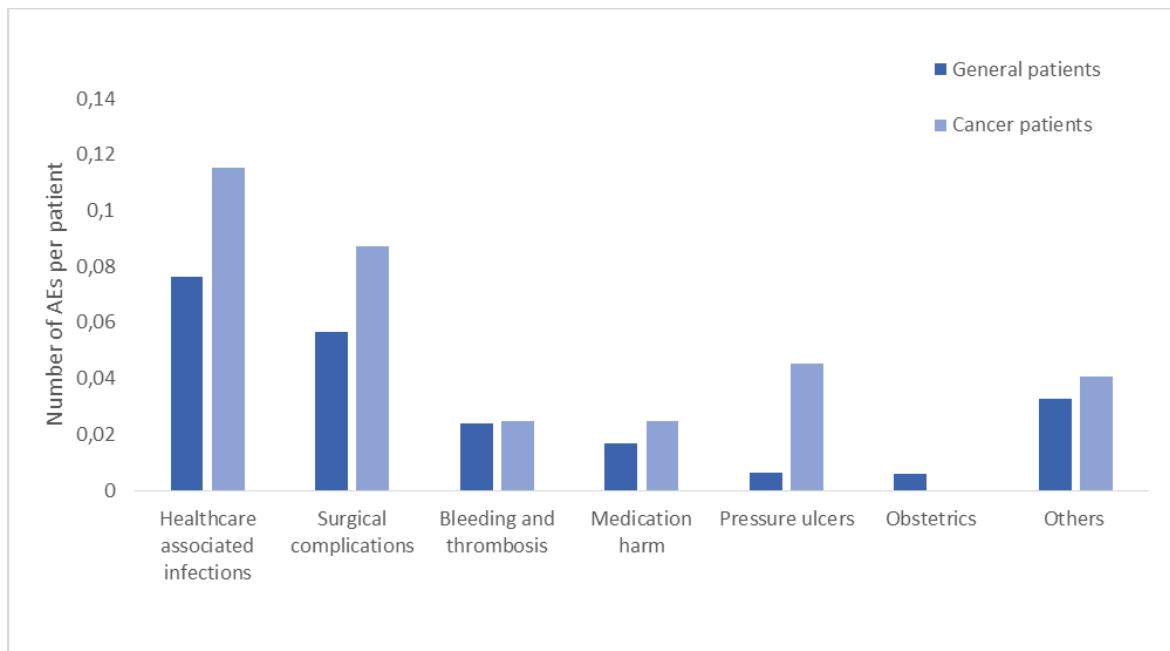
Figure 12 Comparing types of AE between general patients and cancer patients

Comparing patients included in all three papers we see that the rate of surgical complications was identical, while healthcare associated infections and medication harm were identified considerably more often in deceased patients and deceased cancer patients (Figure 13). In Paper II, deceased patients experienced nearly twice the rate of healthcare associated infections per 1 000 patient days compared to the general sample, 42 vs. 33 percent (p<0.001, RR 1.87, 95 % CI 1.36-2.57). These were mainly lower respiratory infections, 25.5 vs. 10.5 percent. Deceased patients also had more than five times the rate of AEs per 1 000 patient days related to medications than the general sample, 28.0 vs. 8.3 percent (p<0.001, RR 5.21, 95 % CI 3.04-8.9). In addition, pressure ulcers were identified more often in deceased patients and bleeding and thrombosis were found more often in deceased cancer patients.
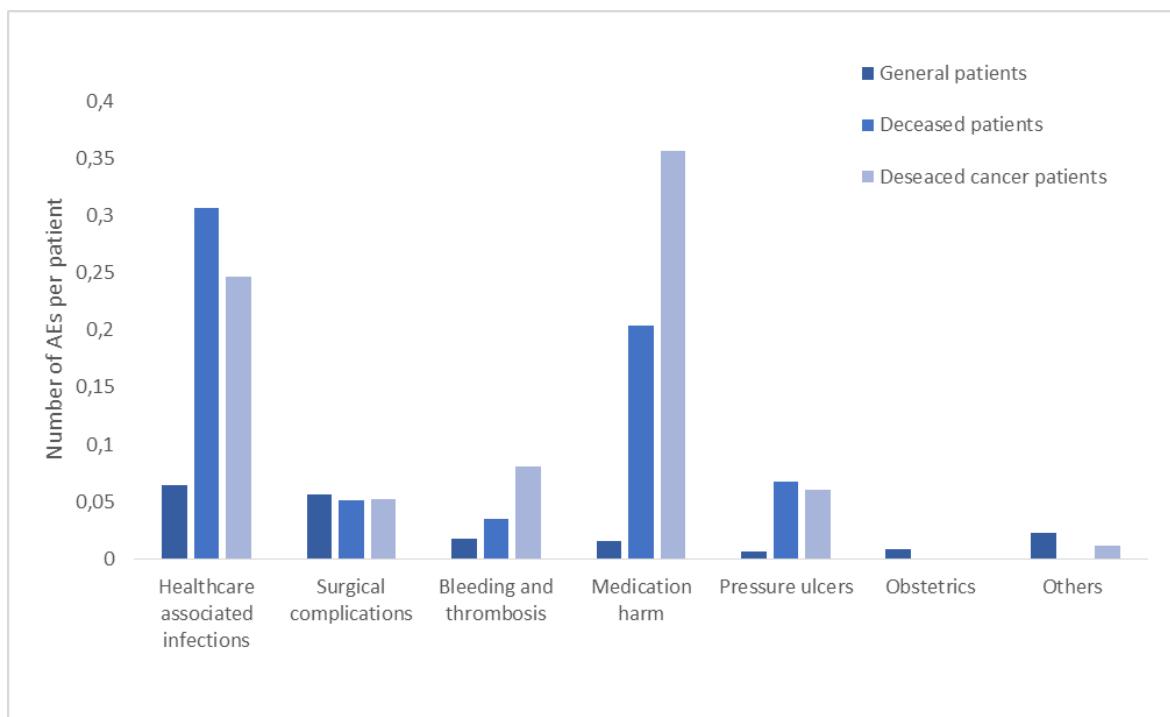
Figure 13 Comparing types of AEs between the three papers

5 Discussion

Key message
- Cancer patients have a 39 percent greater risk of experiencing an AE compared to general patients, mainly due to longer length of stay and older age rather than the cancer itself.
- Patients dying in hospitals experience more than twice as many AEs compared to general patients and cancer patients.
- For nearly one in three deceased cancer patients an AE contributes to death.
- Deceased cancer patients receiving treatment during the last 30 days of life have the highest rate of AEs compared to any other patient groups included in our three papers.

The discussion is structured around our main findings in all three papers. Results are compared across the three papers and in relation to other relevant studies. In addition, we have discussed our findings in relation to clinical practice and tried to elucidate how AEs can be used as a clinically relevant measure of quality and safety in cancer care.

5.1 Adverse events in cancer patients

We find that 24-30 percent of cancer patients experience an AE when admitted to hospital. This is nearly double the frequency of admissions with an AE compared to general hospitalised patients. Our results are in the lower range of the incidence reported in the four oncology studies referred to in 1.3.4 (range 22-51 %) and are similar to the results reported by Mattsson and Lipitz-Snyderman [73][163]. The increase in admissions with AEs and rate of AEs per 1 000 patient days for cancer patients in Paper II compared to what was found in Paper I, can be explained by the fact that all deceased cancer patients were also included in Paper II. Even though the sample sizes are large in both papers, the great variability between the individuals in Paper II is reflected in a wider confidence interval for both admissions with AEs and rates per 1 000 patient days, thereby providing a less precise result in Paper II [164].

One important point to note is that when adjusting for length of stay by calculating AEs per 1 000 patient days there is no difference in rates of AEs comparing hospitalised cancer patients to general patients. Hence, when cancer patients experience nearly double the frequency of admissions with an AE, longer length of stay is a main explanatory factor.

Patients dying in hospitals experience nearly three times as many AEs when admitted to hospital compared to general patients and cancer patients. There is no significant difference between deceased cancer patients included in Paper III and a general sample of deceased hospitalised patients in Paper II. This can be explained partly by the fact that cancer patients accounts for 33 percent of the deceased patients in Paper II. Patients dying in hospital are a highly selected group of patients, who are older, stay longer and have a narrower range of primary diagnoses. Even after adjusting rates for theses variables patients dying in hospitals have nearly twice the rate of AEs per 1 000 patient days compared to samples of general patients. Since adjusting for demographic variables did not alter the IRR for rate of AEs by more than 10 percent, we can conclude that confounding factors do not influence the results to any great extent [165].

Many patients who die in hospitals are very ill and frail from underlying conditions, making them more vulnerable to AEs. In our studies, we have only partly adjusted for comorbidities by including primary and secondary diagnosis as confounding factors. To adjust for this more thoroughly we could have assessed the patients using Charlsons` comorbidity index or Elixhauser comorbidity based on ICD-coding [166, 167]. Doing so would most likely support our observation that patients dying in hospitals are a highly selected group of patients more vulnerable to AEs.

The high rate of AEs for inpatient deaths in our study is similar to reviews of inpatient deaths performed in the Netherlands and a mortality review programme at Mayo Clinic in the USA [140, 153]. Nevertheless, our rates are higher than the incidence rate of all the three studies of inpatient death (range 13-30 %) [168][127, 169] and much higher than any other studies of general hospitalised patients included in section 1.3.4 [54–56, 62].

The high rates of AE found in our studies can partly be explained by the inclusion of AEs originating in primary care prior to admission. The IHI GTT protocol recommends that AEs originating in primary care be included and states that approximately 10 percent of AEs are present on admission (Griffin). A systematic review by Hibbert et al. finds that AEs present on admission vary with a range from 18-40 percent [54]. For our studies the same criteria including AEs originating in primary care prior to admission were used for all patients. We find no significant difference in the frequency of AEs originating in primary care between general patients and deceased patients, 12 vs 19 percent. Frequency of AEs originating in primary care should therefore not have an impact on our finding that deceased patients have twice as high rates of AEs per 1 000 patient days compared to other hospitalised patients.

In Paper I, we found that length of stay was the main risk factor for experiencing an AE, increasing the risk with 5.1 percent for each day spent in hospital. This is supported by other studies reporting that longer length of stay is independently associated with higher rates of AEs [72, 100]. Reporting AEs per 1 000 patient days takes into account length of stay as an important risk factor.

In all our papers, cancer patients have on average two days' longer length of stay than general patients` and for deceased cancer patients the length of stay is even double the length of general patients. This implies that cancer patients are at higher risk of AEs than general patients. However, we do not know if the longer length of stay is due to increased exposure to hazards or because the AEs themselves contribute to longer length of stay. Most likely, a combination of these two factors.

The age of patients is a main risk factor for AEs [23, 100]. In Paper I, we find that for every year increase in age, the risk of an AE increases by 1.3 percent. Cancer patients included in all our papers are approximately 10 years older than other patients`, increasing the risk of AEs by 13 percent. Age is also a strong determinant of cancer risk and an ageing population will lead to an increase of the cancer rate per se. This implies that more patients will need cancer treatment, and thereby increase the burden on cancer care, and risk of AEs in our hospitals [170]. One interesting clinical aspect of this is, that during the last decade old age in itself has not been regarded as a criterion for not receiving cancer treatment. Older cancer patients can be affected by altered physiology, functional and cognitive impairment, multiple coexisting morbidities, increased side effects of treatment and increased need for social support. Knowing that age is an independent risk factor for AEs addresses important considerations for the prognosis and treatment of older cancer patients, arguing that clinicians` treatment recommendations should be influenced by the patients' age [8]. A geriatric assessment can be a useful tool for assessing risk factors and needs of older patients to support the decision-making process.

5.2 Adverse events contribute to death in cancer patients

Severe AEs (severity G, H and I) are identified seven times more often in deceased patients compared to general hospitalised patients. For nearly one in three deceased patients and deceased cancer patients an AE contributes to death. Especially, deceased patients receiving anticancer treatment during the last 30 days of life have a considerably higher rate of AEs contributing to death compared to any other patients included in all three papers.

These rates of AEs contributing to death are higher than in any other GTT studies of general patients or cancer patients included in the systematic reviews in chapter 1.3.4. This can be explained by the fact that patients dying in hospital are a highly selected group of patients who are older, stay longer, are mainly emergency admissions and have a smaller range of primary diagnoses. To have a representative population we argue that in measuring AEs contributing to death, reviews should be based on inpatient deaths rather than a random sample of general hospitalised patients.
The large difference in rates of severe AEs between deceased patients and general samples could also be explained by the sample size. Severe AEs are rare in general hospitalised patients, and when reviewing less than 10 percent of hospitalised patients` we do not get reliable metrics on rarely

occurring AEs. Demographic differences and sample size argue that mortality estimates of AEs rarely contributing to death should not be extrapolated from GTT reviews of small general samples of hospitalised patients. By including all inpatients deaths in Paper II and III we avoid this sampling error, and argue that reviewing all in-patient deaths provides new valid and reliable data of severe AEs which otherwise would go undetected. Measuring AEs contributing to death can be a powerful driver for the safety culture and raise awareness for learning and improvement needed to mitigate future occurrences of patient harm.

In keeping with other studies, we find that regardless of patient groups and setting included in all three papers the majority of AEs are temporary harms. Since the majority of AEs result in morbidity and disability rather than death, we should keep in mind the importance of also monitoring less severe AEs. Comparing rates of temporary harm between the papers we find that deceased patients and especially deceased cancer patient treated during last 30 days of life have a higher rate of temporary harm compared to any other patients. This indicates that deceased patients does not identify less severe temporary harm but rather seems to highlight the reality found in a sample of general patients. Limiting the review to a relatively small proportion of deceased patients could therefore also be more time and resource efficient than monitoring samples of general patients.

5.3 Harmful anticancer treatment given last 30 days of life

There are strong recommendations towards limiting the use of aggressive anticancer treatments for cancer patients near the end of life [41, 171] and death within 30 days of treatment is increasingly recognised as an indicator of quality in oncological care [172]. Nevertheless, we found that one third of deceased hospitalised cancer patients received some kind of anticancer treatment during the last 30 days of their lives. This corresponds to what was found by the UK National Confidential Enquiry into Patient Outcome and Death [173].

