IMMEDIATE TOTAL-BODY CT SCANNING

after severe trauma

Kaij Treskes

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Immediate total-body CT scanning after severe trauma

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Table of contents

Introduction

The global burden of trauma consists of almost 5 million deaths per year and accounts for an estimated 10% of the disability adjusted life years.[1] Because trauma is a leading cause of death among young people without pre-existent morbidity, trauma has a major impact on the disease burden and health economic aspects worldwide.[1]

Patients who suffered major trauma need an assessment and treatment in a structured manner according to the principles of the Advanced Trauma Life Support®.[2] This guideline dictates that the most life threatening injuries are identified and treated immediately. The in-hospital primary survey of trauma patients consists of a screening physical examination and resuscitative measurements and is complemented by radiologic imaging.

The concept of total-body computed tomography (TBCT) was introduced for patients who appear to be severely injured after major trauma. Initially CT was used secondary to conventional imaging (X-ray and ultrasound) and after stabilizing major trauma patients. However, CT scanners were placed closer to or even inside the trauma resuscitation room and scan acquisition times decreased. As a result, CT scanning became an option as primary diagnostic modality and thereby omitting X-ray and ultrasound. This so-called immediate total-body CT (iTBCT) scanning is currently widely used in trauma centers around the world although hard evidence is lacking.[3-8]

Previous studies that investigated the effect on mortality by TBCT after major trauma included patients retrospectively and corrected for differences in clinical characteristics.[9] During these studies trauma team leaders might have had the tendency of withholding TBCT in the unstable patient because of their gut feeling. Another form of bias is formed by the fact that patients who deceased early and did not live long enough to receive TBCT automatically were part of the control group. These forms of bias may have falsely increased mortality rates in control groups and therefore overestimated the effect of TBCT on mortality. When correcting for clinical characteristics, trauma scores (ISS, TRISS) are used which might be altered by the higher detection rate for injuries by TBCT and therefore show better survival for patients who seem more severely injured. Randomization of patients at the start of the initial in-hospital trauma assessment may solve these challenges of bias associated with retrospective studies.

iTBCT is known to shorten the time to diagnosis in comparison to the standard work-up, i.e. X-ray, FAST and selective CT scanning.[3-8] Therefore, it could be hypothesized that iTBCT might not only reduce mortality but also morbidity if time to interven-

tion is reduced as well. On the contrary, the potential mortality or morbidity reduction should outweigh the increased radiation exposure in this relatively young population.

To reduce unnecessary radiation exposure for less severely injured patients the indication for iTBCT should be considered. Studies reconsidering the criteria for iTBCT often do not take the consequences for radiation exposure into account. Furthermore, criteria to perform iTBCT after major trauma are often deduced from clinical characteristics that predict higher mortality or higher injury severity in retrospective studies using the Injury Severity Score (ISS).[10,11] This rationale is well explainable, however only partially and indirectly supported by scientific evidence. An overview of currently available evidence and validation of available sets of criteria for iTBCT is lacking. When formulating criteria for iTBCT these should consist of characteristics available during early trauma care. Trauma scores such as ISS are unsuitable since this is calculated in retrospect.

Specific subgroups of trauma patients deserve special attention when considering iTBCT during the initial assessment. The potentially beneficial effect of iTBCT on mortality or morbidity could be assumed for patients requiring bleeding control interventions[12] and patients with traumatic brain injury (TBI).[13] Since both groups benefit from early and goal directed treatment. Furthermore, a decreased level of consciousness could be considered an indication on itself since clinical indicators for imaging are unreliable owing to the lack of subjective input from the patient during primary survey.[14,15]

In a societal perspective a more thorough cost-effectiveness analysis is necessary to evaluate the financial impact in perspective of the health gain achieved. Direct and indirect medical costs of further implementation of iTBCT in trauma centers are especially of interest for hospital managers.[16,17]

Aim of the thesis

This thesis focuses on the consequences of iTBCT scanning in comparison to the standard work-up and the indication for iTBCT scanning after severe trauma in a large randomized controlled trial. Next to the effect on clinical outcomes, the effect on clinically relevant time intervals, radiation exposure and health economics effects are evaluated. These effects are also evaluated specifically for patients in need for emergency bleeding control interventions. The criteria for iTBCT are reconsidered in order to select the more severely injured patients and reduce the chance on unnecessary radiation exposure for the less severely injured patients.

Outline of the thesis

Chapter 1 describes the results of the REACT-2 study; a multicenter randomized controlled trial, which compares the in-hospital mortality of major trauma patients receiving immediate TBCT with mortality after the standard work-up (STWU) with X-rays, FAST and selective CT scanning of specific body regions. Secondary outcomes are time intervals, radiation exposure, and direct medical costs.

Chapter 2 provides a health care economic point of view on the use of iTBCT compared to STWU after major trauma. Cost-effectiveness is compared between the iTBCT and STWU group.

Chapter 3 focuses on a potential mortality reduction by iTBCT for REACT-2 included patients in need for emergency bleeding control interventions.

Chapter 4 contains a systematic literature review that provides an overview of the currently used criteria for TBCT after blunt trauma.

In **Chapter 5** the prospectively gathered data of the REACT-2 study are used for revising the criteria for iTBCT in order to be more selective and reduce radiation exposure for the less severely injured patients.

Chapter 6 quantifies the expected increase in incidental findings by the use of iTBCT compared to the standard work up with selective CT scanning and aims to confirm an increase of the clinically relevant incidental findings.

Chapter 7 describes the diagnostic usefulness of TBCT scouts in detecting life-threatening chest and pelvic injuries.

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1

Immediate total-body CT scanning versus conventional imaging and selective CT scanning in severe trauma patients: A randomised controlled trial (REACT-2 trial)

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Abstract

Background

Recent literature suggests a survival benefit for trauma patients when they are evaluated with total-body Computed Tomography (TBCT) scanning during the initial trauma evaluation**.** However, level-1 evidence is lacking.

Methods

In this multicentre clinical trial, we randomly assigned 541 trauma patients to immediate TBCT scanning and 542 patients to the standard workup with conventional imaging supplemented with selective CT scanning. Trauma patients having compromised vital parameters, clinical suspicion of life-threatening injuries or severe injury mechanisms were eligible. The primary endpoint was in-hospital mortality. Secondary endpoints were radiation exposure, clinically relevant time intervals, missed injuries and hospital costs.

Findings

The in-hospital mortality rate was not statistically different between groups (TBCT 15.9% vs. standard 15.7%, P=0.923). Subgroup analyses in polytrauma patients also did not reveal a significant difference between groups (TBCT 22.4% vs. standard 24.8%, P=0.457). Substantially more patients in the standard workup group received a lower effective radiation dose (21.0mSv [IQR=20.9-25.2] versus 20.6mSv [IQR=11.8-27.6], P<0.001). The hospital costs were €24,967 (95% CI: €21,880– €28,752) for the TBCT group and €26,995 (95% CI: €23,326–€30,908) for the standard workup group (P=0·439).

Interpretation

Total-body CT scanning was safe, shortened the imaging time and did not increase the hospital costs, but it did not improve survival, and most patients in the standard workup group received a lower radiation dose.

Background

Total-body computed tomography (TBCT) scanning is increasingly used in the primary evaluation of trauma patients, and is performed according to Advanced Trauma Life Support (ATLS)® guidelines.[1] CT scanning is accurate and safe for the detection of traumatic injuries.[2] A significant advantage of the total-body imaging concept as compared to the standard workup with X-rays, ultrasound and selective CT scanning is the rapid and complete overview of life-threatening traumatic injuries. Time benefits in favour of TBCT scanning compared with the standard workup,[3-6] changes in treatment associated with the total-body CT (TBCT) scanning[7] and potential survival benefits[3,8-13] have been described previously.

A potential disadvantage of TBCT scanning of trauma patients is the increased radiation exposure.[14,15] As a side effect, incidental (i.e., trauma-unrelated) findings are more frequently found with TBCT scanning.[16-18] Despite the lack of level-1 scientific evidence for the use of TBCT scanning in the evaluation of trauma patients,[2,19,20] an increasing number of trauma centres have incorporated this imaging strategy in their daily practice.[6,13,21,22] The TBCT scan could be used as a supplemental tool to the standard radiologic imaging or even as a total replacement, without prior conventional imaging (i.e., X-rays and ultrasound).

Most previously performed studies retrospectively included a specific cohort of patients (e.g., polytrauma patients defined as patients with an Injury Severity Score (ISS) of 16 and above).[3,13] Because the ISS is calculated retrospectively at discharge, this parameter is not available in daily clinical practice and cannot be used as a triage method for the selection of severely injured patients. Therefore, intrinsic methodological limitations and the risk of selection bias are confounders in these studies. The need for a randomised clinical trial was highlighted[3] and was the primary conclusion of all systematic reviews.[2,23-27]

We conducted this randomised clinical trial of early assessment with CT scanning in trauma patients (REACT-2) to examine the effect of immediate TBCT scanning as part of the primary evaluation of severe trauma patients on in-hospital mortality, and compared it with that of the standard workup employing conventional imaging supplemented with selective CT scanning. Secondary objectives included radiation exposure, clinically relevant time intervals, missed injuries and hospital costs associated with immediate total-body CT scanning.

Methods

Study design and oversight

REACT-2 was designed as an international, randomised controlled multicentre trial in which immediate total-body CT scanning in severe trauma patients was com-

pared with a standard workup with conventional imaging supplemented by selective CT scanning. The design of the REACT-2 study has been previously described (ClinicalTrials.gov: NCT01523626).[28] The study was approved by the medical ethics committees at all participating centres (AMC MEC 10/145). All participating sites were level-1 trauma centres and academic teaching hospitals. Trauma survey was done by a team consisting of the following well-trained members: a trauma team leader (trauma surgeon or surgical resident in training), an anaesthesiologist, a radiologist, and support staff. Every new member of the trauma team was introduced to the study procedures together with introduction to local trauma protocols. Trauma teams received feedback on followed study procedures by local trial staff within one working day.

Study population

Eligibility criteria were chosen with the aim of enrolling a trauma population with potentially severe injuries. Those with compromised vital parameters, clinical suspicion of life-threatening injuries or severe injury mechanisms were eligible. The complete list of inclusion and exclusion criteria is available in the Appendix, Table 1.

Randomisation and study treatment

At the initial presentation in the trauma room and in the presence of a temporary waiver of informed consent, eligible patients were identified. Subsequently patients were randomly assigned by trained trauma leaders in a centre-stratified 1:1 ratio to either immediate total-body CT scanning without prior conventional imaging or to the standard workup, using ALEA randomisation software available at an iPad or desktop PC in the trauma room. Potential life-saving interventions during the primary survey and prior to imaging included securing the airway by intubation, obtaining intravenous access, chest tube insertion, pericardiocentesis or taking haemorrhage control measures. Indications for selective CT scanning in the standard workup group were predefined according to local protocols (Appendix, Table 2). The multidetector CT scanner was located in the trauma room or in a room adjacent to the Emergency Department (ED). Subsequent medical care was provided according to local protocols based on current international trauma care standards.

At the earliest possible moment after the trauma workup, the patient or their legal representative was informed about the REACT-2 trial. Written informed consent was requested. All patients for whom written informed consent could be obtained were sent 3 questionnaires (EuroQol-5D-3L, HUI-3 and a questionnaire derived from the Dutch Health and Labour Questionnaire for cost-effectiveness analysis)[28] at 3, 6 and 12 months post trauma. Outcomes of the questionnaires will be reported in a separate paper on the cost-effectiveness of TBCT. Patients for whom written informed consent could not be obtained, despite all efforts, were included in the intention-to-treat analysis, except for outcomes based on patient questionnaires (n=170; approved by the Medical Ethics Committee and the Dutch Central Committee on Research Involving

Human Subjects). Data for the 3-, 6- and 12-month follow-up were prospectively collected from clinical and outpatient reports in the hospital databases. If no information could be obtained from this database, the patient and/or their general practitioner were contacted by telephone by one of the authors or research nurses. If a patient was transferred to another hospital, data from this hospital were also included in the analyses.

Radiological imaging

The protocol for the intervention (TBCT) group consisted of a two-step acquisition (from vertex to pubic symphysis) without gantry angulations, starting with a non-enhanced CT of the head and neck (NECT) with arms alongside the trunk. The second scan covers the chest, abdomen and pelvis. The preferred technique for the second scan was a split-bolus intravenous contrast imaging directly after raising the arms alongside the head.[29] CT-scanners at the participating sites were all 64-slice multi-detector row CT scanners. The standard radiologic trauma workup was performed according to ATLS® guidelines.[1] Chest and pelvic x-rays and FAST ultrasound imaging were performed during the ATLS® based primary survey. Following further assessment and resuscitation during the secondary survey, a selective CT-scan could be made from individual body regions with segmented acquisition of the respective body regions.

Endpoints

The primary endpoint was in-hospital mortality, defined as mortality during the index hospital admission after trauma (including patients who were transferred to another hospital following initial admission at one of the participating sites). Secondary endpoints were clinically relevant time intervals during trauma survey, radiation exposure, missed injuries and hospital costs.

The cumulative radiation dose was defined as the sum of all effective doses from all radiologic imaging strategies (e.g., x-rays and CT scans), expressed in millisievert (mSv) and calculated for all radiologic examinations performed in the trauma room and for the complete index admission. The radiation dose was estimated based on the dose catalogue of Mettler et al.[30] With respect to the radiation dose, X-rays of the clavicle were regarded as X-rays of the extremities; X-rays of the face and dental panoramic orthopantomography were regarded as X-rays of the skull; and a retrograde urethrogram was regarded as a pelvic X-ray. The dose for X-rays of the thoracolumbar transition was not provided by Mettler, and was therefore estimated as the average for a thoracic spine X-ray and a lumbar spine X-ray (1.25 mSv). Because average doses for the CT protocols used in a trauma setting were not readily available from the literature, we calculated representative radiation doses for single-pass CT scans of various body regions based on optimised trauma CT protocols at one of the study sites (i.e. AMC, Amsterdam, see Appendix, Table 3).[31] This trauma resuscitation room has a sliding gantry 64-slice CT-scanner (Sensation 64, Siemens Medical Solutions, Forchheim,

Germany) with a multifunctional, radiolucent trauma resuscitation table. Doses of CT scans of the extremities were excluded from the analysis. To calculate effective doses, we used the ImPACT CT Dosimetry spreadsheet (www.impactscan.org/ctdosimetry.htm). Fluoroscopies were excluded because they were not used for diagnostic examinations leading to treatment decisions, which was the limit of the scope of our study.

The hospital costs were assessed for Dutch patients only (89.3%) and included the costs for all diagnostic and therapeutic procedures in the trauma room, ICU and general ward during the index admission. We further included the costs of inpatient and outpatient hospital consultations, repeat hospital admissions and diagnostic and therapeutic procedures during the 6 months of follow-up. Costs for a stay in a nursing home or rehabilitation centre (other than rehabilitation in the index hospitals) were excluded from this analysis. Data on health care volume in the Dutch index hospitals (for all hospitalisations) were gathered uniformly from the hospital information systems. Unit costs were expressed in euros for the base year 2013; unit costs from other calendar years were price indexed using the national general consumer price indices as published by Statistics Netherlands.[32] Patients that died in the hospital were analysed for all outcomes except those that derived from patients' questionnaires.