Predicting how long patients with advanced cancer are expected to live and deciding if they will live long enough to benefit from treatment is challenging. In practice, clinicians often rely on their clinical judgment or intuition when estimating prognosis. However, systematic reviews consistently show that such estimates are often inaccurate and overly optimistic [174]. Knowledge of the patients` performance status and use of prognostic tools can help guide clinicians in decision-making [175, 176]. Moreover, before recommending systemic anticancer treatment clinicians should always fully discuss the aims, likely outcome and possible AEs of treatment with patients, including the option of no treatment [93]. Communication of prognostic information and shared decision-making is fundamental to avoid overuse of anticancer treatment near end-of-life and meet the individual preferences of each patient [93, 177].

Deceased cancer patients receiving treatment during the last 30 days of life have the highest percentage of admissions with AE and the highest rate of AE compared to any other patient groups included in all our three papers. To the best of our knowledge, rates of AEs in this selected population of cancer patients have not been documented before and we have no similar studies to compare our results with. The incidence rate is much higher than found in any other cancer studies or inpatient death studies included in the systematic reviews in section 1.3.4. We find that the odds of experiencing an AE contributing to death are twice as high for patients receiving anticancer treatment during the last 30 days of life. This included all types of AEs whether caused by systemic anticancer treatment, other medications or healthcare acquired infections. It is rarely straightforward to argue that anticancer treatment is the direct cause of death. Most likely, reduced performance status, malnutrition and immunosuppression amplify the effect of AEs related to anticancer treatment and increase the negative impact on the patients` remaining lifetime [91]. Even if these patients are vulnerable and have a limited life expectancy, it indicates that anticancer treatment given during last 30 days of life can hasten death. Considering the narrow therapeutic/toxic ratio and complexity of many systemic anticancer treatments, AEs from cancer treatment will always occur to some extent. However, an AE hastening death is never acceptable and when it does occur we need to review the incident and learn from it to improve future clinical care.

One approach to avoid overuse of systemic anticancer treatment is early integration of specialist palliative care while still providing active cancer treatment. Early referral to palliative care is associated with improved quality of life, fewer acute hospital admissions and less aggressive cancer treatment near the end of life [178–180]. Many large professional organisations such as ASCO, ESMO, EAPC therefore recommend that palliative care should be an integrated part of oncology care for patients with advanced disease [93]. Our findings indicate that patients receiving specialist palliative care had significantly fewer AEs than patients not referred to palliative care. Symptom management is a key element of palliative care. Diagnosing and managing symptoms at an early stage can prevent them from developing into AEs and thereby improve patient safety for cancer patients. This supports recommendations of early integration also in a patient safety perspective.

Knowing the positive associations for quality of life and safety benefits for cancer patients referred to palliative care, the low referral rate (35 %) of deceased cancer patients is problematic. One reason for late referral to palliative care is the perception that palliative care is equal to end-of-life care [181, 182]. However, this is not in line with the present definition of palliative care stating that "palliative care is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life" [183]. Furthermore, oncology practice and palliative care can be described as driven by two different cultures; the tumour-directed approach where the focus is treating the disease; and the patient-directed approach that focuses on the patient with the disease. To achieve integration of palliative care into oncology these two paradigms need to be united in the best interest of the patient

[93]. Other reasons for low referral rates are resources allocated to palliative care and a healthcare system consisting of silos, not structures to support the integration of palliative care throughout the whole continuum of cancer care. In so way, early referral to palliative care itself can be regarded as a relevant clinical measure of quality in cancer care.

5.4 Types of adverse events in cancer patients

Healthcare associated infections (HAI), medication harm and surgical complications were the most common types of AEs in all three studies. HAI and medication harm are identified considerably more often in deceased patients, where especially AEs related to medications are found most often in deceased cancer patients. In addition, deceased cancer patients experience more bleeding/thrombosis compared to other patients.

Cancer patients more often experience AEs related to HAI than general patients and these contributed to death in 58 percent of the deceased cancer patients. HAI were the most common cause of death for patients not receiving treatment during the last 30 days of life. The AEs are mainly lower respiratory infections and other infections. Lower respiratory infections are the most common infection in all three papers, occurring nearly three times as frequently and contributing to nearly half of the inpatient deaths. The incidence rate of HAI continues to escalate, and HAI is considered one of the major safety risks for patients. The higher incidence of HAI in cancer patients can be explained by the severity of illness, age, underlying conditions and use of immunosuppressive medications such as chemotherapy and steroids. In addition, cancer patients have longer length of stay contributing to susceptibility to infections. Multiple factors influence the development of HAI and prevention has proven to be very complex. Preventing HAI is one of the greatest challenges in health care and to succeed all healthcare providers need to take responsibility and enact principles of care to prevent healthcare associated infections [184].

In Paper I, we find that adjusted for length of stay and other demographic variables, the only type of AE cancer patients experience more often is harm related to medication. This is confirmed in Papers II and III where inpatient deaths have five times the risk for medication related AEs. More than 70 percent of medication related AEs contributing to death occur in cancer patients and most of these AEs were related to lethal complications after chemotherapy. Patients receiving anticancer treatment during the last 30 days of life had the highest rate of medication related AEs, more than twice the rate of cancer patients not receiving such treatments. Anticancer treatment related AEs contributing to death only occurred in patients who received such treatment during the last 30 days of life. This confirms other studies identifying chemotherapy as a severe risk factor for AEs in cancer patients [21, 22, 71]. It also particularly accentuates the increased risk of severe AEs when systemic anticancer

treatment is given during the last 30 days of life and should encourage careful when consideration providing systemic cancer treatment to patients near end of life.

In Paper I, we find that cancer patients have a 54 percent greater risk of surgery-related AEs compared to general patients. This is primarily due to events termed "other operative complications". Surgery is the main curative treatment for cancer and this partly explains why receiving curative treatment increases the risk rate of AEs by 74 percent. Our results are consistent with other studies indicating that admission to a surgical department and having surgery increases the rate of AEs [59, 72, 185, 186]. Comparing rates of surgical AEs between general patients, deceased patients and deceased cancer patients in all three papers, there is no significant difference between the groups. The use of surgery is considerably higher (35 percent) for cancer patients in Paper I, compared to deceased cancer patients in Paper III where only five percent had surgery. The use of surgery correlates to being in a curative setting, and surgery does not often contribute to death for cancer patients. This implies that studies of surgery-related AEs should ideally be performed in a general patient population and not by reviewing deceased patients.

5.5 Methodological implications

Since only a small number of cancer patients are hospitalised when they receive systemic anticancer treatment or radiation, monitoring AEs related to these treatments and late term AEs should preferably be done in an ambulatory setting. Using the trigger tool methodology may be just as applicable to review outpatient care, but the inclusion criteria and review process of the GTT method would need to be modified. For this to be time efficient and realistic to carry out, it would be necessary to develop a new and reliable automatic trigger tool with specific oncology triggers identifying AEs.

Adjusting additionally for other characteristics such as age, gender, type of admission and department further decreases the rate of AEs per 1 000 patient days in all our papers. This implies that demographic characteristics significantly affect the rate of AEs. Demographic variables may vary considerably and especially affect small sample sizes. When using the original IHI GTT to monitor AEs within an organisation and only including 240 patients per year, not adjusting for demographic variables raises concern about the GTT method's ability to detect real change.

The use of systemic anticancer treatment is much higher in deceased cancer patients. Knowing that severe AEs are more often identified in deceased patients, identifying severe AEs related to systemic anticancer treatment should preferentially be investigated in deceased cancer patients. Systemic anticancer treatment only contributes to death in patients who received such treatment during the last 30 days of life. Consequently, when measuring anticancer treatment related AEs contributing to death we can be even more pragmatic and limit the inclusion to deceased hospitalised patients treated during the last 30 days of life.

A limitation we faced in the first paper was that the GTT method only records if an AEs had occurred and did not identify supplementary information on type of medication, dosage or polypharmacy that could identify underlying causes for the AE. In the first paper we therefore did not know if these AEs were related to systemic anticancer treatment or other medications. In Papers II and III the generic name of the medication was obtained to better understand the cause of harm and identify specific medications at risk in cancer care. To benefit future improvement, we recommend the generic name of the medication also should be obtained for medication related AE.

We also found that the 23 categories recommended by the Norwegian GTT manual had too many specific surgical types of AEs. When the numbers are small and one AE could be categorised into more than one category it can be hard to compare and monitor rates of AEs over time. To be able to compare data we had to aggregate the types of AE into eight main clinical categories. We would also suggest a revision of the categories recommended in the Norwegian GTT manual, categorising AEs according to the aetiology of the incident leading to the outcome for the patient.

At the same time we lacked specific categories of AEs in oncology. We recommend a separate category of oncology harm including subtypes of AEs related to radiation, the diagnostic process and palliative care. AEs related to systemic anticancer treatment can either be classified within the oncology category or kept as a specific type within the medication category. What is important is that the generic name of the medication is obtained in order to distinguish what type of systemic anticancer treatment (chemotherapy, targeted treatment and immunotherapy) the AE is related to. We argue that making these changes to the GTT method will increase the reliability of the method and provide meaningful data for improvement in cancer care.

5.6 Summary of strengths and limitations

A summary of the strengths and limitations of all three studies is presented in Table 11.

Table 11 Summary of strength and limitations

Strengths	Limitations
Study design	
Adjusted for case-mix in all three papers.	Information bias due to retrospective collection of data.
Large sample sizes in papers I and II.	Observational cohort evaluates association and it is impossible to control for all confounding factors.
Included all deceased patients in papers I and II.	Small sample size in paper III increasing the risk of type 2 error.
Stratified random sampling for general patients in papers I and II.	Too many heterogeneous categories for types of AEs.
Includes all malignancies, solid tumour and haematological cancer.	No specific categories for oncology AEs.
Patients from three hospitals included.	Types of medication causing AEs not documented in paper I.
Manual check of length of stay to use the correct number of days as denominator.	Not validated to an external patient cohort.
Reliable coding practice for C-diagnosis by ICD-10	
Identified type of medication causing an AE in papers II and III.	
Good external validity compared with other studies.	
Use of STROBE guidelines for all three papers.	
Review	
A common definition of AE was applied in all three papers.	Review relies on documentation in the HER.
All reviewers received substantial training.	Risk of hindsight bias, especially reviewing deceased patients.
Consistency in the review team of deceased patients in papers II and III.	Manual review is time demanding.
Using CTCAE classification to identify and grade oncology related AEs.	Use of seven different review teams for general patients in papers I and II.
Adding an extra validation step to the review process in papers II and III shows consistent agreement.	Slightly different review methods used by review teams in paper II.
	Oncology triggers were not previously verified.
Data analysis	
Generalized method was used accounting for different length of stay and different sample sizes	Fair inter-rater reliability between reviewers in paper II.
Poisson or Negative binominal regression used depending on if the counts followed a Poisson distribution.	Due to small sample size in paper III, not advisable to adjust for more than five variables with 10 degrees of freedom.
Types of AEs merged into eight main categories depending on treatment given.	Manual review is difficult to reproduce and compare between studies.

6 Conclusion

Hospitalised cancer patients experience AEs more often than other patients, but this is due to older age and longer length of stay rather than the cancer itself. Especially medication related harm and healthcare associated infections are safety hazards of concern to cancer patients. Patients dying in hospitals differ in several ways from a general hospitalised population, they experience seven times the rate of severe AEs and for nearly one in three deceased cancer patients an AE contributes to death. Measuring AEs contributing to death can be a positive driver for improving safety culture and raising awareness for learning and improvement. We find that a GTT review of all inpatient deaths provides a new valid and reliable measurement of severe AEs contributing to death that otherwise would be undetected.

Despite strong recommendations against use of aggressive anticancer treatments for cancer patients near the end of life, one third of deceased hospitalised cancer patients received some kind of anticancer treatment during the last 30 days of their life. Anticancer treatment given during this period was associated with a significantly increased rate of AEs with twice the odds of having an AE contributing to death.

Identifying specific AEs in cancer care is clearly warranted and can provide real time measures of quality and safety, enhancing improvement in clinical practice and avoiding overtreatment in end-of life cancer care.

7   Implications for future research

The use of machine learning and natural language processing in electronic health records (EHR) is expanding rapidly creating new possibilities for detecting and monitoring AEs. Nordland Hospital Trust has already developed and validated an automatic trigger identification system where only records with triggers are reviewed manually to determine if the triggers represent an AE [126]. To our knowledge, a completely automated identification method for oncology related AEs does not exist. During the last years two different studies has validated cancer specific trigger tools that identify AEs occurring in ambulatory and inpatient settings [23, 115]. However, these triggers do not identify AEs related to immunotherapy as anticancer treatment. Future research should include and validate oncology specific triggers in an automatic identification system of oncology related AEs. Our already existing automatic trigger system should also be developed and validated further to identify and link triggers to treatment given, so the whole identification process of AEs is automated. Such an approach would be time saving and less resource intensive compared to manual retrospective record review.

The ultimate goal of measuring AEs is to provide real-time feedback to healthcare professionals and thereby offer hospitals advanced quality improvement and learning opportunities to mitigate AEs. To achieve this, we need to involve patients more actively. Empirical evidence demonstrates that clinicians under-report the incidence and severity of symptoms compared to patients direct reports [187–189] More importantly, most cancer patients are willing and able to self-report their own symptoms without substantial attrition, even among those with end-stage disease and poor performance status [190, 191]. Patient-reported outcomes (PROs) are already considered the gold standard for data collection in research. Based on this, the National Cancer Institute has developed a patient-centred assessment of AEs version of the CTCAE [192, 193]. The PRO-CTCAE comprises 78 symptomatic oncology relevant AEs. Until now, the PRO-CTCAE is mainly used in clinical trials, but a future opportunity is use of PRO-CTCAE as part of a safety surveillance system to prevent AEs in cancer patients receiving anticancer treatment. If cancer patients report symptoms electronically to a healthcare professional at an early stage, there is a potential to mitigate harm before it gets severe and results in an AE to cancer patients. While new technology and innovations creates new possibilities within healthcare, it is important that we include research on these methods and their implementation in order to validate their reliability and clinical relevance in enhancing patient safety. In doing so, we need to engage patients and families actively at all levels of healthcare and research.