Definitions

Hypotension was defined as a systolic blood pressure below 90 mmHg upon arrival at the trauma room.[33] Traumatic brain injury patients were defined as having a Glasgow Coma Score below 9 at presentation and an Abbreviated Injury Scale head score of 3 or above. Polytrauma patients were defined as patients with an Injury Severity Score (ISS) of 16 or above. Trauma-Injury Severity Score (TRISS) was used to calculate the probability of survival (coefficients for blunt trauma: b0=-0.4499, b1=0.8085, b2=-0.0835 and b3=-1.7430. Coefficients for penetrating trauma: b0=-2.5355, b1=0.9934, b2=-0.0651, b3=-1.1360).[34]

Clinically relevant time intervals were defined as imaging time, time to diagnosis of life-threatening injuries and total time spent in the trauma room. Time intervals were prospectively registered by the trauma team (by one-click/touch buttons on a PC or iPad) starting immediately after the patient entered the trauma room. Imaging time was defined as the time from arrival in the trauma room until the end of imaging in the trauma room. Time to diagnosis was defined as the time at arrival to the time all life-threatening injuries were diagnosed according to the trauma team leader, in accordance with the radiologist.

A serious Adverse Event (SAE) was defined as a life-threatening event during scanning. Every SAE was reported to the research coordinator and the medical ethics committee within 24 hours.

Post-randomisation exclusions were defined as patients who were included by mistake because they did not fulfil the inclusion criteria as assessed by a member of the study group as soon as possible after the moment of inclusion. When a mistake was

suspected, the trauma team leader and the research investigator at the specific sites were contacted. In consultation with these persons, the decision was made whether a patient should be regarded as a post-randomisation exclusion. Missed injuries were defined as injuries not detected during the primary trauma survey and were prospectively registered by research staff (research nurses and clinical investigators). Median length of stay (LoS) during total hospital admission was based on data from admitted patients only. Intensive Care Unit (ICU) LoS and ventilation days were calculated for patients admitted to the ICU. Complications were classified according to the Clavien-Dindo Classification for surgical patients.[35]

Statistical analysis

The detection of a difference in mortality of 5% with a power of 80% and a two-sided alpha of 5% required 539 patients per group. Details of the power analysis have been described previously.[28]

The statistical analyses were performed by the authors and independently by a clinical epidemiologist not involved in the trial. The continuous data with a normal distribution are expressed as means and standard deviation, whereas the non-normally distributed data are presented as medians with interquartile ranges. Independent sample t-tests and Mann-Whitney U Tests were used to compare the parametric (patient characteristics: pulse, systolic blood pressure; outcomes: none) and non-parametric (patient characteristics: age, respiratory rate, GCS, tRTS, RTS, laboratory results, ISS, TRISS; Outcomes: time intervals, radiation exposure, length of stay) continuous data respectively. The chi-squared test and Fisher's Exact test were used to compare the categorical variables (patient characteristics: sex, type of trauma, trauma mechanism, comorbidity, medication, hypotensive at admission, AIS, polytrauma and TBI patients; Outcomes: mortality, complications, transfusions, missed injuries, serious adverse events). A p-value of less than 0.05 was considered statistically significant.

The primary analyses were performed according to the intention-to-treat principle. Per-protocol analyses, excluding crossovers (i.e. patients who received the opposite intervention to which they had been allocated), were also performed. Subgroups were specified in advance (polytrauma and severe traumatic brain injury patients) and were also analysed. Supplementary analyses to account for the presence of missing data as well as for treatment centre effects are reported in the Appendix.

Differences in hospital costs between TBCT scanning and the standard workup of trauma patients were assessed by using non-parametric bootstrapping, drawing 1,000 samples of the same size as the original sample separately for each group with replacement and calculating the 95% confidence intervals for the mean differences after correction for bias and acceleration.[36]

After 275 (25%), 550 (50%) and 700 (65%) patients were included, non-blinded interim analyses for the evaluation of safety rules were performed. No formal stopping rules were predetermined. Instead, the data and safety monitoring board eval-

uated the data and each serious adverse event and decided whether the trial should be continued. To comply with Good Clinical Practice guidelines, a monitoring plan was made.[37] Data monitoring was performed in February 2013, and was repeated after enrolment ended in February 2014.

Results

Study population

Patient enrolment began on April 22, 2011, and ended on January 1, 2014 at 4 hospitals in the Netherlands and one hospital in Switzerland. According to the CONSORT statement, the number of patients involved in the trial from assessment of eligibility to analysis of the primary endpoint is shown in Figure 1. Of all the randomised patients, 203 were excluded after randomisation (details are described in the Appendix, Table 4). In total, 541 patients were randomised to an immediate total-body CT scan and 542 patients to the standard workup group.

There were 6 crossovers (1.1%) in the TBCT group versus 18 (3.3%) in the standard workup group (P=0.21). Other protocol violations, not classified as crossovers by the Steering Committee, were found in 49 (9.1%) TBCT patients versus 62 (11.4%) of the standard workup patients (P=0.196). Details are described in the Appendix, Table 5.

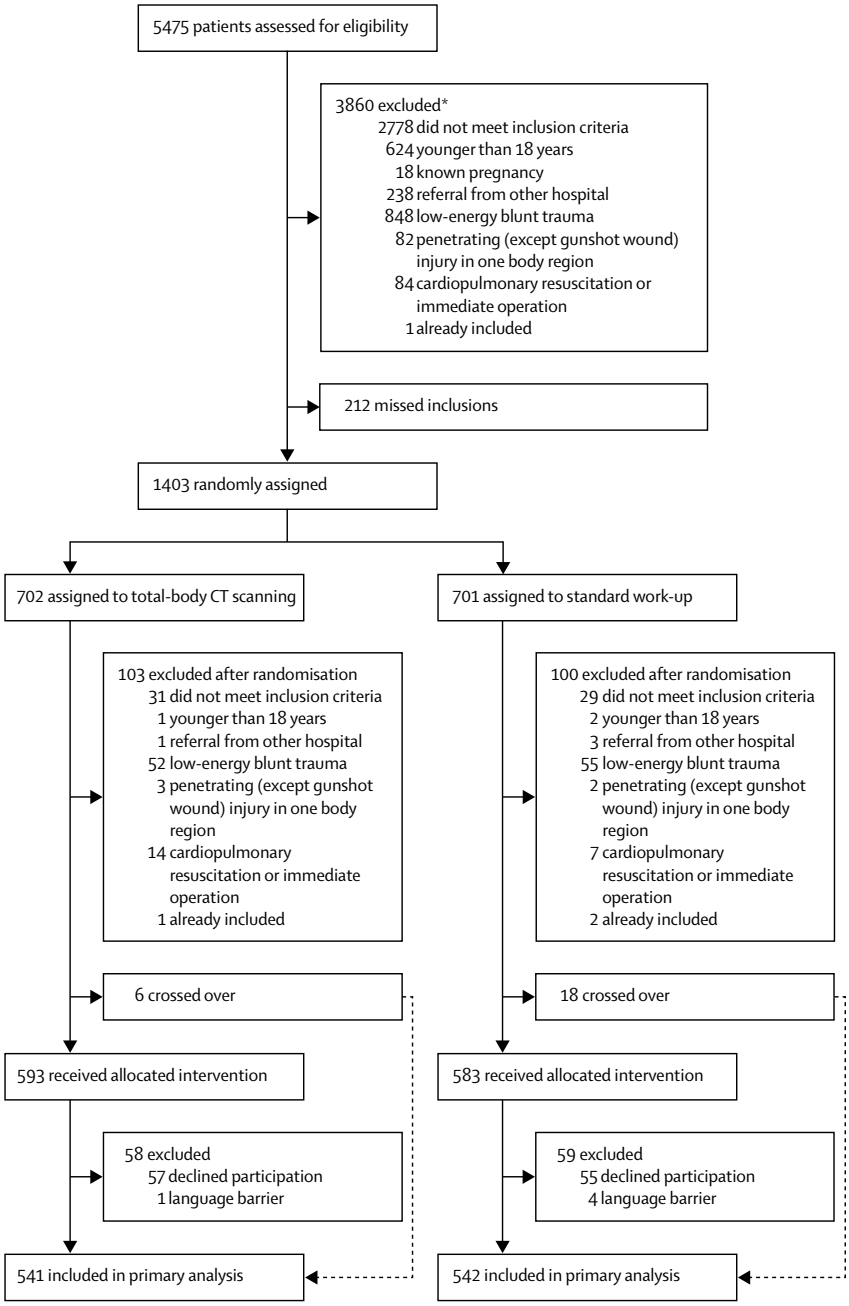
Table 1 shows the baseline demographics and clinical characteristics of the included patients. The groups were comparable for all characteristics except for the number of polytrauma patients (TBCT versus standard workup) (362 [66.9%] vs. 331 [61.1%], P=0.045), haemoglobin level (129 vs. 133 g/dl, P=0.003) and haematocrit level (0.38 vs. 0.39 l/l, P=0.003). Median ISS (20 vs. 19, P=0.405) and the number of patients who received blood transfusions (147 [27%] vs. 150 [28%], P=0.867) were not different between groups. The distribution of ISS in 4 categories is shown in Figure 2.

Primary and secondary endpoints

Data on the primary and secondary endpoints are shown in Table 2. For the primary outcome of in-hospital mortality, no significant difference was found (TBCT 15.9% vs. standard 15.7%, P=0.923). Subgroups analyses of polytrauma patients and Traumatic Brain Injury (TBI) patients also revealed mortality rates without significant differences between the two randomised cohorts as shown in Figure 3.

Radiation exposure in the ED was increased in TBCT patients (20.9 mSv [IQR 20.6-20.9] vs. 20.6 mSv [IQR 9.9-22.1]), and was slightly increased during total hospital admission (21.0 mSv [IQR 20.9-25.2] vs. 20.6 mSv [11.8-27.6]). In the standard workup group, more patients were exposed to a lower radiation dose: 40% had a radiation dose that was below the lowest dose of patients who underwent a TBCT scan. In the standard workup group 250 (46%) patients underwent sequential segmental CT scans of all body regions, comprising a TBCT scan in the end.

Figure 1. Flowchart of the study patients.



Abbreviations: CT; Computed Tomography, GSW; Gun Shot Wounds, cp resuscitation; cardiopulmonary resuscitation.

*3860 patients were excluded, but could have more than 1 reason to be excluded; therefore, the numbers do not total 3860.

Table 1. Baseline demographic and clinical characteristics of the patients*

Characteristic	TBCT (n) vs. Standard (n)†	Total-body CT (n=541)	Standard workup (n=542)
Age (years)	541 vs. 542	42 (27-59)	45 (26-59)
Male sex, n (%)	541 vs. 542	413 (76.3)	411 (75.8)
Blunt trauma, n (%)	541 vs. 542	530 (98.0)	534 (98.5)
Trauma mechanism blunt trauma, n (%)	530 vs. 534		
Fall from height		170 (32.1)	178 (33.3)
MVC – patient as occupant		201 (37.9)	190 (35.6)
MVC – patient as cyclist		65 (12.3)	60 (11.2)
MVC – patient as pedestrian		29 (5.5)	45 (8.4)
Other		65 (12.3)	61 (11.4)
Comorbidity, n (%)	517 vs. 521		
ASA I or II		495 (95.7)	501 (96.2)
ASA III, IV or V		22 (4.3)	20 (3.8)
Relevant medication, n (%)	505 vs. 516		
Coumarin derivatives		17 (3.4)	14 (2.7)
Thrombocyte aggregation inh.		38 (7.5)	28 (5.4)
Insulin		4 (0.8)	3 (0.6)
Pre-hospital vital parameters			
Respiratory rate (per minute)	323 vs. 317	17 (14-20)	16 (14-20)
Pulse (bpm) ‡	470 vs. 478	90 (25)	88 (24)
Systolic BP (mmHg) ‡	451 vs. 459	133 (31)	134 (31)
GCS (points)	528 vs. 533	14 (6-15)	14 (6-15)
Triage Revised Trauma Score	316 vs. 302	6.90 (5.03-7.84)	7.69 (5.03-7.84)
In-hospital vital parameters			
Respiratory rate (per minute)	330 vs. 339	16 (14-20)	16 (13-20)
Pulse (bpm) ‡	528 vs. 531	88 (22)	87 (22)
Systolic BP (mmHg) ‡	530 vs. 530	131 (26)	131 (29)
Hypotensive at admission, n (%)	-	38 (7.2)	44 (8.3)
GCS (points)	541 vs. 542	13 (3-15)	13 (3-15)
Revised Trauma Score	322 vs. 329	6.90 (4.09-7.84)	7.55 (4.09-7.84)
Laboratory results			
Haemoglobin level (g/dl)*	531 vs. 537	129 (113-142)	133 (120-145)
Haematocrit (l/l)*	478 vs. 488	0.38 (0.34-0.41)	0.39 (0.35-0.42)
pH	491 vs. 488	7.34 (7.28-7.38)	7.35 (7.29-7.39)
Base excess (mmol/l)	491 vs. 490	-2.1 (-4.7- -0.5)	-2.1 (-5.1- -0.1)
Abbreviated Injury Scale ≥3, n (%)	541 vs. 542		
Head		247 (45.7)	218 (40.2)
Chest		229 (42.3)	206 (38.0)
Abdomen		49 (9.1)	67 (12.4)
Extremities		150 (27.7)	154 (28.4)
Injury Severity Score (points)	541 vs. 542	20 (10-29)	19 (9-29)
Polytrauma patients, n (%)*§	541 vs. 542	362 (66.9)	331 (61.1)
TBI patients, n (%)§	541 vs. 542	178 (32.9)	151 (27.9)
TRISS, survival probability	317 vs. 301	0.93 (0.65-0.98)	0.94 (0.70-0.99)

*P>0.05 for all between-group comparisons except for haemoglobin level (P=0.003), haematocrit level (P=0.002) and polytrauma patients (P=0.045).

All data are number (%) or median (interquartile range) unless otherwise specified.

† This column displays the number of patients that was analysed for each specific variable.

‡ Mean (SD).

§Polytrauma patients are defined as ISS ≥16. Traumatic Brain Injury (TBI) patients are defined as GCS <9 at presentation and AIS Head ≥3.

MVC denotes Motor Vehicle Collision, ASA denotes American Society of Anaesthesiologists, BP denotes Blood Pressure and TRISS denotes Trauma and Injury Severity Score.

Table 2. Primary and secondary endpoints

Characteristic	TBCT (n) vs. Standard (n)	Total-body CT (n=541)	Standard workup (n=542)	P-value
Mortality§				
In-hospital mortality, n (%)				
All patients, intention-to-treat	**541 vs. 542**	**86 (15.9)**	**85 (15.7)**	**0.923**†
Polytrauma patients ‖	362 vs. 331	81 (22.4)	82 (24.8)	0.457†
Patients with severe TBI ‖	178 vs. 151	68 (38.2)	66 (43.7)	0.311†
24-hour mortality, n (%)				
All patients, intention-to-treat	**541 vs. 542**	**43 (7.9)**	**33 (6.1)**	**0.231**†
Polytrauma patients	362 vs. 331	41 (11.3)	33 (10.0)	0.564†
Patients with severe TBI	178 vs. 151	37 (20.8)	27 (17.9)	0.507†
Time intervals				
Time to end of imaging (minutes)				
All patients, intention-to-treat	**429 vs. 424**	**30 (24-40)**	**37 (28-52)**	**<0.001***
Polytrauma patients	289 vs. 253	32 (24-41)	38 (29-53)	<0.001*
Patients with severe TBI	148 vs. 117	31 (23-41)	35 (27-47)	0.007*
Time to diagnosis (minutes)				
All patients, intention-to-treat	**415 vs. 410**	**50 (38-68)**	**58 (42-78)**	0.001*
Polytrauma patients	276 vs. 245	52 (40-69)	63 (45-81)	0.001*
Patients with severe TBI	141 vs. 114	49 (39-63)	54 (41-73)	0.070*
Time at ED (minutes)				
All patients, intention-to-treat	**423 vs 416**	**63 (47-102)**	**72 (50-109)**	**0.067***
Polytrauma patients	285 vs. 252	69 (49-109)	82 (57-119)	0.011*
Patients with severe TBI	144 vs. 119	66 (49-95)	74 (52-114)	0.083*
Radiation exposure¶				
Trauma resuscitation room (mSv)				
All patients, intention-to-treat	**520 vs. 531**	**20.9 (20.6-20.9)**	**20.6 (9.9-22.1)**	**<0.001***
Polytrauma patients	346 vs. 323	20.9 (20.1-20.9)	20.6 (17.6-22.7)	0.272*
Patients with severe TBI	172 vs. 146	20.9 (20.0-20.9)	20.6 (10.5-22.4)	0.040*
Total during hospital stay (mSv)				
All patients, intention-to-treat	**520 vs. 531**	**21.0 (20.9-25.2)**	**20.6 (11.8-27.6)**	**<0.001***
Polytrauma patients	346 vs. 323	22.3 (20.7-26.5)	22.5 (20.0-33.1)	0.766*
Patients with severe TBI	172 vs. 146	22.7 (20.6-26.4)	21.4 (15.1-29.1)	0.068*
Hospital costs - € (95% CI)	479 vs. 488	24,967 (21,880-28,752)	26,995 (23,326-30,908)	0.439
Complications, n (%)	541 vs. 540	129 (23.8)	124 (23.0)	0.732†
Transfusions in-hospital, n (%)**	540 vs. 542	148 (27.4)	150 (27.7)	0.907†
Length of stay (days) ††				
Total hospital stay	483 vs. 494	10 (4-20)	9 (3-19)	0.110*
ICU stay	286 vs. 295	3 (1-8)	3 (1-8)	0.825*
Ventilation days	286 vs. 295	2 (1-5)	1 (1-6)	0.779*
Tertiary survey				
Missed injuries found, n (%)**	541 vs. 542	45 (8.8)	53 (10.1)	0.448†
Serious Adverse Events, n (%)‡‡	541 vs. 542	3 (0.6%)	1 (0.2%)	0.374‡

Data are number (%) or median (interquartile range [IQR]) unless otherwise indicated.

TBI denotes Traumatic Brain Injury. ED denotes Emergency Department.

*Mann-Whitney U test; †Chi^2 test; ‡Fisher's Exact Test.

§ Outcome remained similar in all endpoints with a per-protocol analysis in which crossovers were excluded.

|| Subgroups were specified in advance. Polytrauma patients are patients with ISS ≥16. TBI was defined as an admission Glasgow Coma Scale (GCS) ≤8 and an Abbreviated Injury Score (AIS)-head of ≥3.
¶ Excluded are patients who died at the ED (6/1.1% TBCT patients vs. 4/0.7% standard workup patients) and patients with incomplete follow-up for radiation exposure (15/2.8% TBCT patients vs. 7/1.3% standard workup patients).
** Number of patients who received blood transfusions during hospital stay (i.e. packed cells, thrombocytes, plasma) and the number of patients for whom missed injuries were detected during the tertiary survey.
††Total hospital stay is unknown in case a patient is transferred to another hospital and date of discharge to own housing conditions could not be retrieved.
‡‡ One other SAE occurred in the post-randomisation patients. Details of the SAEs are described in the Appendix.
P-value: These results should be interpreted with caution, as demonstrated by additional analyses which adjust for treatment centre effects and potential differences at baseline and account for missing data by multiple imputation. Details are described in the appendix, Figure 1-4.

Figure 2. Distribution of Injury Severity Score (ISS) between randomisation groups

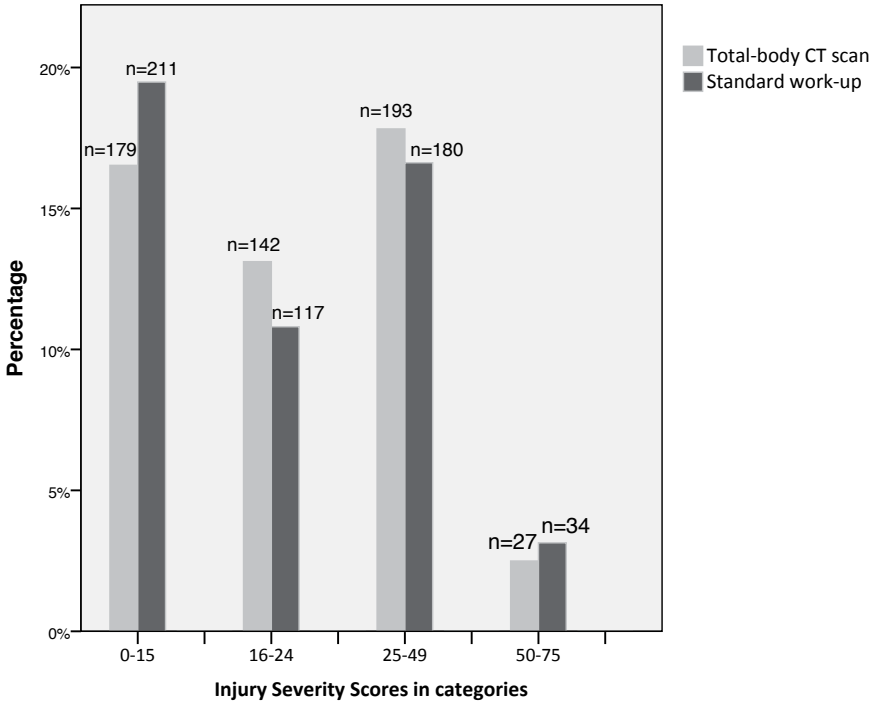
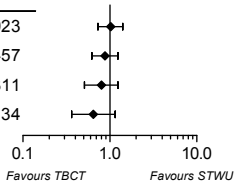


Figure 3. In-hospital mortality ratio's for subgroups

Mortality	TBCT vs. STWU (n)	Total-body CT, n (%)	Standard workup, n (%)	Odds ratio (95%CI)	p
All patients	541 vs. 542	86 (15·9)	85 (15·7)	1·02 (0·73 – 1·41)	0·923
Polytrauma*	362 vs. 331	81 (22·4)	82 (24·8)	0·88 (0·62 – 1·24)	0·457
Severe TBI*	178 vs. 151	68 (38·2)	66 (43·7)	0·80 (0·51 – 1·24)	0·311
Acute interventions	138 vs. 141	25 (18·1)	36 (25·5)	0·65 (0·36 – 1·15)	0·134



TBI denotes Traumatic Brain Injury

* Subgroups were specified in advance. Polytrauma patients are patients with ISS ≥16. TBI was defined as an admission Glasgow Coma Scale (GCS) ≤8 and an Abbreviated Injury Score (AIS)-head of ≥3.

Imaging time in the trauma room (30 min vs. 37 min, P<0.001) and time to diagnosis (50 min vs. 58 min, P<0.001) were decreased in TBCT patients. Time spent in the trauma room was close to significance with less time spent at the ED for TBCT patients (63 minutes vs. 72 minutes, P=0.067). The number of missed injuries found during the tertiary survey were not different between groups (45 [8.8%] vs. 53 [10.1%], P=0.448).

The hospital costs of the institutional stay were €24,967 (95% CI: €21,880– €28,752) for the TBCT group and €26,995 (95% CI: €23,326–€30,908) for the standard workup group (P=0.439).

Adjusted analyses for centre, unbalanced baseline characteristics, and the presence of missing data did not significantly alter the odds ratio's for in-hospital mortality. Multiple imputation resulted in less significant p values but still all less than p<0.1) for time reductions in favour of TBCT among TBI patients for time to end of imaging and among all patients and polytrauma patients for time to diagnosis. Although a difference among polytrauma patients for time spent at the ED was still present after adjustment for centre and baseline characteristics, no (significant) trend was observed after multiple imputation. Details are providedin the appendix.

Per-protocol analysis

In the per-protocol analysis, 24 crossovers (i.e., patients who received the opposite intervention to which they had been allocated) were excluded. No significant differences in outcome were found for all endpoints.

Serious adverse events

Five serious adverse events (SAEs) were reported during the course of the trial. Three were reported in TBCT patients (0.6%) and one SAE occurred in the standard workup group (0.2%). One SAE was reported in a post-randomisation excluded patient. Details of these SAEs can be found in the Appendix.

Discussion

In this randomised multicentre trial, we found no significant difference in immediate total-body CT scanning compared with the standard workup with conventional imaging and selective CT scanning with respect to in-hospital mortality in severe trauma patients. The radiation dose was slightly increased in the TBCT patients, and substantially more patients in the standard workup group received a lower radiation dose. There is a time benefit for time to diagnosis and imaging time in the trauma room in favour of TBCT scanning. The number of missed injuries found during the tertiary survey and hospital costs were not different between groups.

During the last few years, several mostly retrospective studies showed an association between TBCT scanning and survival in trauma patients, as was summarised in 6 systematic reviews.[2,23-27] Huber-Wagner et al. repeatedly showed a decrease in absolute mortality rates and an increase in the probability of survival in polytrauma patients (ISS ≥16) who had received a total-body CT scan (compared with non-TBCT) in a large cohort of patients from the German Trauma Registry.[3,13] The major difference between this study and the REACT-2 trial is that the study of Huber-Wagner and colleagues is retrospective. The authors had to use a risk-adjusted approach and multivariate analysis to adjust for possible confounders. As yet, there is no consensus on the appropriate selection criteria for patients eligible for a TBCT scan. In some centres, the trauma team leader decides whether to select a patient for total-body CT,[11,38] whereas in other centres the selection is based on a 3-tiered structure with vital parameters, clinical suspicion of specific injuries and injury mechanisms, as was used in the present study.[5,39] As a consequence of our randomised design, we included a considerable number of patients with an ISS lower than 16 (35%). This reflects daily practice and the difficulties in preventing over- or undertriage, but possibly confounds the association between survival and total-body CT scanning. Although severely injured patients can be expected to benefit most from the rapid and detailed overview of the TBCT scan, the differences between the two randomised groups might be narrowed due to the relatively high number of patients with less severe injuries. Nevertheless, the subgroup analyses of polytrauma patients and traumatic brain injury patients also revealed no differences with regard to in-hospital mortality. Further refinement of appropriate selection criteria is a challenge for future studies.

The need to limit the amount of the radiation dose is another important factor in determining which patients might benefit from an immediate TBCT scan. CT scanning is associated with a high radiation dose, which could contribute to an increased lifetime cancer risk.[15] The present study shows that 40% of the patients in the standard workup group had a radiation dose below the lowest radiation dose of patients who underwent a TBCT scan. The substantial number of patients in the standard workup group having had a low radiation dose might have been due to having 35% non-polytrauma patients in our study population.

The time benefit with the use of TBCT has been shown previously.[28] The present study too showed time savings to end of imaging, to a lesser extent reductions in time to diagnosis after correction for centre and baseline characteristics, while simultaneously accounting for missing data. Nevertheless, all registered time intervals appear to be relatively long because a TBCT scan can technically be obtained in 5 minutes. Explanations might be that patient transfers, ATLS® primary surveys and life-saving interventions in the trauma room are time-consuming, particularly in severely injured patients, or that registered time intervals are lagging behind the real time intervals.

It must be noted that confidence in the safety of a TBCT scan is a concern of the complete multidisciplinary trauma team. We found a low number of SAEs during the course of the trial. Although all the SAEs occurred during CT scanning, a high risk of SAE was noted by the entire trauma team in these specific cases. We hypothesised that in the case of severe injuries combined with increased age and a compromised medical history, with associated very low probability of survival, the trauma team sometimes accepts extra minutes of diagnostic time and proceeds with CT scanning to exclude salvageable injuries instead of performing potentially futile invasive procedures.

Limitations and strengths

The limitations of this study should be acknowledged. First, the results show that 250 (46%) of the patients in the standard workup group underwent sequential segmental CT scans of all body regions, comprising a TBCT scan in the end. This high percentage might introduce a bias in the interpretation of our results, given the differences between the groups with respect to mortality might be narrowed by the increased amount of non-immediate TBCT scans in the standard workup group. Although we discussed this phenomenon, we aimed to keep the study as close to daily practice as possible and therefore did not impose on the participating centres to change their local protocols for obtaining CT scans of specific body regions.

Second, the number of TBCT scans in the standard workup group might have been increased due to a learning curve experienced by trauma team members during the course of the trial. An alternative to the present study design with respect to imaging protocols would have been that all participating hospitals had to perform a specific imaging and contrast administration protocol in both study arms. However, there is no solid scientific basis for the choice and preference of one imaging protocol over another, and participating hospitals would have had to change their current practice. This requirement likely would have increased the risk of protocol violations. Also, the introduction of a new protocol is associated with the usual learning curve disadvantages. In addition, such a forced use of imaging protocols would ignore the wide variation in imaging protocols used worldwide, thereby limiting the external validity of the trial results.

Third, the calculation of the direct medical costs was performed for the patients of the four Dutch hospitals. Although we could make a valid comparison between the

groups, this limits the internationally generalizability of the absolute cost results.

Fourth, a common limitation in trauma care was the unblinded randomization procedure. Selection bias was not possible, but both surgeons and patients were aware of the randomization outcome.

Furthermore, a certain degree of subjectivity could not be prevented with respect to the inclusion and exclusion criteria. For example, determining whether a trauma mechanism was high- or low-energetic is not a measurable criterion. Defining these criteria gives an appearance of objectivity (e.g., a high-energy trauma defined as "MVC with >50km/hr"), whereas in daily practice individual interpretations by witnesses or ambulance personnel will occur. Our pragmatic design has led to a considerable number of post-randomisation exclusions because of inappropriate enrolment. We did find a wide variety in the amount of post-randomisation exclusions between the participating sites (shown in the Appendix, Table 4), that might be explained by differences in experience with the use of a TBCT scan. Nevertheless, being too strict with regard to the inclusion criteria in an acute setting will lead to a higher rate of excluded patients who otherwise might have potentially benefitted from the TBCT scan.

Lastly, similar arguments are applicable to the number of protocol violations. More experience with the use of a TBCT scan might decrease the number of protocol violations. Protocol violations are not routinely described in previous studies, but that does not mean that they did not occur. The strength of the present study is the clear and detailed description of these violations, which were justified based on clinical grounds in 24% of the cases.

Considering strengths, this is the first international multicentre randomised study of immediate TBCT scanning in severe trauma patients with prospective clinically based inclusion criteria. Its overall design and randomisation stratification protocol per hospital ensured that the randomised cohorts were equal in patient characteristics, treatment modalities and prior probability of survival. Furthermore, the pragmatic design described above will facilitate trial results being generalizable and thus applicable to the various trauma imaging settings worldwide. Finally, the detailed description of the study method, including the missing variables lacking in most studies, increases the chance of reproduction of the trial, which we would warmly encourage.

Conclusion

Immediate total-body CT scanning is safe, shortens the time to end of imaging and does not increase hospital costs. It does not improve survival and many patients evaluated by the standard workup receive a lower total radiation dose. Improvement of selection of patients who benefit from immediate TBCT should be subject of future research.

Contributors

All authors contributed to the study design, writing of the manuscript, and the decision to submit for publication. KT and JCS gathered and analysed the data. MGD performed the cost-analysis. LFB contributed to the radiation dose calculation. JCS wrote the manuscript under supervision of JCG. JCS and KT created the figures under supervision of MGD and JCG. All authors contributed equally in editing the manuscript and accepted the manuscript in its present form.