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Appendices

Appendix I: Types of adverse events according to the Norwegian GTT manual

Hospital acquired infections

    Urinary tract infection

    CVC infection

    Ventilator associated pneumonia

    Other infection

    Lower respiratory infection

Surgical complications

    Infection after surgery

    Respiratory complications after surgery

    Return to surgery

    Injury, repair or removal of organ

    Occurrence of any operative complication

    Switch in surgery

    Bleeding after surgery

Bleeding/thrombosis

    Thrombosis/Embolism

    Bleeding

Patient fall/fracture

    Patient fall

    Fracture

Others

    Allergy

    Medical technical harm

    Deterioration and chronic illness

    Medication harm

    Obstetric harm

    Pressure ulcers

Appendix II: Norwegian GTT Trigger Sheet

Trigger	Care module Triggers	Trigger	Medication Module Triggers
	Care module Triggers		**Medication Module Triggers**
C1	Transfusion or use of blood products	M1	Clostridium difficile positive stool
C2	Code/arrest/rapid response team	M3	INR greater than 6
C3	Acute dialysis	M4	Glucose less than 2.8 mmol/l
C4	Positive blood culture	M5	Rising BUN or serum creatinine greater than 2 times baseline
C5	X-ray or Doppler studies for emboli or DVT	M6	Vitamin K administration
C6	Decrease of greater than 25% in haemoglobin or haematocrit	M7	Benadryl (Diphenhydramine) use
C7	Patient fall	M8	Romazicon (Flumazenil) use
C8	Pressure ulcers	M9	Naloxone (Narcan) use
C9	Readmission within 30 days	M10	Anti-emetic use
C10	Restraint use	M11	Over-sedation/hypotension
C11	Healthcare-associated infection	M12	Abrupt medication stop
C12	In-hospital stroke	M13	Other
C13	Transfer to higher level of care		**Intensive Care Module Triggers**
C14	Any procedure complication	I1	Pneumonia onset
C15	Other	I2	Readmission to intensive care
	Surgical Module Triggers	I3	In-unit procedure
S1	Return to surgery	I4	Intubation/re-intubation
S2	Change in procedure		**Perinatal Module Triggers**
S3	Admission to intensive care post-op	P1	Terbutaline use
S4	Intubation/re-intubation/BiPap in PACU	P2	3rd- or 4th-degree lacerations
S5	X-ray intra-op or in PACU	P3	Platelet count less than 50,000
S6	Intra-op or post-op death	P4	Estimated blood loss > 500 ml (vaginal) or > 1,000 ml (C-section)
S7	Mechanical ventilation greater than 24 hours post-op	P5	Specialty consult
S8	Intra-op epinephrine, norepinephrine, naloxone, or romazicon	P6	Oxytocic agents
S9	Post-op troponin level greater than 40 ng/l	P7	Instrumented delivery
S10	Injury, repair, or removal of organ because of accidental injury	P8	General anaesthesia
S11	Change in anaesthesia procedure	P9	APGAR score <7 after 5 minute
S12	Insertion of artery catheter or central venous catheter	P10	Induced labour
S13	Surgery more than 6 hours		**Emergency Department Module Triggers**
S14	Any operative complication	E1	Readmission to ED within 48 hours
		E2	Time in ED greater than 6 hours

Appendix III: Oncology triggers

Trigger	Oncology Module Triggers
O1	Mucositis / stomatitis
O2	Skin desquamation
O3	Palmar plantar syndrome
O4	Diarrhoea
O5	Constipation
O6	Dysphagia
O7	Aspiration
O8	Vomiting
O9	Urinary tract infection
O10	Neuropathy
O11	Neutropenia (neutrophils <1.0)
O12	Thrombocytopenia (thrombocytes <50)
O13	Hyperglycaemia (glucose >18 mmol/l)
O14	Hypercalcaemia (calcium >2.6 mmol/l)
O15	Hyperkalaemia (potassium >6.0 mmol/l)
O16	Allergic reaction
O17	Anaphylactic reaction
O18	Extravasation
O19	Peripheral or central vascular access infection
O20	Sudden onset confusion
O21	Unexpected medical or surgical emergency / sudden death

Appendix IV: Response letter from the Regional Committee for Medical and Health Research Ethics

Til Barthold Vonen

2013/1823 Metodologiske utfordringer ved måling av pasientsikkerhet hos kreftpasienter

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 29.10.2013. Vurderingen er gjort med hjemmel i helseforskningsloven § 10, jf. forskningsetikklovens § 4.

Forskningsansvarlig: Nordlandssykehuset HF
Prosjektleder: Barthold Vonen

Prosjektomtale (revidert av REK):
Studiens hovedformål er å videreutvikle skademålingsverktøyet GTT for å tilpasse dette til å avdekke flest mulig reelle pasientskader hos kreftpasienter i spesialisthelsetjenesten, både hos inneliggende og polikliniske pasienter. Forbedrede metoder for dokumentasjon av pasientskader kan bidra til at det blir lettere å identifisere områder hvor skadeforebyggende tiltak kan iverksettes.

Vurdering

Etter søknad med prosjektbeskrivelse, legger komiteen til grunn at formålet med prosjektet er kvalitetssikring, og ikke å fremskaffe ny kunnskap om helse og sykdom.

Komiteen viser i den sammenheng til hvordan kvalitetssikring forstås i Helse- og omsorgsdepartementets veileder til helseforskningsloven:

"Kvalitetssikring kan defineres som prosjekter, undersøkelser, evalueringer o.l. som har som formål å kontrollere at diagnostikk og behandling faktisk gir de intenderte resultater. Nasjonale tiltak for å sikre og forbedre kvaliteten i tjenestene inkluderer utvikling av nasjonale kvalitetsindikatorer, samordning og styrking av medisinske kvalitetsregistre og å utarbeide gode faglige retningslinjer. Kvalitetsarbeidet må baseres på systematisk dokumentasjon."

Etter komiteens vurdering faller prosjektet utenfor helseforskningslovens virkeområde, jf. helseforskningsloven § 2, jf § 4 første ledd bokstav a.

Prosjektet kan gjennomføres uten godkjenning av REK, innenfor de ordinære ordninger for helsetjenesten med hensyn til for eksempel regler for taushetsplikt og personvern. Søker bør derfor ta kontakt med enten forskerstøtteavdeling eller personvernombud for å avklare hvilke retningslinjer som er gjeldende.

Vedtak

Prosjektet er ikke fremleggelsespliktig, jf helseforskningsloven § 9, jf forskningsetikkloven § 4.

Komiteens avgjørelse var enstemmig.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Britt-Ingjerd Nesheim
prof. dr. med.
leder REK sør-øst C

Claus Henning Thorsen
seniorrådgiver

Kopi til:
Jan Terje Henriksen, Nordlandssykehuset: jan.terje.henriksen@nordlandssykehuset.no

Nordlandssykehuset ved øverste administrative ledelse: postmottak@nlsh.no

Paper I
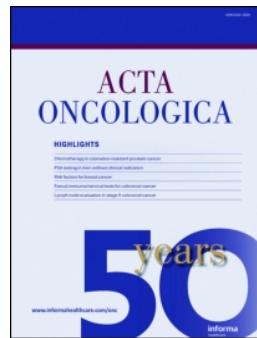
Adverse events in hospitalised cancer patients: a comparison to a general hospital population

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ORIGINAL ARTICLE

Adverse events in hospitalised cancer patients: a comparison to a general hospital population

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ABSTRACT

Background: Patients with cancer are often treated by many healthcare providers, receive complex and potentially toxic treatments that can increase the risk for iatrogenic harm. The aim of this study is to investigate whether hospitalised cancer patients are at higher risk of adverse events (AEs) compared to a general hospital population.

Material and methods: A total of 6720 patient records were retrospectively reviewed comparing AEs in hospitalised cancer patients to a general hospital population in Norway, using the IHI Global Trigger Tool method.

Results: 24.2 percent of admissions for cancer patients had an AE compared to 17.4% of admissions of other patients ($p < .001$, rr 1.39, 95% CI 1.19–1.62). However, cancer patients did not have a higher rate of AEs per 1000 patient days compared to other patients, 37.1 vs. 36.0 ($p = .65$, rr 0.94, 95% CI 0.90–1.18). No particular cancer category is at higher risk. The rate of AEs increases by 1.05 times for each day spent in hospital. For every year increase in age, the risk for AEs increases by 1.3%. Cancer patients more often have hospital-acquired infections, other surgical complications and AEs related to medications.

Conclusions: Because of higher age, longer length of stay and surgical treatment, hospitalised cancer patients experience AEs more often than other patients.

Introduction

The health care system is a complex environment involving both system and individual risk factors for iatrogenic harm. Based on patient characteristics, complexity and seriousness of the illness, some patients are at greater risk of adverse events (AEs) [1,2]. The risk of iatrogenic harm increases with age, length of stay, surgery, emergency services and treatment in intensive care [3]. Patients with cancer are often treated by a variety of healthcare providers, receive complex and potentially toxic treatments that could increase the risk of iatrogenic harm [4]. As new treatments are developed, new safety hazards will evolve. In addition, cancer patients may be more prone to AEs due to the disease itself. Accurate and reliable measurement of AEs remains a challenge in the patient safety field [5]. The Institute for Healthcare Improvement's Global Trigger Tool (IHI GTT) is widely used as a method to measure and monitor AEs in general hospitalised patients [3,6]. Despite this method's high sensitivity and specificity in detecting iatrogenic harm, there are limitations [7–9]. One Danish study raises methodological concerns of the IHI GTT, not being specific enough in monitoring harm in cancer patients [10]. Knowledge of patient safety measures in

cancer is limited, and a disease-specific approach could be of value for targeted improvements in cancer care. The aim of this study is to investigate whether cancer patients have a higher risk of AEs compared to a general hospital population as documented by the IHI Global Trigger Tool.

Material and methods

Study design

The study is a retrospective record review comparing AEs in hospitalised cancer patients and patients with other diseases.

Setting

The study was performed at a public health trust in Norway. Nordland Hospital Trust has three somatic hospitals: one central and two smaller district hospitals, with a total of 524 beds. Cancer patients are treated and hospitalised in all three hospitals, but only the central hospital has a separate department of oncology. The oncology department provides ambulatory chemotherapy, palliative care and radiotherapy. Cancer surgery is primarily performed at the Central Hospital in

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Bodø. None of the hospitals has a separate oncological inpatient unit, so cancer patients are admitted to other department depending on the origin of their cancer.

Study population

Since 2010, all hospitals in Norway are required to review a minimum of 20 randomly selected medical records per month using the IHI GTT method [11]. Nordland Hospital Trust chose from the start to review 140 records monthly to achieve more accurate measurement and better support for local improvement initiatives [12]. From 1 January 2010 to 31 December 2013, a total of 6720 records were reviewed using the IHI GTT method. Ten patient records were randomly sampled, block randomised twice monthly from the discharge list of seven units in the trust (surgery, orthopaedics, internal medicine, gynaecology/obstetrics, neurology/others and the district hospitals of Lofoten and Vesterålen). Patients below the age of eighteen, patients with a length of stay less than twenty-four hours or patients admitted primarily for psychiatric conditions or rehabilitation were excluded [12–14]. Our

Figure 1. Overview population and study design.

analysed sample accounts for 8.5% of the eligible discharges of inpatients from the health trust in the study period. Cancer patients were identified by matching the patient ID number in the sample to cancer diagnosis in the discharge lists of the hospitals. From the total sample size of 6720 records, 812 (12.1%) of the patients had cancer as primary or secondary diagnosis on discharge classified by ICD-10. Age, gender, length of stay, type of admission, hospital, department and cancer characteristics were obtained (Figure 1).

Review method

The review was done according to the Norwegian version of the IHI GTT manual. The Norwegian version is identical to the IHI GTT, except for minor changes to three triggers [13,14]. All review teams were trained according to the IHI protocol for GTT analyses. Seven different teams reviewed records from their unit in the trust. All review teams consist of one physician and two nurses, and only had minor changes in composition during the study period. The review was performed as in two-stages. Two nurses reviewed all records independently and then together reached consensus on presence, category and severity of AEs. The physician then authenticated their findings. Cancer patients were reviewed together with the other patients, and separated afterwards for the study. AEs were defined as 'Unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalization, or that results in death.' [14] The severity of AEs was categorised according to the NCC MERP index [15] (Table 1). AEs were before reviewing grouped into 23 categories according to recommendations in the Norwegian GTT manual. For statistical purpose, the categories were aggregated into eight main categories in the study: hospital-acquired infections, surgical complications, bleeding/thrombosis, patient fall/fracture, medication harm, obstetric harm, pressure ulcer and others.

Statistical analysis

Demographic variables were compared using the Pearson's Chi-squared test and the Mann–Whitney U-test. Incidence rates of AEs, severities and categories were compared using negative binominal regression in generalised linear models. Rates were calculated as AEs per 1000 patient days and as percentage of admissions with one or more AEs. Log patient days were used as offset variable to compare rates per 1000 patient days. For admissions with AEs, the offset variable was set to a fixed value of zero. In addition, we adjusted for demographical variables: age, gender, length of stay, type of admission, hospital, department and year of discharge. A p-value $< .05$ was deemed statistically significant. Data were analysed with IBM SPSS V23.0.

Results

Demographic characteristics

According to the discharge index, cancer diagnosis accounts for 10.8% of patients admitted to the total hospitals population. In our sample, cancer patients represent a stable rate of 12% per year, evenly distributed between the hospitals. Cancer patients are 10.2 years older, stay 2.27 days longer in hospital and are more often male than the general hospital population. Cancer patients are more often admitted electively, and are more likely to be admitted to a surgical department than other patients (Table 2).

Cancer of the large bowel (15%), prostate (13%) and lung (12%) are most common. Gastrointestinal and urinary cancer

Table 1. Severity grading of AEs.

Category	
E	Temporary harm that required intervention
F	Temporary harm that required initial or prolonged hospitalization
G	Permanent patient harm
H	Intervention required necessary to sustain life
I	Harm contributed to or resulted in patient death

Note: Severity categories according to the National Coordinating Council for Medication Error Reporting and Prevention Index (NCC MERP).

Table 2. Characteristics in 6720 patients.

Parameter	Cancer patients n = 812	Other patients n = 5908
Mean age, years (SD)	70.0 (13.0)	59.7 (21.5)*
Min.–Max.	20–102	18–102
Mean length of stay, days (SD)*	8.4 (9.6)	6.1 (7.0)*
Min.–Max.	1–81	1–122
Gender N (%)		
Female	364 (44.8)	3 642 (61.6)*
Male	448 (55.2)	2 266 (38.4)
Type of admission N (%)		
Acute	512 (63.1)	4 291 (72.9)
Planned	300 (36.9)	1 617 (27.4)*
Years 2010–2013 Range (%)	11.3–12.4	87.6–87.9
Hospital range (%)		
Central Hospital Bodø	604 (12.6)	4 196 (87.4)
District Hospital Lofoten	106 (11.0)	854 (89.0)
District Hospital Vesterålen	102 (10.6)	858 (89.4)
Department N (%)		
Internal medicine	236 (29.1)	1 689 (28.6)
Surgery	457 (56.3)	2 290 (38.8)*
Gynaecology	36 (4.4)	1 063 (18.0)*
Neurology	40 (4.9)	599 (10.1)
Other departments	43 (5.3)	266 (4.5)

*$p < .001$.

counts for 51% of the cancers. 59% of the cancer patients have metastases and 65% are in a palliative setting. A majority of the patients (51%) received ordinary medical treatment. Thirty-five percent had surgery or other minor procedures such as biopsies, stent insertion or pleural draining. Fifteen percent received cancer-related treatments such as chemotherapy or radiation (Table 3).

Comparison of AEs

An AE was recorded in 24.2% of admissions for cancer patients compared to 17.4% of admissions for other patients ($p < .001$, rr 1.39, 95% CI 1.19–1.62). Estimating the rate per 1000 patient days, cancer patients have no higher rate of AEs than other patients, 37.1 vs. 36.0 ($p = .65$, rr 0.94, 95% CI 0.90–1.18). Adjusted for demographic variables, there is still no significant difference between the groups but the incidence rate of AEs decreases, 24.4 vs. 26.0 ($p = .35$, rr 0.94, 95% CI 0.82–1.07) (Table 4).

For the total sample, the rate of AEs is 1.05 times greater for each extra day spent in hospital ($p < .001$, 95% CI 1.04–1.06). For every year increase in age, the risk of an AE increases by 1.3%, ($p < .001$, rr 1.013, 95% CI 1.01–1.02). Acute admission increases the risk of AEs by 17% ($p = .01$, rr 1.17, 95% CI 1.039–1.327). Admission to a surgical or gynaecology department increases the rate of AEs by more than 50%. The district hospital in Lofoten has a 30% lower rate of AEs ($p < .001$, rr 0.70, 95% CI 0.580–0.850) (Table 5).

Cancer patients having surgery or minor procedures have an increased rate of 68% for AEs compared to other patients with cancer ($p = .007$, rr 1.68, 95% CI of 1.15–2.46). Receiving treatment with curative intent increases the rate of AEs by 74% ($p = .002$, rr 1.74, CI 95% 1.24––2.46). However, rates are similar for the different cancer categories (Table 3).

Severity of AEs

Most of the AEs are of temporary harm, severity E and F for both cancer patients (88%) and others (89%). Adjusted for demographic variables, there is no difference in severity per admission or per 1000 patient days between cancer patients and other patients.

Type of AEs

Cancer patients more often than other patients experience hospital-acquired infections, 11.5 vs. 7.6% per admission ($p = .001$, rr 1.51, 95% CI 1.20–1.91). Cancer patients primarily have lower respiratory infections (4.5 vs. 2.8%) and other infections (3.2 vs. 1.6%). Cancer patients have a 54% greater risk than other patients of surgically related AE per admission, 8.7 vs. 5.7% ($p = .002$, rr 1.54, 95% CI 1.18–2.00). This is primarily due to events termed 'other operative complications', 3.1 vs. 1.9%. Cancer patients experience twice the rate of medication-related AE per admission, 34 vs. 17% ($p = .005$, rr 2.03, 95% CI 1.23–2.91). Adjusted for length of stay and other demographic variables, cancer patients have a 58% higher risk for medication-related AEs per 1000 patient days, 2.6 vs. 1.6 ($p = .045$, rr 1.58, 95% CI 1.01–2.46) (Table 6).

Discussion

Hospitalised cancer patients have a 39% greater risk of experiencing an AE compared to other patients, but this is due to older age, longer length of stay and surgery rather than the cancer itself. There is no difference in occurrence of AEs by type of cancer, but patients receiving treatment with curative intent and undergoing surgery have a higher rate of AEs.

Length of stay is the main risk factor for experiencing an AE, increasing the risk with 5.1% for each day spent in hospital. In our study, cancer patients stay 2.27 days longer in hospital, increasing the risk for AEs by 11.5%. Other studies have shown that there is a strong correlation between length of stay and rate of AEs [7,16]. The average length of stay in Norway for all hospitalised patients in 2013 was 5.6 days and 6.1 days for cancer patients [17]. Our study correlates with findings for the overall hospital population, while our cancer patients are admitted two days longer than the national average. Increased rates of AEs can both be the cause for or a consequence of longer length of stay [16,18]. Our study was not designed to clarify this question.

A meta-analysis of AEs measured by the GTT, found an average of 29% of admissions with at least one AE and an average of 61 AEs per 1000 patient days [3]. These average rates are higher than we found in our study, but comparing rates are difficult due to differences in study population and case mix. A Norwegian national GTT measurement shows that the total

Table 3. Cancer characteristics and rate of AEs.

		Admissions with AEs		AEs per 1000 patient days	
	Frequency (%)	Percent	p Value	Rate	p Value
Cancer categories			.520		.102
Gastrointestinal	210 (25.9)	26.2		35.9	
Urinary/Male genitalia	208 (25.6)	25.0		39.4	
Respiratory	95 (11.7)	29.5		32.7	
Lymphoma/Haematological	85 (10.5)	18.8		21.0	
Breast	65 (8.0)	23.1		46.4	
Gynaecology	51 (6.3)	17.6		22.7	
ENT	40 (4.9)	17.5		22.9	
Others	58 (7.1)	25.9		17.0	
Metastases			.028		.118
Lymphatic	122 (15.0)	36.5		45.2	
Organ	356 (43.8)	21.2		28.5	
None	334 (41.1)	23.9		32.3	
Treatment intention			.022		.002
Curative	281 (34.6)	30.4		44.9	
Palliative	531 (65.4)	21.3		25.8	
Treatment			.149		.022
Surgery	281 (34.6)	30.9		44.2	
Chemotherapy	77 (9.5)	24.9		31.1	
Radiation	40 (4.9)	27.2		19.2	
None	414 (51.0)	20.4		26.3	

Note: Estimated using negative binominal regression adjusted for demographic characteristics.

Table 4. Incidence rates for AEs.

	Admissions with AEs				AEs per 1000 patient days			
	Frequency	Percent	CI 95%	p Value[a]	Frequency	Rate	CI 95%	p Value[a]
Cancer patients N = 812	197	24.2	20.7–28.2	.000	253	37.1	32.8–42.0	.651
Other patients N = 5908	1027	17.4	16.3–18.6		1295	36.0	34.1–38.0	

Note: Comparison of frequency and rate not adjusted for any other variables.
[a]Negative bi-nominal regression.

Table 5. Incidence rate for AEs.

Parameter	AEs per 1000 patient days	95% CI	Exp(B)	p Value[a]
Patients				
Cancer	24.4	20.7–28.7	0.937	.349
Others	26.0	23.2–29.2	1	
Age			1.013	.000
Gender				
Male	14.9	12.9–17.3	1.010	.851
Female	15.3	13.3–17.7	1	
Type of admission				
Acute	18.5	16.2–21.1	1.174	.010
Planned	12.4	10.5–14.6	1	
Year				
2010	27.2	15.3–21.0	1.049	.511
2011	25.2	14.4–19.8	0.973	.707
2012	22.7	11.0–15.4	0.875	.087
2013	25.9	12.0–17.6	1	
Hospital				
Central Hospital Bodø	17.7	15.8–19.9	0.991	.906
District Hospital Lofoten	13.4	11.1–16.3	0.702	.000
District Hospital Vesterålen	14.6	12.0–17.6	1	
Department				
Internal medicine	13.5	11.7–15.7	0.984	.929
Surgery	23.6	21.1–26.6	1.745	.002
Gynaecology	17.8	14.2–22.4	1.562	.025
Neurology	13.3	10.5–16.9	0.755	.155
Others	10.4	7.21–15.1	1	

Note: Rates adjusted for age, gender, type of admission, year, hospital and department.
[a]Negative Binomial regression with fixed age 60.9 years and length of stay 6.37 days.

harm rate on average was 15.96% for the same time period [19]. This is lower than our rate and could be due to the fact that Nordland Hospital Trust reviews seven times more patient records than other hospitals in Norway [12]. Our results are consistent with findings from Denmark where similar rates of AEs were detected in cancer patients [20].

The district hospital of Lofoten has a 30% lower rate of AE (13.4 per 1000 patient days). This is significantly lower than the Central Hospital of Bodø (17.7 per 1000 patient days) but not much lower than the Local Hospital of Vesterålen (14.6 per 1000 patients days). These findings correlate with the size of the hospitals and are most likely explained by the fact that the local hospitals perform less surgery and have a lower DRG index.

Admissions with AEs tell us what happens to the patients, while AEs per 1000 patient days adjusts for one important risk factor, and makes it more appropriate for monitoring over time. In addition, our data show that adjusting for other characteristics such as age, gender, type of admission and department further decreases the rate of AEs per 1000 patient days to 37.1 vs. 24.4 and 36.0 vs. 26.0 respectively. This implies that demographic characteristics significantly affect the rate of AEs. Demographic variables may vary and especially affect small sample sizes as recommended reviewed in the IHI GTT method. Not adjusting for demographic variables therefore raises concern about the GTT methods ability to detect real change when monitoring AEs even within an organisation.

The age of patients is a main risk factor for AEs [7,21]. Our results indicate that for every year increase in age, the risk of an AE increases by 1.3%. In our sample, cancer patients are 10.2 years older than other patients, increasing the risk by 13%. Age is also a strong determinant of cancer risk and an

Table 6. Comparing type of AEs per admission.

	Cancer patients	Other patients	Admission with AEs cancer vs. other patients			Admissions with AEs adjusted[a] cancer vs. other patients		
	N (%)	N (%)	Exp(B)	p Value	CI 95%	Exp(B)	p Value	CI 95%
Hospital acquired infections	94 (11.5)	451 (7.6)	1.51	.001	1.20–1.91	1.03	.848	0.80–1.32
Urinary tract infection	29 (3.6)	180 (3.0)						
Central venous catheter infection	1 (0.1)	4 (0.1)						
Ventilator associated pneumonia	1 (0.1)	9 (0.2)						
Other infections	37 (4.5)	164 (2.8)						
Lower respiratory infections	26 (3.2)	94 (1.6)						
Surgical complications	71 (8.7)	335 (5.7)	1.54	.002	1.18–2.00	0.99	.920	0.74–1.31
Infection after surgery	12 (1.5)	59 (1.0)						
Respiratory complications after surgery	4 (0.5)	13 (0.2)						
Return to surgery	8 (1.0)	46 (0.8)						
Injury, repair or removal of organ	6 (0.7)	19 (0.3)						
Bleeding after surgery	11 (1.3)	82 (1.4)						
Any other operative complication	25 (3.1)	113 (1.9)						
Switch in surgery	5 (0.6)	3 (0.1)						
Bleeding and thrombosis	20 (5.6)	142 (2.4)	1.02	.933	0.64–1.64	0.74	.228	0.45–1.21
Thrombosis-embolism	5 (0.6)	27 (0.5)						
Bleeding	15 (1.8)	115 (1.9)						
Patient fall and fracture	10 (1.2)	87 (1.4)	0.83	.586	0.43–1.61	0.65	.217	0.33–1.29
Patient fall	9 (1.1)	45 (0.8)						
Fracture	1 (0.1)	42 (0.7)						
Medication harm	28 (3.4)	100 (1.7)	2.03	.001	1.33–3.10	1.87	.005	1.20–2.91
Obstetric harm	0 (0)	36 (0.6)						
Pressure ulcers	7 (0.9)	37 (0.6)	1.37	.446	0.61–3.09	1.05	.904	0.45–2.45
Others	23 (2.8)	107 (1.8)	1.56	.057	0.99–2.46	1.42	.146	0.88–2.29
Allergy	4 (0.5)	23 (0.4)						
Medical technical harm	5 (0.6)	14 (0.2)						
Deterioration of chronic illness	6 (0.7)	15 (0.3)						
Others	8 (1.0)	55 (0.9)						

Note: AEs grouped into 23 categories and aggregated into eight main categories for statistical analysis. Estimated differences using negative binominal regression.
[a]Results adjusted for demographic characteristics.

ageing population will increase the cancer rate per se. This implies that more patients will need cancer treatment, and thus escalate the burden on cancer care, and risk of AEs in our hospitals [22].

Our results are consistent with other studies indicating that admission to a surgical department and having surgery increases the rate of AEs [16,23]. A majority of our cancer patients are admitted to surgical departments and 36% have surgery. Since surgery is the main curative treatment for cancer, this partly explains why receiving treatment with curative intent increase the risk for AEs.

In accordance with other GTT studies on cancer patients, cancer patients more often experience AEs related to hospital-acquired infections (lower respiratory infections and other infections), surgical complications and medication harm [24,25]. Adjusted for length of stay and other demographic variables, the only type of AE cancer patients experience more often is harm related to medication. Unfortunately, we do not know if these AEs relate to chemotherapy or other medications. The GTT method only registers if an AEs has occurred, and does not identify supplementary information such as type of medication, dosage or polypharmacy that could identify underlying causes and benefit further improvement work. Many of the categories are heterogeneous and need to be more specific to provide meaningful data for improvement in cancer care.

Our sample is representative for a general hospitalised population and shows that the majority of cancer patients receive surgery or ordinary medical treatment. Only 15% of the patients receive cancer related treatment such as chemotherapy or radiation. Our study shows that cancer in itself is not a risk factor for AEs, and hospitalised cancer patients seem to have the same general risk factors for AEs as other patients. Having cancer should therefore not affect the reliability of the GTT method when used in an ordinary in-hospital population. The fact that only 15% of hospitalised cancer patients receive medical or radiation related cancer treatments indicates that monitoring AEs related to these treatments preferably should be done in an ambulatory setting.

Limitations

The GTT as a method has limitations that most likely also apply to our study. The reliability of record reviewing is moderate to sustainable when done by a small group of reviewers [9]. In our study, seven different teams (21 reviewers) did the review. Even though the teams had the same training, where fairly consistent and reviewed 960 records during the period, there is a possibility that their judgement of what is an AE, severity grading and classification could vary between the teams and deviate over time. Another GTT study in the health trust has shown substantial agreement between teams, but our study was not designed to look at inter-rated reliability [12]. As a retrospective record review method, the GTT may have limitations regarding documentation bias, since reviewers must rely on information recorded in the patient charts. This could be avoided performing a real time observation study, but does not seem feasible to use as a method to measure AEs over time.