Collaborators

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Appendix

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Trauma patients with one of the following parameters at hospital arrival:

- respiratory rate ≥30/min or ≤10/min
- pulse ≥120/min
- systolic blood pressure ≤100 mmHg
- estimated exterior blood loss ≥500 ml
- Glasgow Coma Score ≤13
- abnormal pupillary reaction

OR

- Patients with a clinical suspicion of one of the following diagnoses:
- fractures from at least two long bones
- flail chest, open chest or multiple rib fractures
- severe abdominal injury
- pelvic fracture
- unstable vertebral fractures / spinal cord compression

OR

- Patients with one of the following injury mechanisms:
- fall from a height (>3 meters / >10 feet)
- ejection from a vehicle
- death of occupant in same vehicle
- severely injured patient in same vehicle
- wedged or trapped chest / abdomen

Exclusion criteria
Trauma patients with one of the following characteristics will be excluded:

- known age <18 years
- known pregnancy
- referred from another hospital
- clearly low-energy trauma with blunt injury mechanism
- any patient with a stab wound in one body region
- any patient who is judged to be too unstable to undergo a CT scan and requires (cardiopulmonary) resuscitation or immediate operation because death is imminent

Table 2. Indications for Selective CT scanning after conventional imaging

CT-brain
A patient with trauma of the head and with at least:
➔ **1 major criterion:**
- EMV ≤13
- loss of consciousness >30 minutes
- haemodynamically unstable
- age ≥60 years
- high-risk trauma
- vomiting
- posttraumatic seizure
- coagulopathy risk factors (primary or by medication)
- focal neurological deficit
- >1 point decline in EMV after 1 hour
- posttraumatic amnesia >4 hours
- clinical suspicion for skull base or facial fractures

➔ **and/or at least 2 minor criteria:**
- age between 40-60 years
- posttraumatic loss of consciousness
- posttraumatic amnesia 2-4 hours
- externally facial injuries without signs of fractures
- 1 point decline in EMV after 1 hour

CT of the cervical spine
1. Always when CT-brain is performed
2. In all patients unless they meet all the Nexus criteria:
   - no posterior midline cervical spine tenderness
   - no focal neurological deficit
   - a normal level of alertness
   - no evidence of intoxication
   - no painful distracting injuries

X-cervical spine
Never indicated. If Nexus deviant: cervical-CT.

Chest CT (with iv contrast)
1. Chest gunshot wound with suspicion of trans-mediastinal route
2. Acute aortic injury
3. Abnormal mediastinum seen at chest radiography.
   - mediastinal widening
   - pleural cap ('apical cap')
   - aorta arc unclear enclosed
   - left main bronchus removed downwards
   - deviated trachea or esophagus
   - filled aortopulmonary window
   - widened paraspinal line
   - widened paratracheal line right
4. Relative indications:
   - type and severity of trauma
   - fractures of costa 1 or 2
   - thoracic spine fracture
   - posterior sternoclavicular luxation
   - hesitation about the existence of pneumothorax / pneumomediastinum or pneumopericardium
   - fractures of the clavicle and shoulder

Abdominal CT (with iv contrast)
1. Penetrating injuries in abdomen, chest and/or flank
2. Deficits found with FAST
   - intra-abdominal free fluid
   - suspicion organ injury
   - suspicion retroperitoneal injury
3. Dislocated pelvic ring fracture and/or dislocated acetabulum fracture
4. Clinical suspicion of intraabdominal injury at physical examination
5. Subjective judgment of severity of injury by trauma leader
   - combined thoracic and pelvic injury
   - 'seatbelt sign'
   - chance fracture

X-thoracic and lumbar spine
Not indicated when chest or abdominal CT is performed (reconstructions can be made)
1. Complaints of the thoracic and lumbar spine
2. Tenderness of the thoracic and lumbar spine in the midline
3. Loss of consciousness
4. Deficits in peripheral neurologic examination
5. Painful distracting injuries

Pelvic CT (with iv contrast)
1. All pelvic ring and acetabulum fractures unless conventional imaging is sufficient for adequate diagnosis and treatment
2. After reposition of hip luxation with suspicion of femoral head fractures and/or acetabulum fracture.
   When CT-abdomen is performed, CT-pelvis is not necessary.

Retrograde urethrogram
1. Male patient with severe pelvic injury (type B and C)
2. Bleeding from the meatus, perineal injury or injury of the outer genital organs
3. Penetrating abdominal injury
4. In women only selectively after inspection

Imaging of the extremities
When fractures/dislocations are suspected: conventional imaging and selective CT.

Table 3. Effective doses for single-pass computed tomography procedures in trauma.

Examination	Average effective dose (mSv)
Total-body	20.9*
Brain	1.8
Face	1.8
Sinuses	0.6
Mastoid	0.36
Cervical spine	3
Chest	5.1
Thoracic spine	12
Shoulder	1
Abdomen	11
Upper abdomen	6.5
Kidney	11
Lumbar spine	12
Pelvis	4.5

Abbreviations: CTA, Computed Tomography Angiography; mSv, millisievert. *Calculated as the sum of CT-brain, cervical spine, chest and abdomen.

Table 4. Post-randomisation exclusions per centre.

	Centre A n=354	**Centre B** n=291	**Centre C** n=363	**Centre D** n=145	**Centre E** n=133	**Total** n=1286
Randomised to Standard workup						
Known age <18 years			2			2
Known pregnancy						0
Referred from another hospital	1		2			3
Clearly low-energy trauma with blunt injury mechanism	9	26	12	5	3	55
Penetrating injury in one body region (except GSW)	1		1			2
Too unstable to undergo CT scan*			1	3	3	7
Second enrolment in trial		1	1			2
Does not fulfil inclusion criteria		14	8	2	5	29
Randomised to TBCT						
Known age <18 years			1			1
Known pregnancy						0
Referred from another hospital			1			1
Clearly low-energy trauma with blunt injury mechanism	17	13	17	5		52
Penetrating injury in one body region (except GSW)		2	1			3
Too unstable to undergo CT scan*	2	3	4	4	1	14
Second enrolment in trial	1					1
Does not fulfil inclusion criteria	2	10	8	6	5	31
Total	**33 (9.3%)**	**69 (23.7%)**	**59 (16.3%)**	**25 (17.2%)**	**17 (12.8%)**	**203 (15.8%)**

CT denotes Computed Tomography, GSW denotes gunshot wounds.

* Too unstable for CT scan ((cardiopulmonary) resuscitation or immediate operation is required because death is imminent).

Table 5. Protocol violations

	Centre A n=321	Centre B n=222	Centre C n=304	Centre D n=120	Centre E n=116	Total n=1083
Randomised to Standard workup						
No chest X-ray performed					1	1
No pelvic X-ray performed	4	5	5	1	11	26
No FAST performed		2	1	3		6
No chest and pelvic X-ray performed		3	4		4	11
No pelvic X-ray and FAST performed	2		3	5		10
TBCT after conventional imaging		1	2			3
Selective CT prior to standard workup		1			2	3
No spinal X-rays performed, spinal CT instead	1			1		2
Randomised to TBCT						
TBCT not completed	2		2	1		5
TBCT not completed + prior FAST					2	2
Chest X-ray performed before TBCT	3	2	2	1		8
Pelvic X-ray performed before TBCT		1				1
FAST performed before TBCT		3	6		1	10
Chest X-ray and FAST performed before TBCT		1	2			3
Chest and pelvic X-ray performed before TBCT	2	2	1	1		6
Chest and pelvic X-ray + FAST performed before TBCT		7	5	2		14
Total	**14 (4.4%)**	**28 (12.6%)**	**33 (10.9%)**	**15 (12.5%)**	**21 (18.1%)**	**111 (10.2%)**
Protocol crossovers		4	5	4	11	24
TBCT instead of standard workup		3	5	0	10	18
Standard workup instead of TBCT		1	0	4	1	6
Total protocol violations	**14 (4.4%)**	**32 (14.4%)**	**38 (12.5%)**	**19 (15.8%)**	**32 (27.6%)**	**(12.5%)**
Total protocol violations with unknown reasons*	11 (3.4%)	28 (12.6%)	19 (6.3%)	13 (10.8%)	32 (27.6%)	103 (9.5%)

*Total number of protocol violations when excluding patients for whom deviation of protocol had a clear clinical reason (e.g., transportation to OR or angiosuite)

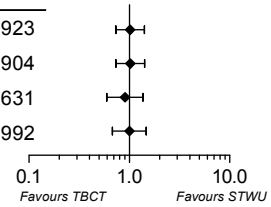
On adjusted analyses and multiple imputation

Adjusted analyses of mortality and time variables were performed to account for treatment centre effects and (potential) baseline differences in haemoglobin, haemotocrit and ISS levels. Odds ratios are provided for mortality. The continuous time variables were log-transformed to achieve normality of data distributions and groups were compared with the Wald test. Geometric means after back-transformation are provided for the time variables. No adjusted analyses have been performed for radiation exposure for lack of achieving normally distributed data after transformation

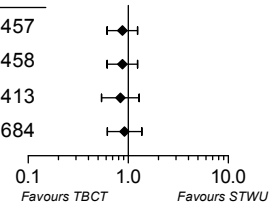
Missing proportions ranged from to 0.2 % to 41.5 %. Missing data in Table 1 and Table 2 of the manuscript were assumed missing at random and were therefore imputed by predictive mean matching. Ten imputations were used and Rubin's rules were used to combine the results. All variables in Table 1 and 2 were predictors except for type of blunt trauma, direct medical costs and derived variables (Revised Trauma Score, polytrauma, traumatic brain injury, TRISS survival probability).

Figure 1. Adjusted analysis for in-hospital mortality

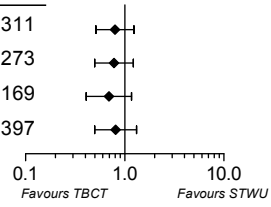
Mortality, all patients	Odds ratio (95%CI)	p
Unadjusted odds ratio	1·02 (0·73 – 1·41)	0·923
Adjusted for centre*	1·02 (0·74 – 1·42)	0·904
Adjusted for centre, Hb, Ht and ISS	0·90 (0·59 – 1·37)	0·631
Adjusted for centre, Hb, Ht and ISS; MI data	1·00 (0·68 – 1·48)	0·992



Mortality, polytrauma patients	Odds ratio (95%CI)	p
Unadjusted odds ratio	0·88 (0·62 – 1·24)	0·457
Adjusted for centre*	0·88 (0·61 – 1·25)	0·458
Adjusted for centre, Hb, Ht and ISS	0·84 (0·54 – 1·29)	0·413
Adjusted for centre, Hb, Ht and ISS; MI data	0·92 (0·62 – 1·37)	0·684



Mortality, patients with severe TBI	Odds ratio (95%CI)	p
Unadjusted odds ratio	0·80 (0·51 – 1·24)	0·311
Adjusted for centre*	0·78 (0·50 – 1·22)	0·273
Adjusted for centre, Hb, Ht and ISS	0·69 (0·41 – 1·17)	0·169
Adjusted for centre, Hb, Ht and ISS; MI data	0·81 (0·50 – 1·32)	0·397



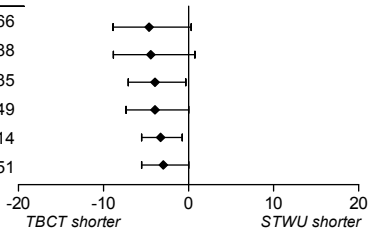
Data was complete or otherwise completely supplemented by MI for 1083 patients except for adjusted analysis for centre, Hb, Ht and ISS without MI; all patients: 992/1083 (89·2%); polytrauma 611/693 (89·2%); TBI 299/329 (90·9%).

* Centre with highest patient volume as reference.

Abbreviations: Hb Haemoglobin, Ht Haematocrit, ISS Injury Severity Score, MI multiple imputation.

Figure 2. Adjusted analysis and multiple imputation for time to end of imaging among TBI patients

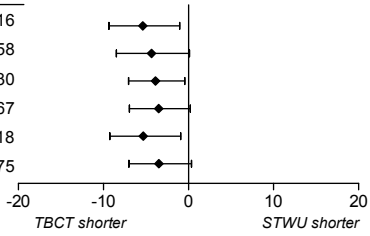
TBI patients	Mean Δ time to end of imaging (95%CI)	p
Unadjusted	-4·64 (-8·87 – 0·33)	0·066
Unadjusted; MI data	-4·44 (-8·83 – 0·76)	0·088
Adjusted for centre*	-3·94 (-7·08 – -0·32)	0·035
Adjusted for centre; MI data	-3·94 (-7·35 – 0·00)	0·049
Adjusted for centre, Hb, Ht, ISS	-3·28 (-5·53 – -0·75)	0·014
Adjusted for centre, Hb, Ht, ISS; MI data	-2·96 (-5·52 – 0·00)	0·051



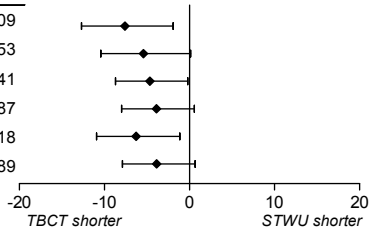
Differences of the geometric means calculated after back-transformation from log transformation.
Data was completely supplemented by MI for 329 TBI patients (100·0%). For unadjusted and for centre adjusted analysis 265/329 (80·5%) patients and for analysis adjusted for centre, Hb, Ht, and ISS 244/329 (74·2%) patients were available.
* Centre with highest patient volume as reference.
Abbreviations: TBI Traumatic brain injury, Hb Haemoglobin, Ht Haematocrit, ISS Injury Severity Score, MI multiple imputation, Δ difference.

Figure 3. Adjusted analysis and multiple imputation for time to diagnosis among all patients and polytrauma patients

All patients	Mean Δ time to diagnosis (95%CI)	p
Unadjusted	-5·36 (-9·35 – -1·04)	0·016
Unadjusted; MI data	-4·35 (-8·48 – 0·13)	0·058
Adjusted for centre*	-3·87 (-7·06 – -0·43)	0·030
Adjusted for centre; MI data	-3·51 (-6·95 – 0·22)	0·067
Adjusted for centre, Hb, Ht, ISS	-5·32 (-9·26 – -0·92)	0·018
Adjusted for centre, Hb, Ht, ISS; MI data	-3·49 (-7·02 – 0·34)	0·075



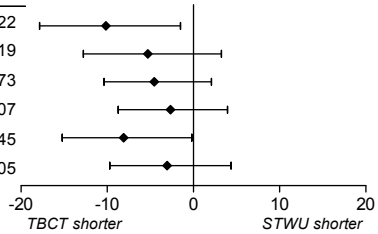
Polytrauma patients	Mean Δ time to diagnosis (95%CI)	p
Unadjusted	-7·59 (-12·70 – -1·92)	0·009
Unadjusted; MI data	-5·42 (-10·44 – 0·14)	0·053
Adjusted for centre*	-4·67 (-8·70 – -0·22)	0·041
Adjusted for centre; MI data	-3·87 (-8·00 – 0·56)	0·087
Adjusted for centre, Hb, Ht, ISS	-6·27 (-10·92 – -1·14)	0·018
Adjusted for centre, Hb, Ht, ISS; MI data	-3·86 (-7·88 – 0·68)	0·089



Differences of the geometric means calculated after back-transformation from log transformation.
Data was completely supplemented by MI for 1083 patients (100.0%). For unadjusted and for centre adjusted analysis 825/1083 (80·5%) patients and for analysis adjusted for centre, Hb, Ht, and ISS 752/1083 (74·2%) patients were available.
Data was completely supplemented by MI for 693 polytrauma patients (100.0%). For unadjusted and for centre adjusted analysis 521/693 (75·2%) patients and for analysis adjusted for centre, Hb, Ht, and ISS 471/693 (68·0%) patients were available.
* Centre with highest patient volume as reference.
Abbreviations: Hb Haemoglobin, Ht Haematocrit, ISS Injury Severity Score, MI multiple imputation, Δ difference.