Nonetheless, GTT is one of the few tools measuring AEs in health care, and is recommended for use in many organisations worldwide. Another limitation of our study is not adjusting for comorbidities, especially since the age difference between the groups is more than 10 years and cancer patients therefore could have more comorbidity.

Conclusions

Hospitalised cancer patients more often than other patients experience AEs, but this is due to older age, longer length of stay and surgery rather than the cancer itself. In addition, our study shows that demographic characteristics affect the rate of AEs, and raise reliability concerns regarding the GTT method's ability to detect real change when monitoring AEs over time. When measuring AEs in a general hospitalised population, the GTT method seems just as reliable for cancer patients as other patients. Since only a small amount of hospitalised cancer patients receives medical or radiation related cancer treatments, we suggest that a method for measuring AEs in an outpatient cancer setting should be developed. Developing cancer specific categories for AEs would also be essential in order to provide meaningful data for improvement in cancer care.

Ethical considerations

The Regional Committee of Ethics in Norway has reviewed the study and categorised it as retrospective health record research, which does not require approval by the committee (2013/1823).

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Paper II

Contribution of adverse events to death of hospitalised patients

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ABSTRACT

Background There is no standardised method to investigate death as a patient safety indicator and we need valid and reliable measurements to use adverse events contributing to death as a quality measure.

Objective To investigate the contribution of severe adverse events to death in hospitalised patients and clarify methodological differences using the Global Trigger Tool method on all inpatient deaths compared with a sample of general hospitalised patients.

Method Retrospective records reviewing using the Global Trigger Tool method.

Results In 0.3% of hospital admissions, adverse events contribute to inpatient death. Patients who die in hospital have twice the rate of adverse events per 1000 patient days compared with general patients, 76.7 vs 36.5 (p<0.001, RR 2.10, 95% CI 1.79 to 2.47). Patients dying in hospital experience seven times the rate of severe adverse events, 38.4% vs 5.2% (p<0.001, RR 2.10, 95% CI 1.79 to 2.47). For 86 out of 377 inpatient deaths, the adverse event is so severe that it contributes to death. 27.9% of severe adverse events contributing to death originate in primary care. Lower respiratory infections (p<0.001, RR 2.81, 95% CI 1.76 to 4.51), medication harm (p<0.001, RR 5.21, 95% CI 3.04 to 8.94) and pressure ulcers (p=0.04, RR 2.23, 95% CI 1.03 to 4.85) are significantly more frequent for inpatient deaths than in the general sample of hospital patients.

Conclusions Patients dying in hospitals experience seven times the rate of severe adverse events. Reviewing all inpatient death by the Global Trigger Tool method discloses new valid and reliable data of severe adverse events contributing to death which otherwise would be undetected.

INTRODUCTION

It has been estimated that adverse events due to medical error are the third leading cause of death in the USA.[1 2] These estimates are based on studies of general hospitalised populations extrapolating that 0.6%–1.1% of admissions result in death due to adverse events.[3 4] Other studies of inpatient deaths indicate that most types of adverse events occur more often in patients dying in hospitals.[5 6] This makes studying inpatient death in an efficient way to identify preventable adverse events and provide valuable information in areas for improvement.[6] A number of studies investigating mortality have found that only 0.5%–6.0% of adverse events contributing to death are preventable.[7–10] However, preventability is often difficult to determine and including this subjective judgement to mortality measures makes the measure even more uncertain.[11] There is no standardised method of investigating death as a patient safety indicator, and uncertainty about the results has lead to an ongoing discussion about using estimated mortality from adverse events as a quality measure in patient safety.[12 13] All the methods used have limitations such as extrapolation of results from samples, data not being based on a representative population or include subjective judgement of expectancy of death or preventability of adverse events. Despite these epidemiological controversies, death is the most severe consequence of an adverse event, and knowing the actual occurrence and type of adverse events contributing to death can be valuable to improve patient safety.

Retrospective record reviewing with trigger tools is a widely used methodology for a systematic review of adverse events in patient records, with high sensitivity and specificity compared with other methods.[4 14] Most trigger tool analyses are performed on samples of general hospitalised patients that involve few deaths and may therefore not provide valid epidemiological estimates of all patients dying in hospitals. Similar studies conducted on inpatient deaths are mainly based on samples and include judgement of preventability in assessing adverse events contributing to death.[6–10] Instead of collecting data on many less severe adverse events that rarely result in death, an in-depth analysis of all hospital deaths could provide more valid and reliable data on severe adverse events that otherwise are undetected.

The aim of our study is to investigate the contribution of severe adverse events to death in hospitalised patients and clarify methodological differences using the Global Trigger Tool (GTT) method on all inpatient deaths compared with a sample of general hospitalised patients.

METHOD
Study design
The study is a retrospective record review using the GTT method to compare adverse events in a sample of general hospitalised patients to review all inpatient deaths from 1 January 2013 to 31 December 2013.

Setting
The study was performed at Nordland Hospital Trust in Norway. This is a public health trust consisting of three hospitals: one central and two smaller district general hospitals, with 524 beds in total. The three hospitals cover a population of approximately 136 000 people and offer most surgical and medical specialties.

Study population
The sample of general hospitalised patients includes 1680 patient records. Ten patient records were randomly sampled twice monthly through block randomisation from the discharge list of seven functional units in the trust (surgery, orthopaedics, internal medicine, gynaecology/obstetrics, neurology/others and the district hospitals of Lofoten and Vesterålen). Patients under the age of 18, patients with a length of stay <24 hours or patients admitted primarily for psychiatric conditions or rehabilitation were excluded.

For the inpatient death sample, all 377 patients who died in the three hospitals during 2013 were included. Five patients under the age of 18 were excluded (figure 1).
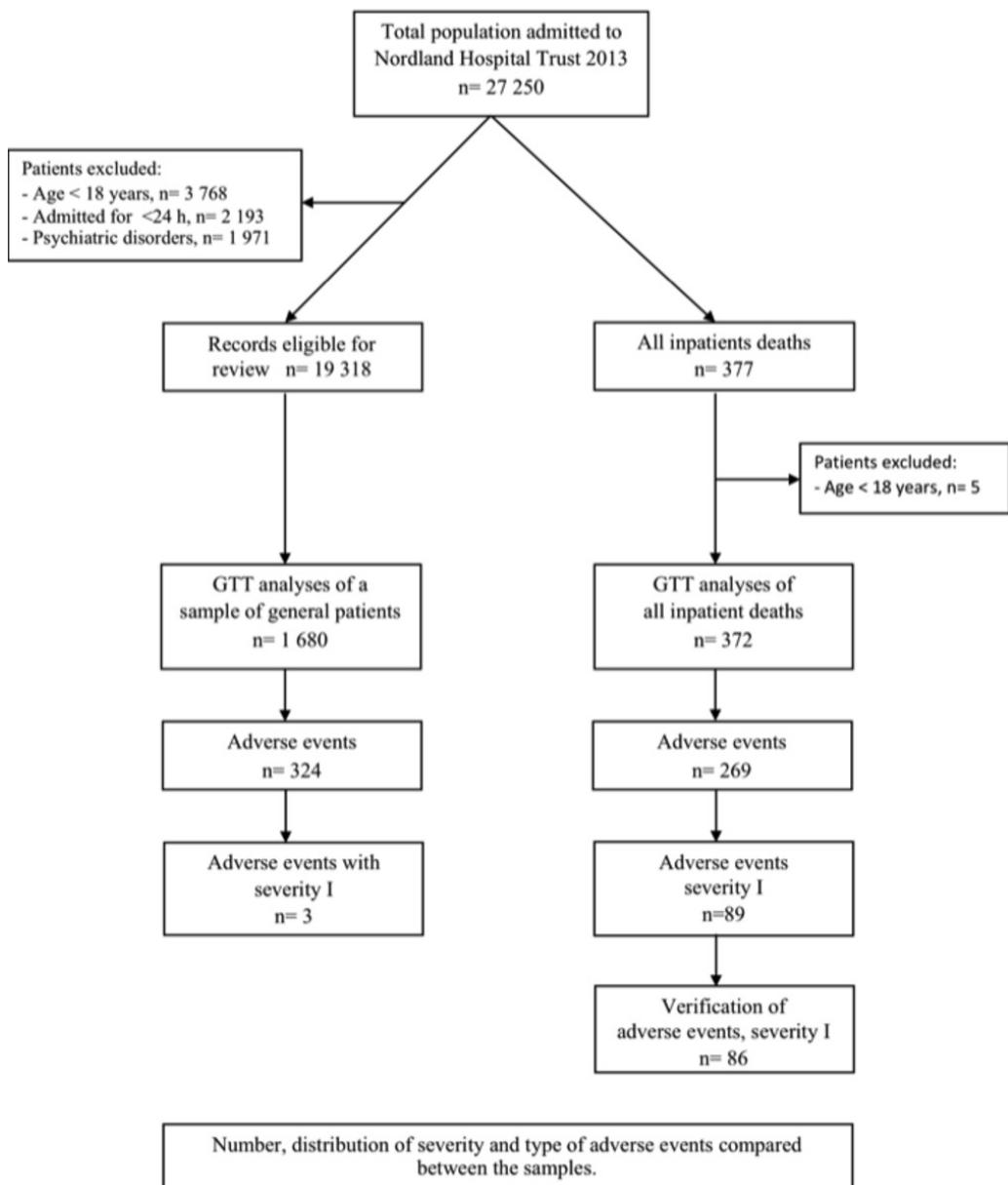

Figure 1 Study population and design. GTT, Global Trigger Tool.

GTT review of a general sample

Nordland hospital trust since 2010 has routinely performed GTT reviews of general hospitalised patients. Our general sample consist of 1680 patient records routinely reviewed in 2013. Seven different teams performed a two-stage review according to the Norwegian version of The Institute of Healthcare Improvement GTT manual.[15 16] Two nurses reviewed all records independently before they together reached consensus on presence, category and severity of adverse events. A physician then verified their findings.

GTT review of inpatient deaths

During 6 months in 2015, an independent team of two nurses and one physician reviewed the records of all hospital deaths during 2013. The review was done in the same way as the general sample, but the physician reached consensus together with the nurses. Then, two other physicians independently re-reviewed the records of adverse events contributing to death and agreed/disagreed on the adverse event, severity and type of harm. Finally, the physician from the primary review team and the verifying physicians discussed the findings and reached consensus.

Definition and classification of adverse events

Adverse events were defined as: '*Unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalisation, or that results in death*'.[16] The severity of adverse events was categorised according to the National Coordinating Council for Medication Error Reporting and Prevention Index (NCC MERP index),[17]:

► Category E: temporary harm that required intervention.
► Category F: temporary harm that required initial or prolonged hospitalisation.
► Category G: permanent patient harm.
► Category H: intervention required necessary to sustain life.
► Category I: harm contributes to patient death.

Adverse events were categorised into 23 categories according to recommendations of the Norwegian GTT manual.[15] For statistical purpose, the categories were aggregated into eight main categories in the study: hospital-acquired infections, surgical complications, bleeding/thrombosis, patient fall/fracture, medication harm, obstetric harm, pressure ulcer and others. Table 1 gives an overview of the original categories and their aggregation. Adverse events associated with medical care given prior to or during hospitalisation were included to evaluate the total number of adverse events. For medication-related adverse events, the generic name was obtained. In addition, we obtained age, gender, length of stay, hospital, department, type of admission, primary and secondary diagnosis on discharge classified according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) system.

Statistical analysis

Demographic variables were compared using the Pearson's X^2 test and the Mann-Whitney U test. Incidence rates of adverse events, severities and categories of adverse events were compared using Poisson regression in generalised linear models. Rates were calculated as adverse events per 1 000 patient days and as the percentage of admissions with one or more adverse events. Log patient days were used as an offset variable to compare rates per 1000 patient days, and for admissions with adverse events, the offset variable was set to a fixed value of 0. In addition, we adjusted for the demographic variables such as age, gender, length of stay, hospital, department, type of admission and primary diagnosis. A p value <0.05 was deemed statistically significant. Data were analysed with IBM SPSS V.24.0.0.2.

RESULTS

Demographic characteristics

Patients dying in the hospital are on average older than 18.7 years, stay 5.2 days longer, are mainly emergency admissions and die more frequently in departments of internal medicine compared with patients discharged alive from hospital. Their three most common primary diagnoses are circulatory disorders, respiratory disorders and cancer (table 2).

Comparison of adverse events

Analysing all inpatient deaths, adverse events contributed to death in 0.3% of all hospital admissions. Forty-six per cent of admissions for inpatient death experience one or more adverse events, compared with 16.3% of admissions in the general sample (p<0.001, RR 2.83, 95% CI 2.34 to 3.43). Inpatient deaths have twice the rate of adverse events per 1000 patient days compared with the general sample, 76.7 vs 36.5 (p<0.001, RR 2.10, 95% CI 1.79 to 2.47). Adjusting for demographic variables did not alter the result regarding the rate of adverse events per 1000 patient days, 6.1 vs 3.1 (p<0.001, RR 1.94, 95% CI 1.58 to 2.39).

Severity of adverse events

More severe adverse events (severity G, H and I) were identified for inpatient deaths than in the general sample, 38.4% vs 5.2%. Adjusted for demographic variables, admissions with adverse events and rates of adverse events per 1000 patient days for inpatient deaths are significantly higher for severe adverse events (severity G, H and I) (p<0.001, RR 24.0, 95% CI 11.47 to 50.13). There is no significant difference between the samples in rates of temporary adverse events (severity E and F) per 1000 patient days (p=0.138, RR 1.19, 95% CI 0.95 to 1.50) (table 3). For inpatient deaths, 89 adverse events were primarily categorised as severity I. After verification and consensus, two adverse events were dismissed, one changed severity and two changed types of harm, concluding with 86 adverse events contributed to death

Table 1 Comparing types of adverse events

| | General sample | Inpatient deaths | Severity I | Admission with adverse events Inpatient deaths vs General patients | | | Adverse events per 1000 patient days Inpatient deaths vs General patients | | |
	N (%)	N (%)	N (%)	Exp (β)	P value	95% CI	Exp (β)	P value	95% CI
Hospital-associated infections	**108 (33.3)**	**114 (42.1)**	**44 (51.2)**	**1.98**	**0.000**	**1.43 to 2.74**	**1.87**	**0.000**	**1.36 to 2.57**
Urinary tract infection	44 (13.6)	18 (6.6)	2 (2.3)	0.99	0.965	0.51 to 1.90	0.99	0.967	0.51 to 1.90
Central venous catheter infection	0 (0)	0 (0)	0 (0)						
Ventilator-associated pneumonia	2 (0.6)	3 (1.1)	1 (1.2)						
Other infections	28 (8.6)	25 (9.2)	0 (0)						
Lower respiratory infections	34 (10.5)	68 (25.3)	41 (47.7)	3.29	0.000	2.03 to 5.34	2.81	0.000	1.76 to 4.51
Surgical complications	**95 (29.3)**	**19 (7.0)**	**13 (15.1)**	**0.92**	**0.792**	**0.50 to 1.69**	**0.97**	**0.923**	**0.54 to 1.76**
Infection after surgery	21 (6.5)	2 (0.7)	0 (0)						
Respiratory complication surgery	1 (0.3)	3 (1.1)	1 (1.2)						
Return to surgery	14 (4.3)	1 (0.4)	8 (9.3)						
Injury, repair or removal of organ	7 (2.2)	7 (2.6)	3 (3.5)						
Bleeding after surgery	21 (6.5)	2 (0.7)	1 (1.2)						
Any other operative complication	31 (9.6)	4 (1.5)	0 (0)						
Switch in surgery	0 (0)	0 (0)	0 (0)						
Bleeding and thrombosis	**30 (9.3)**	**13 (4.8)**	**6 (7.0)**	**1.70**	**0.177**	**0.79 to 3.69**	**1.65**	**0.198**	**0.77 to 3.55**
Thrombosis–embolism	7 (2.2)	10 (3.7)	4 (4.7)						
Bleeding	23 (7.1)	3 (1.1)	2 (2.3)						
Patient fall and fracture	**20 (6.2)**	**13 (4.8)**	**2 (2.3)**	**1.71**	**0.204**	**0.75 to 3.86**	**1.36**	**0.477**	**0.58 to 3.17**
Patient fall	16 (4.9)	6 (2.2)	1 (1.2)						
Fracture	4 (1.2)	7 (2.6)	1 (1.2)						
Medication harm	**27 (8.3)**	**76 (28.0)**	**17 (19.8)**	**6.28**	**0.000**	**3.64 to 10.85**	**5.21**	**0.000**	**3.04 to 8.94**
Obstetric harm	**14 (4.3)**	**0 (0)**	**0 (0)**						
Pressure ulcers	**11 (3.4)**	**25 (9.2)**	**0 (0)**	**2.17**	**0.059**	**0.97 to 4.83**	**2.23**	**0.043**	**1.03 to 4.85**
Others	**19 (5.9)**	**9 (3.3)**	**4 (4.7)**	**1.05**	**0.928**	**0.39 to 2.79**	**0.86**	**0.754**	**0.33 to 2.24**
Allergy	9 (2.8)	3 (1.1)	0 (0)						
Medical technical harm	3 (0.9)	1 (0.4)	1 (1.2)						
Deterioration of chronic illness	2 (0.6)	0 (0)	1 (1.2)						
Others	5 (1.5)	5 (1.9)	2 (2.3)						

23 types of adverse events aggregated into eight categories (bold text) for statistical purpose. Estimated differences using Poisson Regression adjusted for demographic variables.

Table 2 Characteristics of patients

Parameter	General patients n=1680	Inpatient deaths n=372
Mean age, years (SD)	58.8 (21.3)	77.5 (13.2)*
18–102	18–102	18–102
Mean length of stay, days (SD)*	5.3 (5.9)	9.4 (11.7)*
1–86	1–86	1–65
Gender, N (%)*		
Female	993 (59.1)	182 (44.9)
Male	687 (40.9)	190 (51.1)
Type admission, N (%)*		
Acute	1211 (72.1)	364 (97.8)
Planned	469 (27.9)	8 (2.2)
Hospital, N (%)*		
District Hospital Lofoten	240 (14.3)	56 (15.6)
District Hospital Vesterålen	240 (14.3)	87 (23.4)
Central Hospital Bodø	1200 (71.4)	227 (61.0)
Department, N (%)*		
Internal medicine	486 (28.9)	258 (69.4)
Surgery	680 (40.5)	93 (25.0)
Neurology	151 (9.0)	17 (4.6)
Gynaecology	276 (16.4)	0
Other departments	87 (5.2)	3 (0.8)
Primary diagnosis, N (%)*		
Infections	28 (1.7)	23 (6.2)
Cancer	112 (6.7)	78 (21.0)
Endocrine and haematological	86 (5.1)	6 (1.6)
Neurological disorders	69 (4.1)	4 (1.1)
Circulatory disorders	164 (9.8)	102 (27.4)
Respiratory disorders	127 (7.6)	93 (25)
Gastrointestinal disorders	144 (8.6)	25 (6.7)
Skeletal and muscular disorders	21 (1,3)	3 (0.8)
Urinary disorders	150 (8.9)	16 (4.3)
Pregnancy and birth	231 (13.8)	0
Damage and poisoning	170 (10.1)	16 (4.3)
Unspecific symptoms	114 (6.8)	4 (1.1)
Other disorders	264 (15.7)	18 (4.8)
Origin of adverse events, N (%)*		
Primary care	43 (11.6)	51 (19.0)
Hospital	329 (88.4)	218 (81.0)

*Differences between groups for all characteristics, p<0.0001.

Table 3 Distribution of adverse events by severity

Adverse events	Severity categories				
	E	F	G*	H*	I*
General patients n=324	174 (53.7)	133 (41.0)	12 (3.7)	2 (0.6)	3 (0.9)
Inpatient deaths n=269	90 (33.4)	76 (28.3)	12 (4.5)	5 (1.9)	86 (32.0)

*Estimated differences per 1000 patient days using Poisson regression adjusted for demographic variables, p<0.001. Severity categories according to the NCC MERP index.

general sample. For inpatient deaths, 27.9% of adverse events contributing to death were present on admission and originated in primary care. Inpatient deaths where the adverse event originate in primary care has a shorter length of stay (6.9 vs 15.8 days) and patients are on average 6.7 years older (84.4 vs 77.7 years) compared with inpatient deaths where adverse events originate after admission to hospital.

Type of adverse events
For inpatient death, we identify more healthcare-associated infections than in the general sample, 42.4% vs 33.0%. These are mainly lower respiratory infections, 25.5% vs 10.5%. Inpatient deaths have more than five times the risk rate for adverse events related to medications than the general sample, 28.0% vs 8.3%, and twice the risk rate of developing pressure ulcers, 9.2% vs 3.4% (table 1).

Type of adverse events contributing to death
Lower respiratory infections with 47.7% and medication adverse events with 19.8% are the most common types of adverse events contributing to death among the 86 inpatient deaths. Patients dying of lower respiratory infections are on average 82 years old and stay in hospital on average 16.9 days. Patients acquiring the lower respiratory infection in primary care have a significantly shorter length of stay than those with a hospital-acquired infection, 6.0 vs 22.5 days. Medication adverse events contribute to death for 17 of the inpatient deaths. Twelve of these patients have cancer as a primary or secondary diagnosis, whereof 8 patients experience lethal complications after chemotherapy (table 1).

DISCUSSION
Patients dying in hospitals differ from general hospitalised patients in several ways and experience seven times the rate of severe adverse events. GTT review of all inpatient deaths and a sample of general hospitalised patients disclose different measures and perspectives that need to be considered using adverse events contributing to death as a valid and reliable quality measure.

The high ratio of adverse events for inpatient deaths in our study is similar to reviews of inpatient deaths done

for inpatient deaths compared with three adverse events in the general sample.

Origin of adverse events
Nineteen per cent of adverse events originated in primary care for inpatient deaths compared with 11.6% in the

in the Netherlands and a mortality review programme at Mayo Clinic in the USA.[5 6] Nevertheless, our rates are higher than most other studies undertaken on general hospitalised patients.[18–20] Even though we have a higher rate of adverse events contributing to death than other studies, adverse events contributing to inpatient deaths only account for 0.3% of all hospital admissions. This is lower than the 0.6%–1.3% of adverse events contributing to death extrapolated in previous general GTT studies.[3 4] This difference can be explained by large random variation when extrapolation is based on small numbers of adverse events contributing to death.

The high rate of adverse events in our study can partly be explained by the inclusion of adverse events originating in primary care, prior to admission. Patients dying in the hospital are a highly selected group of patients who are older, stay longer, are mainly emergency admissions and have a smaller range of primary diagnoses. From a previous study, we know that the risk of adverse events increases by 1.3% for every year increase in age and 5.1% for each day spent in the hospital.[21] To have a representative population, we argue that measuring adverse events contributing to death should be based on inpatient deaths rather than generalisation of reviews of general hospitalised patients.

Even after adjusting rates of adverse events for demographic variables and primary diagnosis patients dying in hospitals have nearly twice the rate of adverse events per 1000 patient days. This indicates that rates of adverse events for inpatient deaths are influenced by other factors than just demographic characteristics. Many patients who die in hospitals are very ill and frail from underlying conditions, making them more vulnerable to adverse events. It is rarely straightforward to establish that an adverse event has led directly to death. More often, the adverse event is one of many factors contributing to death. This does not diminish the importance of the event, but should instead encourage us to monitor and treat these patients with utmost care and caution.

Inpatient deaths experience seven times the rate of severe adverse events than found in the general GTT sample, and much greater rates compared with any other general GTT studies.[18–20] Our general sample includes 8.7% of hospitalised patients in our trust, including 8.8% of the inpatient deaths. In our general sample, we found only three adverse events so severe that they contributed to death. This difference in the rate of adverse events contributing to death could be due to differences in sample size, and the fact that adverse events contributing to death are rare in general hospitalised patients. Then again, we find no significant difference in the rate of more common temporary adverse events (severity E and F) between the two samples. We argue that using the GTT method on a general hospitalised population is appropriate for identifying more common temporary adverse events, but the sample size is too small to provide reliable metrics of rarely occurring severe adverse events.

By including all inpatients deaths, we avoid this sampling error. Our data demonstrate that reviewing all inpatient deaths can provide new valid and reliable data of severe adverse events which otherwise would be undetected.

To evaluate the total number of adverse events resulting from medical care, we included all adverse events associated with care given prior to hospitalisation. Nearly one-third of adverse events contributing to death are present on admission and originates in primary care. These patients are on average older than other inpatient deaths and are often admitted from a nursing home. On average, they die within a week after admission and have a much shorter length of stay than patients acquiring their adverse event during hospitalisation. Our study does not investigate more deeply the circumstances around these admissions. Nevertheless, it raises questions as to whether the patient should have been admitted before or not admitted at all. Given that nearly one-third of patients are admitted with an adverse event contributing to death, it seems likely that the quality of care provided in primary care prior to admission to some degree affects the mortality measures of hospitals.

Baines *et al* have found that inpatient deaths have a lower proportion of surgical-related adverse events and a greater proportion of preventable hospital-acquired infections.[5] In our study, we find that healthcare-associated infections, medication harm and pressure ulcers are significantly more frequent among inpatient deaths than in the general sample. We identified a greater proportion of surgically related adverse events among inpatient deaths but adjusting for demographic variables, there is no significant difference between the samples.

We find that lower respiratory infections are the most common severe adverse event, occurring nearly three times as frequently and contributing to the death of nearly half of the inpatient deaths. Pneumonia is one of the most common infections requiring hospitalisation,[22] and for one-third of these patients, pneumonia originating in primary care contributed to death. The prevalence of lower respiratory infections in our study may be accounted for by the inclusion of adverse events originating in primary care. Studies over the last decade have shown that healthcare-associated pneumonia, for instance, acquired in nursing homes, differs from community-acquired pneumonia in terms of pathogens, symptoms and prognosis.[23 24] Delayed recognition of symptoms and delayed delivery of appropriate antimicrobial therapy result in excess mortality.[25] These patients are older and have a greater burden of comorbidities, so patients at risk of healthcare-associated pneumonia are also those at increased risk of dying from their underlying conditions. This makes the causality of death hard to establish. Due to this, many clinicians have judged lower respiratory infections difficult to prevent. Judging preventability is a subjective process varying between reviewers, affected by culture and are changing over

time.[11 26] Healthcare-associated and hospital-acquired pneumonia are nevertheless important causes of severe adverse events that need to be considered when trying to improve patient safety. We argue that not judging preventability provides a more robust and reliable measurement of adverse events contributing to death.

Inpatient deaths have five times the risk for medication-related adverse events. Nearly all of the medication adverse events contributing to death were related to the treatment given in hospitals. More than 70% of severe medication adverse events contributing to death occur in patients with cancer, and most of these adverse events were related to lethal complications after chemotherapy. This makes medication adverse events primarily a safety issue in hospitals and confirms other studies identifying chemotherapy as a severe risk factor for adverse events in patients with cancer.[27 28]

Strengths and limitations

This study has the standard limitations of retrospective patient record reviewing such as information bias and poor to moderate reliability. The review process was performed in a slightly different way for the two samples. The step where the physician comes to consensus with the nurses for the inpatient death sample can have influenced what was considered an adverse event and its severity. Hindsight bias could be another limitation. Knowing the outcome and its severity on the judgement of causation could influence the judgement.[29] The outcome of inpatient death is death, compared with the general sample where the outcome and the severity of the adverse events are largely unknown at the start of the review process. Hindsight bias may have led to an overestimation of the number and severity of adverse events for the inpatient death sample. To reduce the risk of hindsight bias, we added an extra step in the reviewing process of the inpatient death sample, where two independent physicians reviewed and discussed the most severe adverse events contributing to death once more before consensus was reached. The good correlation between the reviewing physicians could indicate a low effective hindsight bias, and we argue that adding this extra step increases the validity of the results for the inpatient deaths. Another strength of our study is that all inpatient deaths in our hospital trust are included, avoiding selection bias and providing a more accurate measurement of the contribution of adverse events to death in hospitalised patients.

CONCLUSION

Patients dying in hospitals differ in several ways from a general hospitalised population and experience seven times the rate of severe adverse events. GTT review of general hospitalised patients primarily identifies more common temporary adverse events, while a review of all inpatient deaths provides a new valid and reliable measurement of severe adverse events contributing to death that otherwise would be undetected. Demographic differences and sample size argue that mortality estimates of adverse events rarely contributing to death should not be extrapolated from GTT reviews of small general samples of hospitalised patients.