Figure 4. Adjusted analysis and multiple imputation for ED time among polytrauma patients

Polytrauma patients	Mean Δ ED time (95%CI)	p
Unadjusted	-10·14 (-17·85 – -1·50)	0·022
Unadjusted; MI data	-5·29 (-12·76 – 3·25)	0·219
Adjusted for centre*	-4·53 (-10·37 – 2·09)	0·173
Adjusted for centre; MI data	-2·65 (-8·71 – 3·96)	0·407
Adjusted for centre, Hb, Ht, ISS	-8·10 (-15·22 – -0·18)	0·045
Adjusted for centre, Hb, Ht, ISS; MI data	-3·06 (-9·71 – 4·36)	0·405



Differences of the geometric means calculated after back-transformation from log transformation.
Data was completely supplemented by MI for 693 polytrauma patients (100·0%). For unadjusted and for centre adjusted analysis 537/693 (77·5%) patients and for analysis adjusted for centre, Hb, Ht, and ISS 487/693 (70·3%) patients were available.
* Centre with highest patient volume as reference.
Abbreviations: Hb Haemoglobin, Ht Haematocrit, ISS Injury Severity Score, MI multiple imputation, ED Emergency Department, Δ difference.

Serious Adverse Events (SAEs) described in detail

Patient A: An 81-year-old woman was randomised for immediate total-body CT. Because of respiratory and haemodynamic instability (blood pressure [BP] 80/40 mmHg, pulse [P] 80/min, Glasgow Coma Score [GCS] 3, on-scene endotracheal intubation) the randomisation result was not followed and chest and pelvic X-rays and FAST were performed. A pneumothorax was seen on the chest x-ray and two chest tubes were placed. Before starting the CT brain the trauma team decided to not resuscitate in case of cardiac arrest. CT scanning was interrupted because of respiratory instability. The patient died shortly after.

Patient B: A 75-year-old man was randomised for immediate total-body CT. Because blood pressure and pulse were considered acceptable (BP 130/100 mmHg, P 110/min, GCS 3, on-scene endotracheal intubation), the trauma team decided to proceed with the CT scan. During the scanning, the clinical condition of the patient deteriorated and the scan was interrupted. Physical examination and ultrasound did not reveal a cardiac tamponade or tension pneumothorax. The patient died due to his traumatic injuries after a short period of cardiopulmonary resuscitation and insertion of a chest tube.

Patient C: A 74-year-old woman was randomised for immediate total-body CT. There was a discrepancy between the detection of carotid and femoral pulsations, but the vital parameters were considered acceptable (BP 128/95 mmHg, P 80/min, GCS 3, on-scene endotracheal intubation). Therefore, the trauma team decided to proceed with a CT scan to guide therapeutic interventions. When the total-body CT scan was almost finished, the patient developed severe bradycardia and the scan was interrupted. During cardiopulmonary resuscitation, the CT brain was evaluated and the traumatic brain injury was diagnosed as incompatible with life. The cardiopulmonary resuscitation was discontinued and the patient died.

Patient D: an 86-year-old woman was randomised for conventional imaging. Upon arrival at the Eemergency Department the vital parameters were marginal (BP 94/52 mmHg, P 69/min, GCS 3, on-scene endotracheal intubation). Given her compromised medical history, the decision was made not to resuscitate in case of an event during scanning. After conventional imaging there was an indication for TBCT. During the scan there was no cardiac output. The patient died in the trauma room.

There was also 1 SAE reported in the post-randomisation exclusions. This 86-year-old woman was randomised for immediate total-body CT, but should have been excluded. During the scanning, a massive pneumothorax was found and the scan was interrupted. Two chest tubes were inserted and shortly after this procedure the patient died, following a short period of cardiopulmonary resuscitation.


2

Cost-effectiveness of immediate total-body CT scanning in severe trauma patients (REACT-2 trial)

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Submitted

Abstract

Objective

To determine the cost-effectiveness of immediate total-body CT (iTBCT) scanning compared with conventional radiological imaging with selective CT scanning (standard work-up) during the initial trauma evaluation.

Methods

In this multicenter randomized clinical trial, adult patients with a high suspicion of severe injuries were included at the trauma center to receive either iTBCT scanning or standard work-up. Hospital health care costs were determined for the first six months following trauma. Health outcomes included being alive and being alive without serious morbidity. The probability of iTBCT being cost-effective was calculated for various levels of willingness-to-pay per extra patient alive or patient alive without serious morbidity.

Results

A total of 928 Dutch patients with complete clinical follow-up were included. Mean costs of hospital care were €25,809 (95% bcaCI: €22,617 to €29,137) for the iTBCT group (N=456) and €26,155 (95% bcaCI: €23,050 to €29,344) for the standard work-up group, saving €346 (95% bcaCI: -€4,987 to €4,328; P=0.876). The percentages of patients alive at six months were similar. The difference in percentages of patients alive without serious morbidity was 61.6% in the iTBCT group versus 66.7% in the standard work-up group (difference 5.1%, P=0.104. The probability of iTBCT being cost-effective in keeping patients alive remained below 0.56 in the whole group, but was higher in multitrauma patients (0.8-0.9) and in patients with traumatic brain injury (over 0.9).

Conclusions

From a hospital health care provider perspective, immediate total-body CT scanning should economically be the diagnostic strategy of first choice in multitrauma or traumatic brain injury patients.

Background

Immediate total-body computed tomography (iTBCT) scanning during initial trauma assessment was recently evaluated clinically - regarding (in-hospital) mortality, times to end of imaging and diagnosis, radiation exposure, safety and hospital outcomes - against conventional imaging supplemented with selective CT scanning (standard work-up) as its best alternative.[1] While the REACT-2 multicenter randomized clinical trial showed reduced times to diagnosis and end of imaging in the trauma room, no gain in reducing mortality was observed. iTBCT scanning increased the minimum level of radiation exposure, but simultaneously, excess exposure of 25 mSv or more became unlikely, while such levels were still frequently observed under the standard work-up regimen. More readmissions during the first six months after trauma were observed.

This level 1 scientific evidence may so far have been neither very supportive, nor very discouraging to hospital managers and medical professionals in taking investment decisions in favor of facilitating iTBCT scanning in the trauma room. Another relevant, yet underexposed issue of iTBCT scanning of trauma patients in this context of decision making concerns the health economic aspects. Alongside the REACT-2 trial a health economic evaluation was conducted to inform hospital health care managers and professionals in the Netherlands on the cost-effectiveness of iTBCT scanning of trauma patients suspected of being severely injured, with the standard work-up as its comparator.

Methods

The REACT-2 study design

The design of the REACT-2 multicenter randomized controlled trial of iTBCT scanning versus the standard work-up for patients with potentially major trauma has been announced (ClinicalTrials.gov: NCT01523626) and reported previously.[1,2] The study was approved by the institutional review boards at all participating centers of which four resided in the Netherlands and one in Switzerland. We enrolled adult trauma patients with compromised vital parameters and clinically suspected of life-threatening injury or severe injury mechanisms. Eligible patients were randomly assigned to either iTBCT scanning without prior conventional imaging or to the standard work-up in a 1:1 ratio with stratification for center. With permission of the institutional review board, the trauma patient or the legal representative was informed about the REACT-2 trial at the first convenient moment following the trauma work-up. Upon written informed consent gathering of medical data and patient reported outcomes took place. In absence of written informed consent despite all efforts, medical data were still gathered (again, with permission) and reported, but these alive patients were excluded from the intention to treat analyses of patient reported outcomes.

Imaging strategies

The CT-scanner was located in the trauma room or adjacent room. The protocol for the iTBCT group consisted of a two-step acquisition (from vertex to pubic symphysis) without gantry angulations starting with a Head and Neck Non-Enhanced CT (NECT) with arms alongside the body. The second scan covered chest, abdomen and pelvis. The preferred technique for the second scan was a split-bolus intravenous contrast of the body directly after raising the arms alongside the head, if not precluded by injuries. The radiologist decided on the use of contrast and if so, in which phase it was applied.

In the standard work-up group chest and pelvic x-rays and FAST ultrasound were performed during the ATLS® primary survey. After further assessment and resuscitation during the secondary survey a selective CT-scan could be made from individual body regions with (segmented) acquisition of the respective body segments (possibly turning cumulatively into a whole body scan as well). The standard radiologic trauma work-up is worldwide performed according to ATLS® guidelines.[3]

Type of health economic evaluation, outcomes, perspectives and time horizon

The economic evaluation of iTBCT scanning of potentially severely injured trauma patients was performed as a cost-effectiveness analysis with the costs per patient alive (with or without serious morbidity) and the costs per patient alive without serious morbidity at the end of follow-up as distinct outcome measures. All Dutch patients with a known health status at the end of follow-up were included. Patients were classified into one of six stages, ordered by increasing severity: 'recovered', 'still recovering without remaining handicap', 'still recovering with remaining handicap', 'handicapped, stable', 'handicapped, progressive', 'deceased'. Serious morbidity (or worse) was defined as 'still recovering with remaining handicap' or any stage that was more severe. The cost-effectiveness analysis was performed from a hospital health care perspective to assist hospital managers in deciding how to provide in-hospital trauma care efficiently.

Conform study protocol[2] the time horizon for all analyses was restricted to 6 months post trauma. With a time horizon of 6 months, no discounting of costs and effects was done to account for time preferences.

Cost components, resources, unit costing

Hospital costs included the costs of initial trauma care, of ICU-stay, and general ward stay during the index admission, including all diagnostic (e.g. imaging, function tests, lab tests) and therapeutic procedures (e.g. intubation, surgery, radiographic intervention, rehabilitation). They further covered inpatient and outpatient hospital consultations, repeat hospital admissions, and diagnostic and therapeutic procedures during 6 months of follow-up. Costs of stay in a nursing home or rehabilitation center (other than rehabilitation in the index hospitals) were not incorporated.

Data on health care volume in the Dutch index hospitals (both, during initial and during repeat hospitalizations) were gathered uniformly from the hospital information systems with the help of local back-office managers (see Acknowledgements). If no information could be obtained from this database, the patient and/or its general practitioner were contacted by telephone by one of the authors (KT, JCS) or research nurses (see Acknowledgements). If a patient was transferred to another hospital after initial admission, data from this hospital admission (duration of inpatient stay, therapeutic interventions, imaging procedures) and on the subsequent out-patient visits were also included in the analysis.

Unit costs of different costs components were taken from the Dutch costing guideline for health care research.[4] Considering however that trauma care is regionally centralized in highly specialized centers and that the Dutch hospitals participating in this trial were all academically affiliated, we selected unit costing levels for care in university hospitals when appropriate. The unit costs for major healthcare components were: €627 for a hospital inpatient day at the general ward, €2,380 for a day at the intensive care unit, €141 for an inpatient or outpatient hospital consultation. For a day at the medium care facility a unit cost of €1,254 was used (doubling the unit costs of the general ward and about half the costs of a day at the intensive care ward). All unit costs of diagnostic and therapeutic procedures were determined in one of the participating academic centers and ranged from less than one euro for a single blood test to several ten thousands of euros for complex surgery; the average costs per procedure, including 'back-office' costs, were slightly above €25 in this multi-trauma patient group.

Unit costs were expressed in Euros for the base year 2013 during the study period; unit costs from other calendar years were price indexed using the national general consumer price indices as published by Statistics Netherlands.[5]

Analysis sets, demographics and economic analysis

Originally, the trial was meant to run as a full international trial including trauma centers from the Netherlands, Switzerland and the United States of America (US). Unfortunately, while the trauma surgeons of the large USA trauma center were able and willing to participate, the associated radiologists decided not to contribute for financial reasons. Late replacement by a center from the United Kingdom became obsolete, because of the lengthy institutional review board procedure in this particular patient group. Considering further that costing data were only partially available for the Swiss institute, we decided to restrict the economic analysis to the patient data set (89.3% of all patients) relevant for decision making in the Netherlands.

Normally and non-normally distributed continuous data are reported with means and standard deviations (SD), respectively medians and interquartiles. Differences in casemix between study arms were assessed with independent sample t-tests or Mann-Whitney-U Tests for continuous data and Chi-2 tests and Fisher's Exact tests for categorical variables as appropriate.

Differences in costs and health outcomes between iTBCT-scanning and the standard work-up of trauma patients were assessed by calculating the 95% confidence intervals for the mean differences after correction for bias and using accelerated non-parametric bootstrapping, drawing 5,000 samples of the same size as the original sample separately for each subgroup (see below) and with replacement.[6] Incremental cost-effectiveness (ICER) ratios were calculated, expressing the extra costs per (i) extra patient alive and (ii) extra patient alive and without serious morbidity. Cost-effectiveness planes of differences in costs by differences in health outcomes were drawn, again following non-parametric bootstrapping. The corresponding cost-effectiveness acceptability curves were derived to show the probability of iTBCT-scanning being cost-effective for a range of values of the societal willingness to pay for health improvement.

A point-estimated scenario analysis was performed with a more stringent definition of 'being alive at 6 months without serious morbidity' by only including patients who were fully recovered. Another point estimated scenario analysis was performed to account for potentially missing data in 7.1% and 8% of patients for whom non-observed volumes and costs of diagnostic and therapeutic procedures, respectively out-patient hospital consultations were set to zero in the main analysis; in the alternative scenario, non-observed volumes and costs for patients were set to the means per treatment group, based on available data.

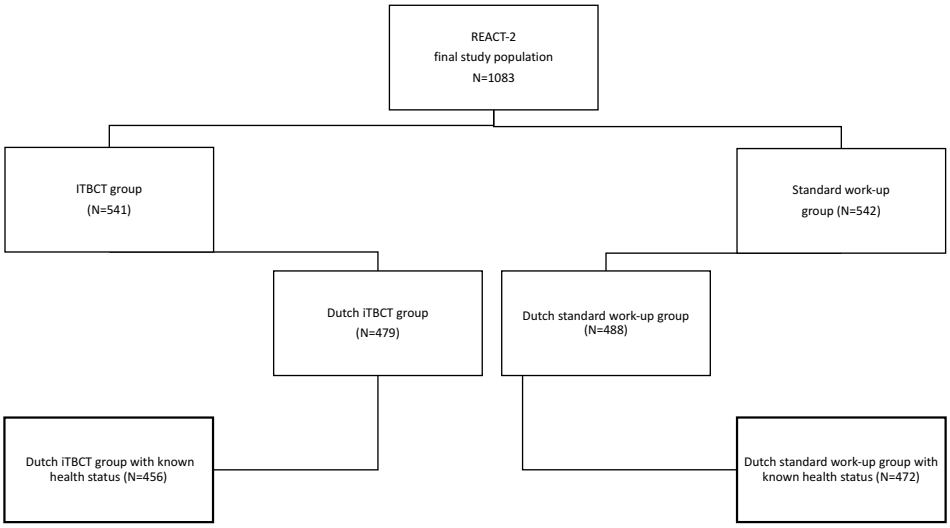
Preplanned subgroup analyses were performed for multitrauma patients, defined as having an Injury Severity Score of at least 16, and for severe traumatic brain injury (TBI) patients, defined as having a Glasgow Coma Score no greater than 8 on admission and an Abbreviated Injury Scale head score of 3 or above. The abovementioned bootstrapping procedures were stratified for multitrauma status and severe brain injury status in order to maintain consistency between the main analyses and the preplanned subgroup analyses.
All analyses were performed intention-to-treat. Microsoft Access 2010 and SPSS version were the applied software platforms. A p-value less than 0.05 was considered statistically significant.

Results

Study population

Patient enrolment began on April 22, 2011, and ended January 1, 2014. Eventually, 1,083 trauma patients were included in the clinical analysis set.[1] The number of patients included in the cost-effectiveness analyses was 928 (see Figure 1).

Figure 1. Selected patients from the REACT-2 multicenter randomized clinical trial



Of the 541 patients in the iTBCT group, 62 Swiss patients were excluded and another 23 Dutch patients had no known health status after 6 months, resulting in 456 iTBCT patients available for the cost-effectiveness analyses (bold solid rectangle on the left). Of the 542 patients in the standard work-up group 54 Swiss patients were excluded and the health status of 16 Dutch patients was unknown, resulting in 472 standard work-up patients available for the cost-effectiveness analyses (bold solid rectangle on the right)

Table 1 shows baseline demographics and clinical characteristics of the cost-effectiveness analysis set of patients (N=928). Median age was 43 years (26-59), 76.4% was male, 97.8% presented with blunt trauma, 66.3% with multitrauma. The median Injury Severity Score was 21 (10-30). Randomization groups were comparable for all characteristics.

Differences in costs

iTBCT patients (n=456) spent 11.4 (95% bias-corrected and accelerated confidence interval (bcaCI): 9.9 to 13.1) in-hospital days at the general ward, 3.6 (95% bcaCI: 3.0 to 4.3) days at the intensive care unit (ICU) and 0.8 (95% bcaCI: 0.5 to 1.0) days at the medium care unit (MCU), costing respectively €7,171 (95% bcaCI: €6,216 to €8,241), €8,560 (95% bcaCI: €7,088 to €10,155) and €941 (95% bcaCI: €652 to €1,273). On average, a patient spent 15.8 (95% bcaCI: 13.9 to 17.8) days in the hospital at a cost of €16,671 (95% bcaCI: €14,553 to €18,929).

In contrast, standard work-up patients (n=472) spent 9.7 (95% bcaCI: 8.5 to 10.9) in-hospital days at the general ward, 4.2 (95% bcaCI: 3.5 to 5.1) at the ICU and 0.6 (95% bcaCI: 0.4 to 0.8) at the MCU, costing respectively €6,081 (95% bcaCI: €5,348 to €6,812), €10,029 (95% bcaCI: €8,221 to €12,061), and €749 (95% bcaCI: €499 to €1,057). On average, a patient spent 14.5 (95% bcaCI: 12.8 to 16.2) days in the hospital at a cost of €16,860 (95% bcaCI: €14,559 to €19,228).

Table 1. Baseline characteristics of patients with known health status at end of follow-up

Characteristic	iTBCT (n) § vs. Standard workup (n)	iTBCT (n=456)	Standard workup (n=472)	P-value
Age in years		42 (27-59)	44 (25-59)	0.936*
Male sex		348 (76.3)	361 (76.5)	0.952†
Blunt trauma		445 (97.6)	463 (98.1)	0.656‡
Trauma mechanism blunt trauma	445 vs. 463			0.453†
Fall from height		134 (30.1)	149 (32.1)	
MVC – patient as occupant		187 (42.0)	176 (37.9)	
MVC – patient as cyclist		46 (10.3)	52 (11.2)	
MVC – patient as pedestrian		23 (5.2)	35 (7.5)	
Other		55 (12.4)	52 (11.2)	
Abbreviated Injury Scale ≥3				
Head		224 (49.1)	203 (43.0)	0.062†
Chest		198 (43.4)	182 (38.6)	0.132†
Abdomen		44 (9.6)	63 (13.3)	0.078†
Extremities		125 (27.4)	139 (29.4)	0.492*
Injury Severity Score (IQR)		22 (10-33)	21 (9-30)	0.276*
Polytrauma patients ||		315 (69.1)	300 (63.6)	0.075*
TBI patients, ||		165 (36.2)	143 (30.3)	0.057*
TRISS, survival probability	279 vs. 273	0.92 (0.61-0.98)	0.93 (0.68-0.98)	0.403†

Data are reported as count (percentage) or as median (interquartile range) unless otherwise indicated. MVC denotes Motor Vehicle Collision, TBI denotes Traumatic Brain Injury, TRISS denotes Trauma and Injury Severity Score.

* Mann-Whitney U test; † Chi^2 test; ‡ Fisher's Exact test.

§ This column displays the numbers of patients if their total was less than 928.

|| Polytrauma patients are defined as ISS ≥16. Traumatic Brain Injury (TBI) patients are defined as GCS <9 at presentation and AIS Head ≥3.

An iTBCT instead of standard workup seemed associated with the trade-off of half a day shorter at the ICU (-0.6; 95% bcaCI: -1.8 to 0.5) for nearly two days extra at the general ward (1.7; 95% bcaCI: -0.2 to 3.8). The resulting savings, -€189 (95% bcaCI: -€3,519 to €3,124) were non-significant (P=0.914).

Similar mean numbers of diagnostic and therapeutic procedures were performed for iTBCT patients (349.5; 95% bcaCI: 292.4 to 420.2) (n=418) and standard work-up patients (329.5; 95% bcaCI: 282 to 382) (n=436). The corresponding costs too were comparable: €8,790 (95% bcaCI: €7,333 to €10,406) versus €8,909 (95% bcaCI: €7,686 to €10,260) respectively; the difference -€119 (95% bcaCI: -€2,103 to €1,861) being non-significant (P=0.907).

iTBCT patients received on average 8.3 (95% bcaCI: 7.6 to 9.0) specialists' consultations at a mean costs of €1,168 (95% bcaCI: €1,073 to €1,269) (n=422). Standard work-up patients received on average 8.1 (95% bcaCI: 7.5 to 8.8) specialists' consultations at a mean costs of €1,144 (95% bcaCI: €1,059 to €1,233) (n=440). The difference between the groups, €25 (95% bcaCI: -€109 to €160), was non-significant (P=0.717).

The total hospital costs during the 6 months following the trauma were €25,809 (95% bcaCI: €22,617 to €29,137) on average for iTBCT patients (n=456) and €26,155 (95% bcaCI: €23,050 to €29,344) on average for standard work-up patients (n=472). The difference in favor of iTBCT, a saving of €346 (95% bcaCI: -€4,987 to €4,328), was non-significant (P=0.876).

Differences in health

At 6 months of follow-up, 82.3% (764/928) patients had survived, 82% (374 of 456) in the iTBCT group and 82.6% (390/472) in the standard work-up group. The difference of 0.6% survived patients in favor of standard work-up was non-significant (Pearson Chi2=0.059; P=0.808).

The percentage of patients alive and without serious morbidity was 61.6% (281/456) in the iTBCT group and 66.7% (315/472) in the standard work-up group. The difference of 5.1% was non-significantly in favor of the standard work-up group (Pearson Chi2=2.64; P=0.104). If the more stringent definition was used and still recovering without remaining handicap at the end of the sixth month was also considered as having a serious morbidity, then the percentages dropped considerably to 36.6% (167/456) in the iTBCT group and 39.2% (185/472) in the standard work-up group. This difference of 2.6% was not significant (Pearson Chi2=0.652; P=0.419).

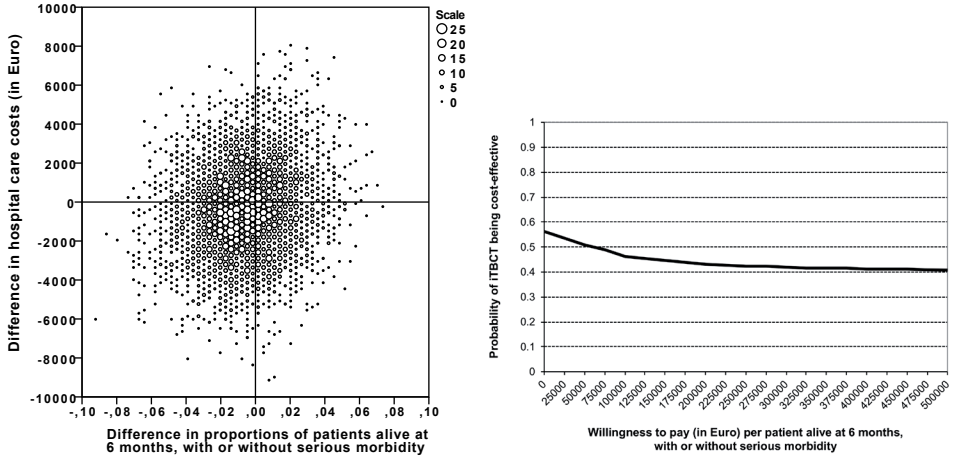
Incremental cost-effectiveness

Based on the point estimates and considered from a hospital health care perspective, iTBCT saved €56,761 per life lost and €6,765 per lost patient alive without serious morbidity. The cost-effectiveness planes and corresponding cost-effectiveness acceptability curves are shown in Figures 2a-d. iTBCT was cost saving in 56.2% and more effectively kept patients alive for at least 6 months in 39.9% (irrespective of serious morbidity) or 3.5% (without serious morbidity) of all bootstraps. The probability of iTBCT being cost-effective ranges from 56.2% to 40.9% depending on the societal willingness to pay up to 500 thousands of euros per patient alive for at least 6 months post-trauma. The probability of iTBCT being cost-effective ranges from 56.2% to 3.9% depending on the societal willingness to pay up to 500 thousands of euros per patient alive at 6 months post-trauma without serious morbidity.

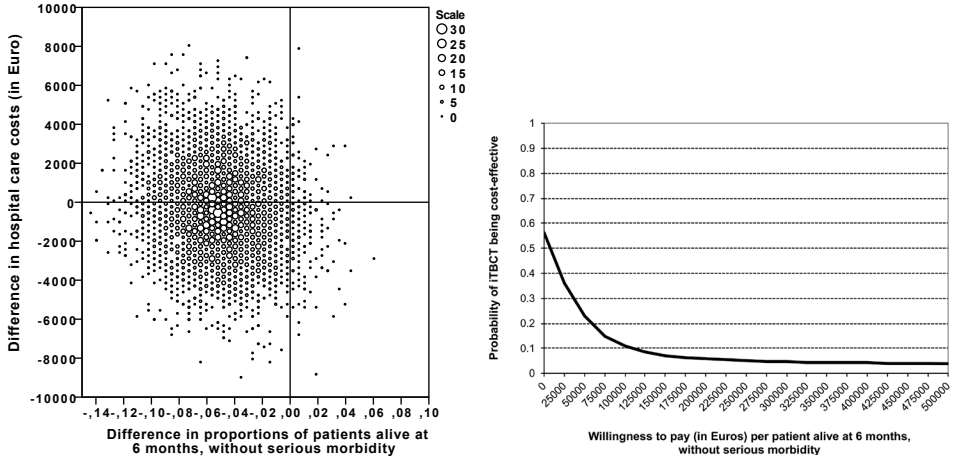
Scenario analyses

Under the more stringent definition, iTBCT saved €13,452 per lost patient who is fully recovered at 6 months post-trauma. Assuming non-zero, mean values per treatment group for non-observed volumes and costs of diagnostic and therapeutic procedures as well as out-patient hospital consultations, the base case results decreased by 17.9% to €46,590 per life lost, €5,553 per lost patient alive without serious morbidity, and €11,042 per lost patient who is fully recovered at 6 months post-trauma.

Figure 2. Cost-effectiveness of iTBCT versus standard work-up



2a (left): Cost-effectiveness plane following 5,000 bootstraps showing differences in hospital health care costs and proportions of patients alive at 6 months with or without serious morbidity between iTBCT and standard workup. Larger dots represent higher bootstraps counts (scale legend). iTBCT may be more costly and more effective (upper right quadrant), more costly and less effective (upper left), cheaper and less effective (lower left), or cheaper and more effective (lower right). 2b (right): Cost-effectiveness acceptability curve showing the probability of iTBCT being cost-effective for different values of willingness to pay up to 500K euros per patient alive at 6 months with or without serious morbidity.



2c (left): Cost-effectiveness plane following 5,000 bootstraps showing differences in hospital health care costs and proportions of patients alive at 6 months without serious morbidity between iTBCT and standard workup. 2d (right): Cost-effectiveness acceptability curve showing the probability of iTBCT being cost-effective for different values of willingness to pay per patient alive at 6 months without serious morbidity.

Subgroup multitrauma patients

The total hospital costs in the first half-year following trauma were €32,093 (95% bcaCI: €27,881 to €36,919) on average for iTBCT multitrauma patients (n=315) and €35,063 (95% bcaCI: €30,547 to €39,999) on average for standard work-up multitrauma patients (n=300). The difference in favor of iTBCT, a saving of €2,970 (95% bcaCI: -€9,839 to €3,756), was non-significant (P=0.391).

At 6 months of follow-up, 74.6% (459/615) multitrauma patients had survived, 75.6% (238/315) in the iTBCT group and 73.7% (221/300) in the standard work-up group. The difference of 1.9% survived multitrauma patients in favor of iTBCT was non-significant (Pearson Chi2=0.29; P=0.59). The percentage of multitrauma patients alive at 6 months without serious morbidity was 49.5% (156/315) in the iTBCT group and 52.7% (158/300) in the standard work-up group. The difference of 3.1% in favor of the standard work-up group was non-significant (Pearson Chi2=0.607; P=0.436).

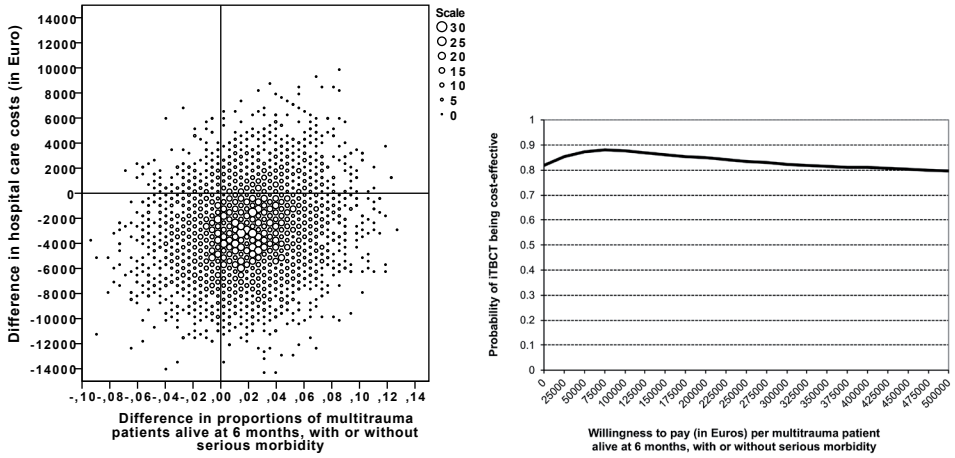
Based on the point estimates and considered from a hospital health care perspective, iTBCT saved €157,235 per multitrauma life gained and €94,500 per lost multitrauma patient alive without serious morbidity. The cost-effectiveness planes and corresponding cost-effectiveness acceptability curves are shown in Figures 3a-d. Among multitrauma patients iTBCT was cost saving in 81.7% and more effectively kept patients alive for at least 6 months in 72.7% (irrespective of serious morbidity) or 22.0% (without serious morbidity) of all bootstraps. The probability of iTBCT being cost-effective ranges from 88.0% to 79.6% depending on the societal willingness to pay up to 500 thousands of euros per multitrauma patient alive for at least 6 months post-trauma. The probability of iTBCT being cost-effective ranges from 81.7% to 27.7% depending on the societal willingness to pay up to 500 thousands of euros per multitrauma patient alive at 6 months post-trauma without serious morbidity.

Contrastingly, in single trauma patients (N=313) and based on point estimates, iTBCT (N=141) was dominated by the standard work-up (N=172) with non-significantly increased hospital care costs, €1153 (95% bcaCI: -€3,813 to €5,588; P=0.637), and non-significantly decreased numbers of patients alive by -1.8% (Pearson Chi2=1.01, P=0.315) or numbers of patients alive without serious morbidity by -2.6% (Pearson Chi2=0.6, P=0.439).