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Paper III

1 **Adverse events in deceased hospitalised cancer patients as a**

2 **measure of quality and safety in end-of-life cancer care**

3

4

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25

Abstract

Background: Anticancer treatment exposes patients to negative consequences such as increased toxicity and decreased quality of life, and there are clear guidelines recommending limiting use of aggressive anticancer treatments for patients near end of life. The aim of this study is to investigate the association between anticancer treatment given during the last 30 days of life and adverse events contributing to death and elucidate how adverse events can be used as a measure of quality and safety in end-of-life cancer care

Methods: Retrospective cohort study of 247 deceased hospitalised cancer patients at three hospitals in Norway. The Global Trigger Tool method were used to identify adverse events. We used Poisson regression and binary logistic regression to compare adverse events and association with use of anticancer treatment given during the last 30 days of life.

Results: 30 % of deceased hospitalised cancer patients received some kind of anticancer treatment during the last 30 days of life, mainly systemic anticancer treatment. These patients had 62 % more adverse events compared to patients not being treated last 30 days, 39 vs. 24 adverse events per 1 000 patient days (p<0.001, OR 1.62 (1.23 – 2.15). They also had twice the odds of an adverse event contributing to death compared to patients without such treatment, 33 vs. 18 % (p=0.045, OR 1.85 (1.01 – 3.36)). Receiving follow up by specialist palliative care reduced the rate of AEs per 1 000 patient days in both groups by 29 % (p= 0.02, IRR 0.71, CI 95% 0.53 – 0.96).

Conclusions: Anticancer treatment given during the last 30 days of life is associated with a significantly increased rate of adverse events and related mortality. Patients receiving specialist palliative care had significantly fewer adverse events, supporting recommendations of early integration of palliative care in a patient safety perspective.

Key words: Adverse event, end of life, palliative care, Global Trigger Tool, patient safety

2

Background

Effectiveness and safety are essential elements of value-based cancer care that need to be considered when making decisions about treatment during the entire continuum of the disease [1–3]. Striking the right balance between the two is a major clinical challenge, especially when the disease progresses towards the end of life. At this stage discontinuing anticancer treatment is one of five recommendations to reduce unnecessary treatment and increase the value of healthcare for patients with advanced cancer [4, 5].

Survival is of critical concern for cancer patients, but near the end of life the quality of care and how patients spend their remaining time is just as important [6, 7]. Nevertheless, up to one out of five cancer patients receives anticancer treatment during the last 30 days of life without clear benefit of prolonging survival. The treatment also exposes them to the risk of severe negative consequences such as increased toxicity and decreased quality of life [8–10]. A meta-analysis of the efficacy and safety of anticancer treatment compared to palliative care found no difference in overall survival and significantly more severe adverse events among patients receiving anticancer treatment during the last 30 days of life [11]. This emphasises the need not to focus just on survival, but also the need to assess symptoms, toxicities and complications of anticancer treatment by systematically measuring adverse events [12].

Today, quality measures for end-of-life cancer care generally examine utilisation of healthcare services and use of systemic anticancer treatment, radiotherapy and specialist palliative care during the last month of life [13–15]. Although severe adverse events in cancer care are considered an important outcome measure with high clinical value, current measurements do not include adverse events as an indication of quality and safety in end-of-life cancer care [16].

76

77 Thus, the objectives of our study is to investigate the association between anticancer treatment

78 given during the last 30 days of life and adverse events contributing to death and see if

79 adverse events can be used as a measure of quality and safety in end-of-life cancer care.

80

81 **Methods**

82 **Study design**

83 The study is a retrospective cohort study of deceased hospitalised cancer patients. We

84 performed a standardised retrospective record review using the Global Trigger Tool (GTT) to

85 identify adverse events contributing to death related to anticancer treatment given during the

86 last 30 days of life.

87

88 **Setting**

89 The study was conducted at a public health trust in Northern Norway, providing healthcare to

90 a population of 136 000 inhabitants. Nordland Hospital Trust has three somatic hospitals; one

91 central teaching hospital and two smaller district general hospitals. Cancer patients are treated

92 and hospitalised in all three hospitals, but only the central hospital has a separate oncology

93 and haematology department providing ambulatory chemotherapy and palliative radiotherapy.

94 All three hospitals has a specialist palliative care team providing both internal and ambulatory

95 care to patients referred to them. None of the hospitals has a separate oncological inpatient

96 unit. Accordingly, the primary care of hospitalised cancer patients is provided by other

97 specialists (e.g. internist, surgeon and neurologist) depending on the origin of the cancer, who

98 then consults an oncologist or palliative care if needed.

99

100

4

Study population

The cohort includes all cancer patients with solid tumours and haematological malignancies, 18 years or older who died in one of the three hospitals. Since there were no previous studies indicating incidence rates of adverse events contributing to death in this selected population we did a consecutive sampling of all cancer patients who died in the three hospitals between January 1st 2012 and December 31st 2013. Of the 737 deceased hospitalised patients, 16 children under the age of 18 years were excluded. 247 (34 %) patients had cancer as primary or secondary diagnosis on discharge classified by the ICD-10 system. These cancer patients were divided into one group that had received any kind of anticancer treatment and a second group that had not received any anticancer treatment during the last 30 days of life. From the electronic patient records we obtained baseline demographics such as age, gender, length of stay, hospital, department, primary and secondary diagnosis on discharge. We also reviewed the patient records for the type of cancer, presence of metastases, setting (diagnostic, curative or palliative), the last date of administration of parenteral or oral anticancer treatment (chemotherapy, targeted agents and immune therapy), the use of radiotherapy and cancer directed surgery, as well as the date for involvement of specialised palliative care.

Retrospective review

During six months in 2015, a team of two oncology nurses and one oncologist did a structured review of the patient records. The review was conducted according to the Norwegian version of the Institute of Healthcare Improvement GTT manual [17, 18]. The method is a two-stage process where the nurses independently review all records using triggers to identify adverse events. To the 48 general triggers, we added 21 specific oncology triggers developed by the 1000 Lives Plus Campaign in Wales, UK [19]. The two nurses independently identified the presence, category and severity of the AEs, before they discussed their findings with the

126   oncologist and together reached consensus. To validate the results, two other physicians

127   independently re-reviewed the records of adverse events contributing to death and

128   confirmed/rejected the adverse event, severity and type of harm.

129

130   **Definition and classification of adverse events**

131   We defined an adverse event as: "Unintended physical injury resulting from or contributed to

132   by medical care that requires additional monitoring, treatment or hospitalization, or that

133   results in death" [18]. The severity of AEs was categorised according to the NCC MERP

134   index [20]. Adverse events were recorded into six main categories: healthcare acquired

135   infections, surgical complications, bleeding/thrombosis, medication harm, pressure ulcer and

136   others. For medication-related adverse events, the generic name was documented.

137

138   **Statistical analysis**

139   We summarised the data using descriptive statistics and compared the groups using the Mann-

140   Whitney U test for non-parametric continuous variables, and the Chi square, Fisher`s exact or

141   Linear-by-Linear test for categorical variables. There were no missing data. Incidence rates of

142   adverse events, severities and categories of adverse events were compared using Poisson

143   regression for generalised linear models. Binary logistic regression was used to analyse if

144   adverse events were significantly associated with use of anticancer treatment during the last

145   30 days of life. To reduce the probability of Type I errors (Bonferronis` correction) the

146   number of variables included were limited to five. Building a model we first assessed which

147   variables were a potential confounder, before we adjusted for length of stay, age, gender and

148   primary malignancies. A p-value of <0.05 was considered significant. We used the statistical

149   package IBM SPSS Statistics V.25.0 to analyse the data.

150

Results

Patient characteristics

Most patients had advanced cancer and were in a palliative care setting. Sixty percent of the patients received some kind of anticancer treatment, mainly systemic anticancer treatment. Patients receiving treatment during the last 30 days of life had a longer length of stay and were more often admitted to the central hospital. Patients with lung cancer, lymphoma and haematological malignancies were more likely to receive treatment during the last 30 days of life. Table 1 compare characteristics between patients receiving anticancer treatment during the last 30 days of life with patients not receiving such treatment.

Table 1 Characteristics

Variable	No anticancer treatment last 30 days *n*= 174		Anticancer treatment given last 30 days n=73		*P* value[a]
	n	%	*n*	%	
Age (years) - median (min - max)	72	(18 - 93)	74	(40 - 91)	NS
Length of stay (days) - median (min - max)	8	(0 - 84)	12	(0 - 68)	0.03
Gender					NS
Female	68	39 %	28	38 %	
Male	106	61 %	45	62 %	
Hospital					<0.01
District Hospital Lofoten	27	16 %	6	8 %	
District Hospital Vesterålen	47	27 %	11	15 %	
Central Hospital Bodø	100	57 %	56	77 %	
Department					NS
Internal medicine	76	44 %	44	60 %	
Surgery	91	52 %	25	34 %	
Others	7	4 %	4	6 %	
Primary malignancy					0.02
Upper gastrointestinal	34	20 %	5	7 %	
Colorectal	27	15 %	4	5 %	
Lung	38	22 %	21	29 %	
Breast	7	4 %	4	5 %	
Gynecological	5	3 %	2	3 %	
Urological	8	5 %	6	8 %	
Male genitalia	11	6 %	4	5 %	
Hematological and lymphoma	17	10 %	22	30 %	
Unknown origin	15	8 %	2	3 %	
Other [b]	12	7 %	3	4 %	
Treatment intent					<0.001
Palliative	135	78 %	67	92 %	
Curable	2	1 %	3	4 %	
Diagnostic	37	21 %	3	4 %	
Anticancer treatment					<0.001
Systemic treatment	64	37 %	52	71 %	
Radiotherapy	5	3 %	14	19 %	
Surgery	5	3 %	7	10 %	
No treatment	100	57 %	0	0 %	
Specialist palliative care					NS
>30 days before death	33	19 %	11	15 %	
<30 days before death	32	18 %	14	19 %	
Not involved	109	63 %	48	66 %	

[a] The *p* value measures the difference between the two groups and was set to 0.05. NS not significant.

[b] The group consist of patients with cancer from head-neck, sarcoma, malignant melanoma, eye and CNS.

Treatment during the last 30 days of life

Anticancer treatment of any kind was given to 30 percent of patients during the last 30 days of life. Treatment given during the last 30 days was mainly systemic anticancer treatment (21 %). In addition, 8.5 percent of the patients received radiotherapy during the last 30 days of life, where of more than half during the last 10 days of life. Specialised palliative care was provided equally to both groups, 34 vs. 37 percent (Table 1).

Adverse events

Patients receiving anticancer treatment during the last 30 days of life had 46 percent more adverse events than patients not treated during the last 30 days of life, 82 vs. 56 adverse events per 1 000 patient days (p<0.01, RR 1.46, CI 95% 1.10 – 1.94). Patients receiving treatment during the last 30 days of life experienced both more temporary adverse events (severity E and F) and more severe adverse events contributing to death (severity I), (Figure1). Patients in both groups receiving specialist palliative care had significantly fewer adverse events than patients not referred to palliative care, 52 vs. 73 adverse events per 1 000 patient days (RR 0.71, p= 0.02 CI 95% 0.53 – 0.96).

Types of adverse event

The most common types of adverse events were healthcare-acquired infections and medication related adverse events (Figure 2). There was no difference in the rate of healthcare-acquired infections between the groups. Patients receiving treatment during the last 30 days of life had significantly higher rates of medication related adverse events, 21 vs. 9 adverse events per 1 000 patient days (p<0.001, RR 2.35, CI 95 % 1.55 – 3.58). Twenty-four percent of patients receiving systemic anticancer treatment had an adverse event related to the treatment. Bleeding or thrombosis also occurred more often in patients receiving treatment

9

186   during the last 30 days, 5 vs. 2 adverse events per 1 000 patient days (p=0.003, RR 2.62, CI

187   95 % 1.09 – 6.34). For more detailed description of types of adverse events se supplementary

188   materials.

189

190   **Adverse events contributing to death**

191   An adverse event contributed to death in 22 percent of all deceased hospitalised cancer

192   patients. Patients receiving anticancer treatment during the last 30 days of life experienced

193   nearly double the rate of adverse events contributing to death compared to patients not being

194   treated during the last month of life, 33 vs. 18 percent (p=0.045, adjusted OR 1.85, CI 95 %

195   1.014 – 3.359). Adverse events contributing to death were mainly medication harms and

196   healthcare acquired infections. Systemic anticancer treatment contributed to death in 11

197   percent of patients receiving systemic anticancer treatment, all given during the last 30 days

198   of life. For patients not receiving treatment during the last 30 days of life, healthcare acquired

199   infections contributed to death for 58 percent of the patients. An adverse event contributed to

200   death more commonly in patients with lymphoma and haematological malignancies, 27 vs. 13

201   percent, (p=0.025, S_{res} 2.1). Radiotherapy did not contribute to the death of any patient.

202

203   **Discussion**

204   There are clear guidelines recommending limiting use of aggressive anticancer treatments for

205   cancer patients near end of life [4, 12]. Still we found that one third of deceased hospitalised

206   cancer patients received some kind of anticancer treatment during the last 30 days of their

207   lives. Patients receiving anticancer treatment during the last 30 days of life also had an

208   increased rate of adverse events compared to cancer patients not given treatment in this

209   period. Most of the adverse events were temporary harms requiring medical intervention,

210   often initiating or prolonging hospitalisation (severity E and F). Even less severe adverse

10

211 events can cause an extra burden of harm and reduce the quality of life during the limited

212 remaining time, when many patients prefer to be at home with their families [6, 21].

213

214 We found that one in five deceased hospitalised cancer patients had an adverse event

215 contributing to death. This included all types of adverse events whether caused by systemic

216 anticancer treatment, other medications or healthcare acquired infections. In a previous study

217 we found that hospitalised cancer patients had an increased risk of adverse events in general

218 compared to other hospitalised patients, and that they more often experienced adverse events

219 related to medications [22].

220 Our findings are higher than those of registry studies showing that 4 – 27 percent of cancer

221 patients die as a complication of anticancer treatment, but these studies do not specifically

222 investigate occurrence of adverse events [14, 15, 23]. We also found that patients receiving

223 anticancer treatment during the last 30 days had twice the odds of having an adverse event

224 contributing to death compared to patients without such treatment. Considering that an

225 adverse event can often be one of many factors contributing to death, it could be that

226 receiving treatment in the last 30 days of life adds yet another layer of treatment related

227 adverse events with an increased risk of hastening death.

228

229 Nearly one third of our deceased hospitalised cancer patients received some kind of

230 anticancer treatment during the last 30 days of life, mainly systemic anticancer treatment.