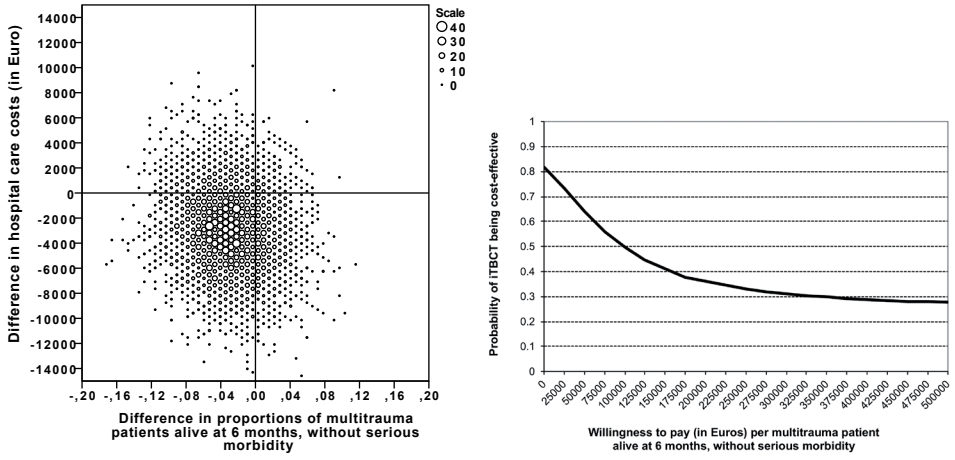
Subgroup traumatic brain injury patients

The total hospital costs in the first half-year following trauma were €33,393 (95% bcaCI: €28,370 to €38,766) on average for iTBCT TBI patients (n=165) and €36,352 (95% bcaCI: €30,344 to €42,719) on average for standard work-up TBI patients (n=143). The difference in favor of iTBCT, a saving of €2,959 (95% bcaCI: -€11,201 to €4,990), was non-significant (P=0.468). At 6 months of follow-up, 58.1% (179/308) TBI patients had survived, 61.2% (101/165) in the iTBCT group and 54.5% (78/143) in the standard work-up group. The difference of 6.7% survived TBI patients in favour of iTBCT was non-significant (Pearson Chi2=1.40; P=0.237). The percentage of TBI patients alive at 6 months with-

Figure 3. Cost-effectiveness of iTBCT versus standard work-up in multitrauma patients



3a (left): Cost-effectiveness plane following 5,000 bootstraps showing differences in hospital health care costs and proportions of multitrauma patients alive at 6 months with or without serious morbidity between iTBCT and standard workup. 3b (right): Cost-effectiveness acceptability curve showing the probability of iTBCT being cost-effective for different values of willingness to pay up to 500K euros per multitrauma patient alive at 6 months with or without serious morbidity.



3c (left): Cost-effectiveness plane following 5,000 bootstraps showing differences in hospital health care costs and proportions of multitrauma patients alive at 6 months without serious morbidity between iTBCT and standard workup. 3d (right): Cost-effectiveness acceptability curve showing the probability of iTBCT being cost-effective for different values of willingness to pay up to 500K euros per multitrauma patient alive at 6 months without serious morbidity.

out serious morbidity was 35.2% (58/165) in the iTBCT group and 40.6% (58/143) in the standard work-up group. The difference of 5.4% in favor of the standard work-up group was non-significant (Pearson Chi2=0.954; P=0.329).

Based on the point estimates and considered from a hospital health care perspective, iTBCT saved €44,385 per gained TBI patient alive and €54,716 per lost TBI patient alive without serious morbidity. The cost-effectiveness planes and corresponding cost-effectiveness acceptability curves are shown in Figures 4a-d. Among TBI patients (N=308) iTBCT was cost saving in 76.3% and more effectively kept patients alive for at least 6 months in 88.0% (irrespective of serious morbidity) or 16.9% (without serious morbidity) of all bootstraps. The probability of iTBCT being cost-effective ranges from 94.9% to 90.8% depending on the societal willingness to pay up to 500 thousands of euros per TBI patient alive for at least 6 months post-trauma. The probability of iTBCT being cost-effective ranges from 76.3% to 20.4% depending on the societal willingness to pay up to 500 thousands of euros per TBI patient alive at 6 months post-trauma without serious morbidity.

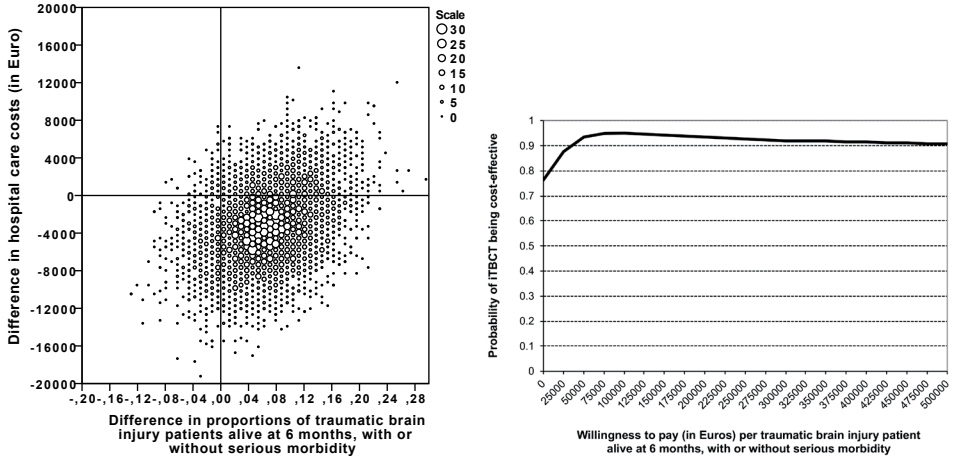
Contrastingly, in patients without TBI (N=620) and based on point estimates, iTBCT (N=291) in comparison with standard work-up (N=329) non-significantly decreased hospital care costs by -€241 (95% bcaCI: -€5,632 to €5,461; P=0.941), numbers of patients alive by -1.% (Pearson Chi2=0.301, P=0.583) or numbers of patients alive without serious morbidity by -1.5% (Pearson Chi2=0.194, P=0.659).

Discussion

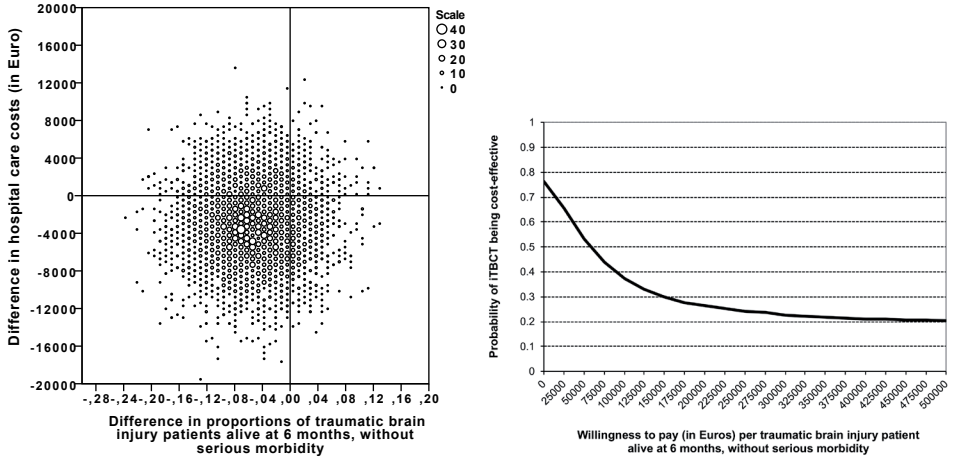
The REACT-2 trial generally demonstrated that iTBCT and standard radiological imaging in trauma patients after major trauma have comparable outcomes at 6 months post-trauma regarding hospital care costs and proportions of patient alive and patients alive without serious morbidity. However, the cost-effectiveness analysis from the hospital care provider perspective suggested that iTBCT is more efficient than the standard work-up in keeping *multitrauma* or *traumatic brain injury* patients alive for at least 6 months, given the per patient cost savings of almost 3,000 euros and survival rates that are slightly, although non-significantly higher by 1.9%, respectively 6.7%. Hence, iTBCT would health economically be the strategy of first choice in at least 3 out of every 4 patients.

The role of iTBT is more debatable when the cost savings are off-set against the non-significantly lower rates of patients alive at 6 months without serious morbidity (minus 3.1% in multitrauma and 5.4% in traumatic brain injury patients compared with standard work-up). The diagnostic strategy of first choice then becomes dependent on the societal willingness-to-pay to prevent serious morbidity. Results have been reported for willingness-to-pay levels up to half a million euros; above the 500K pla-

Figure 4. Cost-effectiveness of iTBCT versus standard work-up in traumatic brain injury patients



4a (left): Cost-effectiveness plane following 5,000 bootstraps showing differences in hospital health care costs and proportions of traumatic brain injury patients alive at 6 months with or without serious morbidity between iTBCT and standard workup. 4b (right): Cost-effectiveness acceptability curve showing the probability of iTBCT being cost-effective for different values of willingness to pay up to 500K euros per traumatic brain injury patient alive at 6 months with or without serious morbidity.



4c (left): Cost-effectiveness plane following 5,000 bootstraps showing differences in hospital health care costs and proportions of traumatic brain injury patients alive at 6 months without serious morbidity between iTBCT and standard workup. 4d (right): Cost-effectiveness acceptability curve showing the probability of iTBCT being cost-effective for different values of willingness to pay up to 500K euros per traumatic brain injury patient alive at 6 months without serious morbidity.

teau, the probabilities of iTBCT being cost-effective tend to freeze. The higher the willingness-to-pay, the lower the probability of iTBCT being cost-effective.

These results of iTBCT seemingly more efficient in keeping multitrauma patients as well as traumatic brain injury patients alive, while becoming under debate as the preferred strategy the higher the willingness-to-pay to prevent serious morbidity, are paradoxical. Further data analysis revealed that >80% of patients with serious morbidity at 6 months will remain handicapped, but are actually still recovering. At 6 months post-trauma, the worst that might happen (death) had already happened, progressive handicap was observed infrequently (1% in the traumatic brain injury group). In view of this, ITBCT could well have its place in the diagnostic work-up for multitrauma patients and traumatic brain injury patients, thereby putting most emphasis on the survival rates in combination with the costs savings in these target subpopulations. It also stresses the need to apply the most adequate set of indication criteria available to preselect the trauma patients with multiple traumata and/or traumatic brain injury. Taking an investment decision on facilitating immediate total body CT scanning near or at the trauma room should certainly come on the agenda of major, level-1 trauma centers in the Netherlands.

The absence of statistically significant differences in health outcomes between iTBCT and the standard work-up may have originated from the high proportion of patients (40-50%) in the standard workup group who received sequential segmental CT scans of all body regions, comprising a TBCT scan in the end. The standard work-up does not lack behind in effectiveness and continuing the standard work-up is not immediately unethical.

A cost-utility analysis with the costs per quality adjusted life year (QALY) as outcome was also planned alongside the REACT-2 trial, but analyses could only be performed in a convenience subsample of 615 patients, including all deceased patients and only alive patients who reported their quality of life status during follow-up. In this convenience sample with low external validity, only marginal, near zero differences in QALYs (<0.0067 across all subgroups: data available upon request) in favor of iTBCT were observed. The cost-utility analysis was considered non-informative in addition to the cost-effectiveness analysis reported in this paper.

Van Vugt et al. reported a reduction of direct medical costs by iTBCT, probably due to faster work-up times that decreases personnel costs during the trauma room assessment. This analysis however did not relate the costs to the effectiveness in terms of survival or morbidity.[7] The cost-utility analysis by Lee et al. focuses on a simulation for less injured patients (median ISS 5, GCS 14 or 15) and concludes TBCT to be cost-effective since it reduces the need for clinical observation of patients who did underwent selective CT scanning.[8] The present study focuses on cost-effectiveness in terms of mortality and morbidity reduction for the more severely injured patient and makes it incomparable to the study of Lee et. al.

The time horizon of this cost-effectiveness analysis was 6 months post trauma. Most health economic costing guidelines suggest a lifetime horizon as the base case scenario. However, trauma care for severely injured patients often is only the beginning of a time-consuming trajectory towards optimal recovery with very heterogeneous patterns of follow-up care and for the elderly patients often in the presence of co-existing morbidities. Moreover, diagnostic strategies preceding trauma care are applied at the *very* beginning of these trajectories and it is uncertain to what extent longer term health care consumption and health outcomes are still attributable to the initially chosen diagnostic approach. Additionally, in absence of a clear absolute difference in health outcomes, a time horizon of 6 months seems defensible in practice.

One should be cautious while extrapolating the study results to other countries because of differences in demography, geographical accessibility to trauma centers, and financing of health care.

Hopefully though, the randomized design, stratified by treatment center and with highly comparable study groups of iTBTC and standard work-up concerning patient characteristics and survival probability based on trauma severity scores may inspire hospital managers to redesign their local in-hospital diagnostic trauma work-up logistics, if not already done so.

Conclusion

From a hospital health care provider perspective, immediate total-body CT scanning should economically be the diagnostic strategy of first choice for multitrauma or traumatic brain injury patients in trauma centers.

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3

Emergency bleeding control interventions after immediate total body CT scans in trauma patients

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Abstract

Background

Immediate total-body CT (iTBCT) is often used for screening of potential severely injured patients. Patients requiring emergency bleeding control interventions benefit from fast and optimal trauma screening. The aim of this study was to assess whether an initial trauma assessment with iTBCT is associated with lower mortality in patients requiring emergency bleeding control interventions.

Methods

In the REACT-2 trial patients who sustained major trauma were randomized for iTBCT or for conventional imaging and selective CT scanning (Standard work-up; STWU) in five trauma centers. Patients who underwent emergency bleeding control interventions following their initial trauma assessment with iTBCT were compared for mortality and clinically relevant time intervals to patients that underwent the initial trauma assessment with the STWU.

Results

In the REACT-2 trial 1083 patients were enrolled of which 172 (15.9%) underwent emergency bleeding control interventions following their initial trauma assessment. Within these 172 patients 85 (49.4%) underwent iTBCT as primary diagnostic modality during the initial trauma assessment. In trauma patients requiring emergency bleeding control interventions, in-hospital mortality was 12.9 % (95% CI 7.2%-21.9%) in the iTBCT group compared to 24.1 % (95% CI 16.3%-34.2%) in the STWU group (p=0.059). Time to bleeding control intervention was not reduced; 82 min (IQR 57-121) vs. 98 min (IQR 62-147), p=0.108.

Conclusions

Reduction of mortality in trauma patients requiring emergency bleeding control interventions by iTBCT could not be demonstrated in this study. However, a potentially clinically relevant absolute risk reduction of 11.2% (95% CI -0.3% to 22.7%) in comparison with STWU was observed.

Background

Improvements in speed and accuracy of Computed Tomography (CT) make immediate Total Body CT (iTBCT) feasible as a diagnostic tool in the primary care for severe trauma patients. iTBCT scanning in trauma patients is safe, shortens the time to end of diagnostic imaging and does not increase direct medical costs.[1] However, it does not improve survival in the total group of severe trauma patients.[1] Which patients exactly could benefit from this fast and detailed diagnostic approach remains unclear.

Patients requiring emergency bleeding control interventions benefit from fast and optimal trauma screening, obtaining as much information on the bleeding site(s) as is safely possible. iTBCT during the initial trauma assessment might improve survival in this specific patient group. Time to surgery is reported to be shorter for patients requiring emergency surgery after total-body CT scanning.[2] Potential survival benefits associated with total-body CT scanning in severely injured patients requiring bleeding control measurements have been described previously.[3]

The aim of this study was to assess whether an initial trauma screening with iTBCT is associated with lower in-hospital mortality and shorter clinically relevant time intervals in patients requiring emergency bleeding control interventions compared to trauma screening with conventional imaging and selective CT scanning of specific body regions.

Methods

Study design and patient selection

In the REACT-2 trial non-pregnant patients, 18 years and over, who sustained a major trauma, were included on compromised vital parameters, clinical suspicion of specific severe injuries or high risk trauma mechanism in five trauma centers in the Netherlands and Switzerland between April 21, 2011 and January 1, 2014. Patients were considered eligible when meeting one or more of the inclusion criteria and none of the exclusion criteria shown in the appendix.