231 Similarly to other studies we found that patients receiving treatment during the last 30 days of

232 life had a longer length of stay, were treated at larger hospitals and more often had lung

233 cancer, lymphoma or haematological malignancies [24–28]. In other studies, the use of

234 anticancer treatment during the last 30 days of life varied from 6 - 43 %, depending on

235 country and patients included [29–31]. Our results are consistent with similar studies

236   including all types of malignancies [15, 32], but the rates are higher than in registry studies of

237   solid tumours indicating that Norway has among the lowest (6-10 %) use of systemic

238   anticancer treatment during the last 30 days of life in Europe [23, 29]. Thus comparison of the

239   results can be problematic due to differences in study design and included population [13].

240

241   Similar to other studies we find that medication harms and healthcare acquired infections

242   were the most common adverse events [22, 33], but their occurrences differed between the

243   groups. While healthcare acquired infections contributed to death of cancer patients in both

244   groups, anticancer treatment related adverse events, contributing to death only occurred in

245   patients who received such treatment during the last 30 days of life. Consequently, when

246   measuring anticancer treatment related adverse events contributing to death we can be more

247   pragmatic and limit the inclusion to deceased hospitalised patients treated during the last 30

248   days of life.

249

250   It is rarely straightforward to argue that anticancer treatment is the direct cause of death. Most

251   likely, reduced functional status, malnutrition and immunosuppression amplify adverse events

252   related to anticancer treatment and increase the negative impact on the patients` remaining

253   lifetime [34]. Our study is not designed to investigate if these treatment-related adverse events

254   affects survival, but nevertheless our results indicate that systemic anticancer treatment given

255   during last 30 days of life can hasten the death of patients.

256

257   The proportion of patients treated with radiotherapy during the last 30 days of life in our

258   study, was similar to the results of other studies [23, 35]. While radiotherapy in contrast to

259   systemic anticancer treatment did not contribute to any deaths in our study, it still must be

260   considered of little benefit when given during the last 30 days of life. The benefit of

261 radiotherapy near end of life is questionable with only one out of four patients reporting

262 symptom relief [36]. Patients receiving radiotherapy are also more often hospitalised and die

263 in hospitals [23, 35]. Nearly half of our patients received radiotherapy during the last ten days

264 of life, which must be considered futile and a misuse of the patients´ time and focus.

265 Radiotherapy can provide needed palliation to patients with advanced cancer, but

266 fractionation regimes should reflect life expectancy and sometimes it is better to provide

267 palliative relief in other ways.

268

269 Early referral to palliative care is associated with improved quality of life, fewer acute

270 hospital admissions and less aggressive cancer treatment near the end of life [37–39]. Our

271 findings indicate that patients receiving specialist palliative care had significantly fewer

272 adverse events than patients not referred to palliative care. Symptom management is a

273 key element of palliative care. Diagnosing and managing symptoms at an early stage can

274 prevent them from developing into adverse events and thereby improve the patient

275 safety for cancer patients. This supports recommendations of early integration also in a

276 patient safety perspective. However, our study is not designed to determine if the reduction

277 in adverse events is due to specialised palliative care or due to discontinuing of anticancer

278 treatment.

279 Even though palliative care should be an integrated part of oncology, patients are often first

280 referred to palliative care when anticancer treatment ends [40]. Knowing the positive

281 associations for the quality of life and safety benefits for cancer patients referred to

282 palliative care, the low referral rate (35 %) of deceased cancer patients is worrisome.

283 Availability of specialist palliative care are equal to all cancer types at our hospital and

284 the palliative care teams has regular follow up with all departments. Nevertheless, the

285 culture for referral may vary between specialties. One reason for the low referral to

286 palliative care could be the perception that palliative care is equal to end-of-life care.

287 Since the study was conducted in 2012 – 2013 this perception has gradually changes

288 and palliative care is increasingly actknowledged as an important part of good quality

289 cancer care that should be integrated early in the course of disease [40].

290 Other reasons for low referral rates could be resources allocated to palliative care and a

291 healthcare system consisting of silos, not structures to support the integration of

292 palliative care across all specialties and throughout the whole continuum of cancer care.

293 In so means, early referral to palliative care itself can be regarded as a relevant clinical

294 measure of quality in cancer care.

295

296 Strength of our study is the completeness of the data. We have included all cancer patients

297 who died during a two-year period at our hospitals. Norway has one of the highest rates of

298 hospital deaths for cancer patients and cancer patients receiving treatment during the last 30

299 days of their lives are often hospitalised and die in hospital [29, 32]. We therefore argue that

300 our study population is representative of cancer patients cared for by a general hospital trust.

301 But, given the considerable variations in oncology practice within and across countries, the

302 generalizability of our finding can be debated [29]. The main limitation of our study is that it

303 is from only one hospital trust in Norway.

304 Known limitations of retrospective record reviewing such as information bias and subjective

305 judgments may also apply to our study. Conscious of these limitations we have used a

306 standardised review method (GTT method) with high sensitivity and specificity compared to

307 other methods detecting adverse events [41]. To address limitations with the method of poor

308 to moderate reliability, the review was conducted by a consistent and experienced oncology

309 team [42–44]. In addition, we assessed the validity of our findings by having two physicians

310 independently re-review and verify adverse events contributing to death. We found good

14

311 correlation between the reviewers, where the severity changed only once and type of adverse

312 event changed twice. However, when studying the intensity and safety of end-of-life care a

313 retrospective design has the advantage since we only know the exact period before death

314 retrospectively. A retrospective design allows for easy identification of cohorts of relevant

315 patients and avoidance of inclusion bias [45].

316

317 **Conclusion**

318 Anticancer treatment given during the last 30 days of life is associated with a significantly

319 increased rate of adverse events with twice the odds of having an adverse event contributing

320 to death. Patients receiving specialist palliative care had significantly fewer adverse

321 events, supporting recommendations of early integration of palliative care in a patient

322 safety perspective. Identifying these adverse events is clearly warranted to improve clinical

323 practice and avoid overtreatment in end-of life cancer care. Doing so with a standardised

324 review method on a limited number of deceased hospitalised cancer patients proved to be

325 efficient, and can provide a pragmatic real time measure of quality and safety in end-of-life

326 cancer care.

327

328 **List of abbreviations**

329 GTT   Global Trigger Tool

330 NCC MERP   National Coordinating Council on Medical Error Reporting and Prevention

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Declarations

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics, in Norway has reviewed

the study and categorised it as retrospective health record research, which does not require

approval by the committee. Reference number 2013/1823.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding

author on reasonable request.

Competing interests

The authors declare that hey have no competing interests.

Authors' contributions

ECH and BV designed the study. ECH led the review and collection of data. ECH, supervised

by BV analysed the data. ECH, BV, CvP and CN together interpreted the data. ECH led the

writing of the paper, while all the other authors contributed to revising the manuscript. All

authors contributed substantially to the writing of the paper, and all reviewed and approved

the final draft.

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Fig. 1
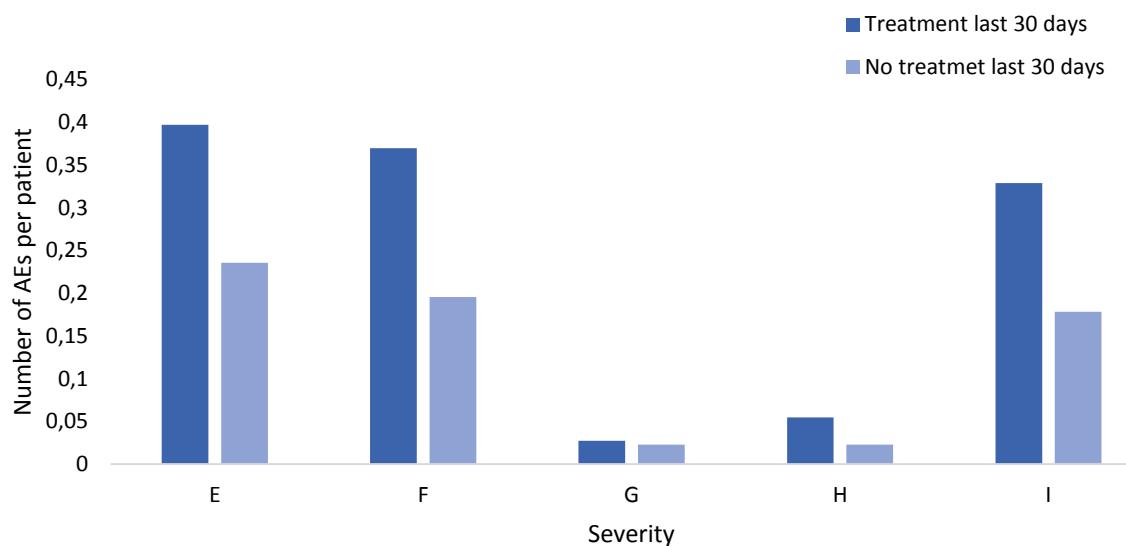
Fig. 1
Severity of adverse events per patient categorised according to the NCC MERP Index.
Comparing severity of adverse events between patient receiving or not receiving anticancer treatment during the last 30 days of life.
Category E: temporary harm that required intervention
Category F: temporary harm that required initial or prolonged hospitalisation
Category G: permanent patient harm
Category H: intervention required necessary to sustain life
Category I: harm contributes to patient death
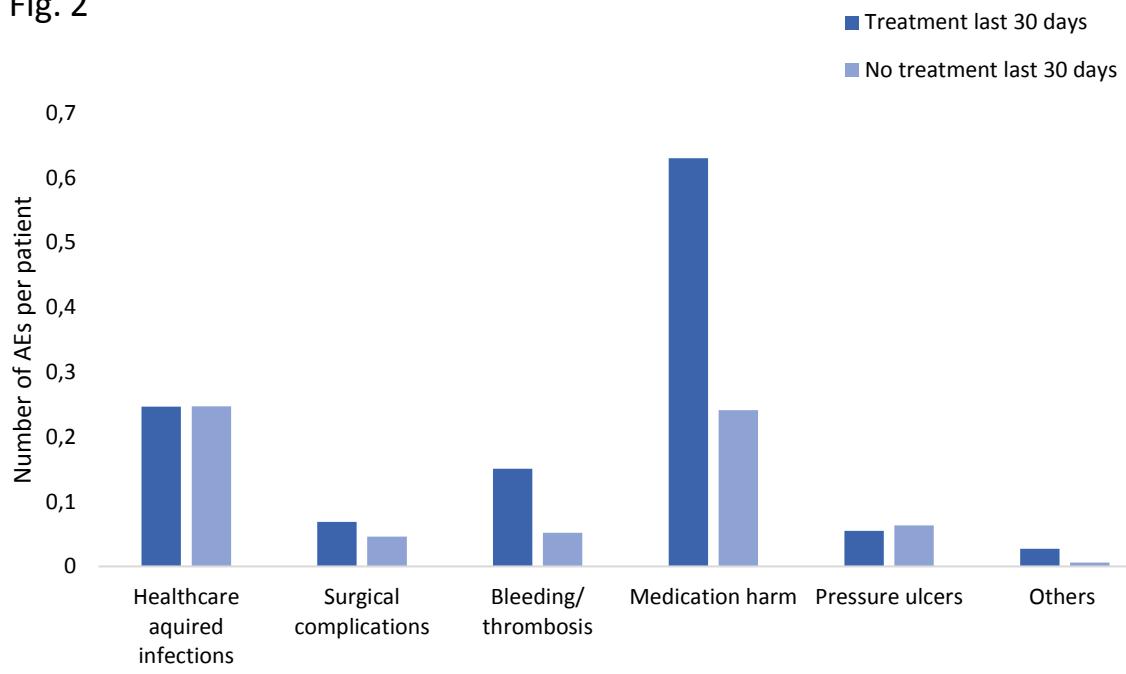
Fig. 2
Type of adverse events per patient
Comparing types of adverse events between patient receiving or not receiving anticancer treatment during the last 30 days of life.

Supplementary material

	Number of AE						Number of AE contributing to death				
	Anticancer treatment given last 30 days n=73		No anticancer treatment given last 30 days n=174		Total sample n=247		Anticancer treatment given last 30 days n=73		No anticancer treatment given last 30 days n=174	
	Sum	Percent	Sum	Percent	Sum	Percent	Sum	Percent	Sum	Percent
Healthcare aquired infections	**18**	**20.5 %**	**43**	**38.4 %**	**24**	**43.6%**	**6**	**25.0 %**	**18**	**58.1 %**
Urinary tract infection	4		10		1		0		1	
CVC infection	0		1		0		0		0	
Ventilator associated pneumonia	0		0		0		0		0	
Other infections	4		10		7		2		5	
Lower respiratory infections	10		22		16		4		12	
Surgical complications	**5**	**5.7 %**	**8**	**7.1 %**	**2**	**3.6 %**	**0**	**0 %**	**2**	**6.5 %**
Infection after surgery	0		1		0		0		0	
Respiratory complications after surgery	1		0		0		0		0	
Return to surgery	0		0		0		0		0	
Injury, repair or removal of organ	1		4		1		0		1	
Bleeding after surgery	1		1		0		0		0	
Other operative complication	2		2		1		0		1	
Switch in surgery	0		0		0		0		0	
Bleeding/thrombosis	**11**	**13.6 %**	**9**	**8.0 %**	**6**	**10.9 %**	**2**	**8.3 %**	**4**	**12.9 %**
Thrombosis/Embolism	10		5		6		2		4	
Bleeding	1		4		0		0		0	
Medication harm	**46**	**53.4 %**	**42**	**35.7 %**	**22**	**40.0 %**	**16**	**66.7 %**	**6**	**19.4 %**
Systemic cancer treatment	20		7		13		13		0	
Anticoagulants	1		3		4		2		2	
Steroids	4		4		3		1		2	
Overhydration	7		3		1		0		1	
Opioids	8		12		0		0		0	
Antibiotics	5		8		0		0		0	
Anxolotica	1		2		0		0		0	
Others	0		3		1		0		1	
Pressure ulcers	**4**	**4,5 %**	**11**	**9.8 %**	**0**	**0 %**	**0**	**0 %**	**0**	**0 %**
Others	**2**	**2.3 %**	**1**	**0.9 %**	**1**	**1.8 %**	**0**	**0 %**	**1**	**3.0 %**
Patient fall/fracture	1		1		1		0		1	
Allergy	0		0		0		0		0	
Medical technical harm	0		0		0		0		0	
Deterioration of cronic illness	0		0		0		0		0	
Others	1		0		0		0		0	
Total	**86**		**114**		**55**		**24**		**31**	