Patients were randomized for iTBCT or conventional imaging with selective CT of specific body regions. Decision of eligibility by the trauma leader as well as documentation of the indication by a trauma team member was performed before the start of radiologic imaging. Potential life-saving interventions were performed prior to radiologic imaging when indicated, e.g. endotracheal intubation or chest tube placement. iTBCT was performed without preceding conventional imaging and consisted of an unenhanced CT of the head and neck and a contrast enhanced CT of thorax, abdomen and pelvis. The design of the REACT-2 study has been previously described (ClinicalTrials.gov: NCT01523626) and published.[1,4] The REACT-2 study was approved by the medical research ethics committees at all participating centers (AMC MEC 10/145).

For this study patients who underwent emergency bleeding control interventions following their initial trauma assessment were selected for further analysis. Emergency bleeding control interventions were defined as thoracotomy, laparotomy, external fixation of the pelvis or extremities and angiographic embolization. Multitrauma patients were defined by an Injury Severity Score (ISS) ≥ 16 for an exploratory subgroup analysis. In addition to the intention-to-treat analysis, a per-protocol analysis was performed in which crossovers (i.e. patients who received the opposite intervention to which they had been allocated) were excluded.

Time intervals were prospectively recorded and started as the patient arrived in the trauma resuscitation room. Time to end of imaging was defined as the time from arrival in the trauma room to the end of imaging of the initial trauma assessment. Time to diagnosis was defined as the time from arrival to the time all life-threatening injuries were diagnosed according to the trauma team leader. Time at the ED (Emergency Department) was defined by the time of arrival to the time of departure from the trauma room. Time to intervention was defined by the time of arrival to the time an emergency bleeding control intervention was initiated. Hypotension was defined as systolic blood pressure below 90 mmHg.

Statistical analysis

Continuous data with a normal distribution are presented as means and standard deviations. The non-normally distributed data are presented as medians with interquartile range. Independent sample t-tests and Mann-Whitney U tests were used to compare the parametric and non-parametric continuous data respectively. The Chi-squared test or Fisher's exact test was used to compare the categorical variables. The 95% confidence intervals for proportions were calculated with the modified Wald method. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 24 (SPSS inc., Chicago, Illinois).

Results

In the REACT-2 trial 1083 patients were enrolled of which 172 (15.9%) underwent emergency bleeding control interventions directly following their initial trauma assessment. Within these 172 patients 85 (49.4%) underwent iTBCT as primary diagnostic modality. Median ISS was 27 (IQR 20-41) in the iTBCT group compared to 29 (IQR 18-41) in the standard work-up (STWU) group (p=0.994). Hypotension at admission was present in 21.7 % of the iTBCT group compared to 20.0 % in the STWU group (p=0.788). Baseline demographic and clinical characteristics are presented in Table 1.

In 85 patients in the iTBCT group 108 emergency bleeding control interventions were performed. In the STWU group 109 emergency bleeding control interventions were performed in 87 patients. In the iTBCT group more patients underwent external

Table 1. Demographic and clinical characteristics*

Characteristic	Total-body CT (n=85)	Standard workup (n=87)
Age (years) †	41 (26-56)	46 (28-60)
Male sex, n (%)	69 (81.2)	66 (75.9)
Blunt trauma, n (%)	82 (96.5)	85 (97.7)
Comorbidity, n (%)		
ASA I or II	78 (96.3)	79 (97.5)
ASA III, IV or V	3 (3.7)	2 (2.5)
In-hospital vital parameters		
Respiratory rate (per minute) †	16 (14-20)	16 (14-20)
Pulse (bpm) ‡	99 (20)	95 (26)
Systolic blood pressure (mmHg) ‡	117 (28)	115 (28)
GCS (points) †	11 (3-15)	11 (3-15)
Revised Trauma Score †	7.11 (4.09-7.84)	6.90 (4.09-7.84)

*P>0.05 for all between-group comparisons.

† Median (interquartile range).

‡ Mean (SD).

ASA denotes American Society of Anaesthesiologists

fixations of the extremities than in the STWU group (56.5 % vs. 40.2 %, p=0.033). Injury severity parameters and surgical characteristics are presented in Table 2.

In-hospital mortality was 12.9 % (95% CI 7.2%-21.9%) in the iTBCT group compared to 24.1 % (95% CI 16.3%-34.2%) in the STWU group (absolute risk reduction: 11.2%, 95% CI -0.3% to 22.7%; p=0.059). Time to diagnosis was reduced for patients who underwent iTBCT: 45 min. (IQR 35-60) vs. 57 min. (IQR 43-85), p=0.009. Time to bleeding control intervention was not reduced: iTBCT 82 min. (IQR 57-121) vs. STWU 98 min. (IQR 62-147), p=0.108. Outcomes for patients requiring emergency bleeding control interventions are presented in Table 3 and time intervals are displayed in Figure 1.

In an exploratory analysis in the group of multitrauma patients in-hospital mortality was reduced after iTBCT compared to the STWU group: 13.3 % (95% CI 7.2%-23.0%) vs. 27.8 % (95% CI 18.7%-39.1%), with an absolute risk reduction of 14.4% (95% CI 1.6% to 27.3%, p=0.030). Time to diagnosis was reduced for patients who underwent iTBCT: 47 min. (IQR 35-61) vs. 57 min. (IQR 42-83), p=0.033. Time to bleeding control intervention was not reduced: iTBCT 78 min. (IQR 56-120) vs. STWU 92 min. (IQR 62-125), p=0.306. Outcome for multitrauma patients (ISS ≥16) requiring emergency bleeding control interventions are presented in Table 2 of the appendix.

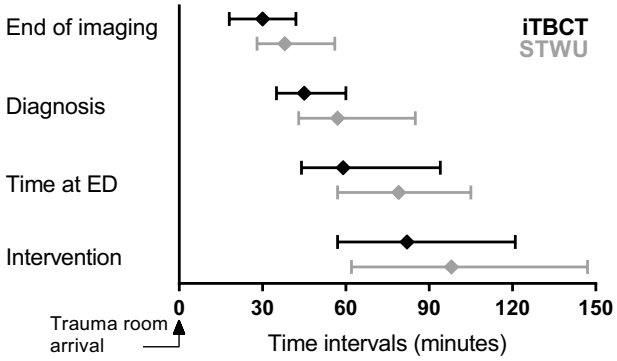
In the per-protocol analysis, two crossovers were excluded. No relevant differences in outcome were found for all endpoints in comparison to the original intention-to-treat analysis as shown in Table 3 of the appendix. With multivariate analyses on in-hospital mortality corrected for center and type of intervention and analyses on time to intervention stratified for center and type of intervention no relevant differences were found in comparison to the original analyses.

Table 2. Injury severity and surgical characteristics*

Characteristic	Total-body CT (n=85)	Standard workup (n=87)
Abbreviated Injury Scale ≥3, n (%)		
Head	37 (43.5)	32 (36.8)
Chest	52 (61.2)	51 (49.5)
Abdomen	27 (31.8)	38 (43.7)
Extremities	62 (72.9)	57 (65.5)
Emergency interventions, n (%)	108	109
Thoracotomy	7 (8.2)	6 (6.9)
Laparotomy	20 (23.5)	32 (36.8)
External fixation of the pelvis	19 (22.4)	19 (21.8)
External fixation of extremities	48 (56.5)	35 (40.2)
Angiographic embolization	14 (16.5)	17 (19.5)
Injury Severity Score (points)	27 (20-41)	29 (18-41)
Multitrauma patients, n (%)†	75 (88.2)	72 (82.8)
TBI patients, n (%)†	29 (34.1)	24 (27.6)
TRISS, survival probability	0.84 (0.30-0.97)	0.89 (0.48-0.98)

*P>0.05 for all between-group comparisons except for external fixation of extremities (p=0.033).
Data are number (%) or median (interquartile range).
† Multitrauma patients are defined as ISS ≥16. Traumatic Brain Injury (TBI) patients are defined as GCS <9 at presentation and AIS Head ≥3.
TRISS denotes Trauma and Injury Severity Score.

Figure 1. Clinically relevant time intervals



Medians and inter-quartile ranges of clinically relevant time intervals (minutes) are displayed per randomisation group. p<0.05 for time to end of imaging, time to diagnosis and time at ED.
iTBCT denotes immediate Total-Body CT, STWU denotes Standard Work-up, ED denotes emergency department.

Table 3. Outcome for patients requiring emergency bleeding control interventions

Characteristic	Total-body CT n=85	Standard workup n=87	P-value
Mortality; n, % (95%CI)			
In-hospital mortality	n =11 12.9% (7.2-21.9)	n = 21 24.1% (16.3-34.2)	0.059*
24-hour mortality	n = 4 4.7% (1.5-11.9)	n = 6 6.9% (2.9-14.5)	0.747†
Time intervals; minutes (IQR)			
Time to end of imaging	30 (18-42)	38 (28-56)	0.006‡
Time to diagnosis	45 (35-60)	57 (43-85)	0.009‡
Time at ED	59 (44-94)	79 (57-105)	0.041‡
Time to intervention	82 (57-121)	98 (62-147)	0.108‡
Complications; n, % (95%CI)	n = 39 45.9% (35.7-56.4)	n = 42 48.3% (38.1-58.6)	0.753*
Length of stay; days (IQR)			
Total hospital stay	23 (12-37)	20 (10-33)	0.606‡
ICU stay	5 (2-12)	6 (2-12)	0.909‡
Ventilation days	3 (1-9)	3 (1-8)	0.928‡

Data are number, % (95% confidence interval by modified Wald) or median (interquartile range).
* Chi^2 test; † Fisher's Exact Test; ‡ Mann-Whitney U test.
OR denotes odds ratio, CI denotes confidence interval and ED denotes Emergency Department.

Discussion

This study could not demonstrate a beneficial effect on survival of iTBCT for trauma patients requiring emergency bleeding control interventions. However, a potentially clinically relevant absolute risk reduction of 11.2% (95% CI -0.3% to 22.7%) in comparison with STWU was observed. The original study had been powered to detect an absolute risk reduction of 5% (from 12% to 7%) in severe trauma patients, irrespective of their need for emergency bleeding control interventions, but was underpowered for the analysis in the subgroup requiring such intervention.

The potential reduction of mortality by iTBCT after major trauma could be the effect of a faster trauma work-up. In addition, the complete information by iTBCT before treatment could sharpen the indication of the intervention and help the team to prepare and prioritize in case of multiple targets for interventions. This hypothesis is further supported by other studies. Wada et al. also reported reduced mortality for patients receiving TBCT before emergency bleeding control measurements in a retrospective study in two trauma centers.[3] In contrast to Wada et al. and the present study, Wurmb et al. report unchanged mortality by TBCT for patients requiring any surgery immediately after resuscitation in multiple trauma patients in a retrospective single center study. However, they concluded that an improvement of outcome might be assumed since the patients receiving TBCT were more severely injured.[2] This differ-

ence in injury severity could be explained by the use of a triage scheme for the TBCT group, selecting more severely injured patients for TBCT.

Huber-Wagner et al. report reduced mortality for trauma patients in moderate and severe shock that underwent TBCT in a large retrospective multicenter study.[5] Ordonez et al. report no mortality reduction for hemodynamically unstable trauma patients after CT, however did report a survival benefit for hemodynamically unstable patients with an ISS ≥25 in a single center retrospective study. Furthermore, they report changes in indication and planning for surgery in a substantial part of the patients.[6] This further supports the use of TBCT for severely injured bleeding patients requiring fast treatment.

The relationship between iTBCT and mortality could be further supported if we could demonstrate not only a reduction for time to diagnosis but also a reduction for time to intervention. Several studies did find a benefit for time to intervention after TBCT in retrospective studies.[2, 3, 7] In the present study there was a wide range of time to intervention intervals which could be the effect of potential confounders as center of treatment and/or different intervention types. Analyses on time to intervention stratified for center and type of intervention did not show differences compared to the original analyses.

The decision to perform an iTBCT is based on information obtained during the pre-hospital phase and during the in-hospital primary survey. Criteria for TBCT in trauma patients are diverse,[8] and often the imaging itself is needed for identification of a severely injured patient with the necessity for emergency bleeding control interventions. Selecting the appropriate patients for iTBCT and minimize radiation exposure for the less severely injured patients remains a challenge.

A limitation of our study is that this subgroup analysis was unplanned at the design stage, resulting in a lack of statistical power for detection of the observed clinically relevant contrast between the mortality rates. During the enrollment of our trial associations between TBCT and emergency bleeding control interventions were reported and made this subgroup of specific interest and therefore legitimize the additional analysis on these patients. Strength of this multicenter study is the assessment of a prospectively enrolled and randomized population. Further research should be performed to confirm the suggested reduction of mortality by iTBCT in trauma patients requiring bleeding control interventions. Furthermore, future research should focus on how to select patients who could benefit from iTBCT after trauma.

Conclusion

This study could not demonstrate a beneficial effect on survival by the fast and detailed diagnostic work-up by immediate total-body CT for trauma patients requiring emergency bleeding control interventions. There is probably a lack of statistical

power for detection of the potentially clinically relevant risk reduction for mortality by iTBCT. Further research should be performed to confirm the suggested reduction of mortality by iTBCT in trauma patients requiring bleeding control interventions.

Collaborators

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Appendix

Table 1. Indications for immediate total-body CT in trauma patients used in REACT-2 trial

Trauma patients with one of the following parameters at hospital arrival:
- respiratory rate ≥30/min or ≤10/min
- pulse ≥120/min
- systolic blood pressure ≤100 mmHg
- estimated exterior blood loss ≥500 ml
- Glasgow Coma Score ≤13

OR

Patients with a clinical suspicion of one of the following diagnoses:
- fractures from at least two long bones
- flail chest, open chest or multiple rib fractures
- severe abdominal injury
- pelvic fracture
- unstable vertebral fractures / spinal cord compression

OR

Patients with one of the following injury mechanisms:
- fall from a height (>3 meters / >10 feet)
- ejection from a vehicle
- death of occupant in same vehicle
- severely injured patient in same vehicle
- wedged or trapped chest / abdomen

Contra indications

Trauma patients with one of the following characteristics were excluded:
- known age <18 years
- known pregnancy
- referred from another hospital
- clearly low-energy trauma with blunt injury mechanism
- any patient with a stab wound in one body region
- any patient who is judged to be too unstable to undergo a CT scan and requires (cardiopulmonary) resuscitation or immediate operation because death is imminent

Table 2. Outcome for multitrauma patients (ISS ≥16) requiring emergency bleeding control interventions

Characteristic	Total-body CT n=75	Standard workup n=72	P-value
Mortality; n, % (95%CI)			
In-hospital mortality	n = 10 13.3% (7.2-23.0)	n = 20 27.8% (18.7-39.1)	0.030*
24-hour mortality	n = 3 4.0% (0.9-11.6)	n = 6 8.3% (3.6-17.3)	0.320†
Time intervals; minutes (IQR)			
Time to end of imaging	30 (17-42)	38 (27-56)	0.019‡
Time to diagnosis	47 (35-61)	57 (42-83)	0.033‡
Time at ED	65 (45-99)	79 (57-107)	0.139‡
Time to intervention	78 (56-120)	92 (62-125)	0.306‡
Complications; n, % (95%CI)	n = 38 50.7% (39.6-61.7)	n = 38 52.8% (41.4-63.9)	0.798*
Length of stay; days (IQR)			
Total hospital stay	23 (12-40)	21 (10-35)	0.640‡
ICU stay	6 (2-14)	6 (2-14)	0.910‡
Ventilation days	4 (1-9)	4 (1-8)	0.968‡

Data are number, % (95% confidence interval by modified Wald) or median (interquartile range).

* Chi^2 test; † Fisher's Exact Test; ‡ Mann-Whitney U test.

OR denotes odds ratio, CI denotes confidence interval, ISS denotes Injury Severity Score and ED denotes Emergency Department.

Table 3. Outcome by per-protocol analysis for patients requiring emergency bleeding control interventions

Characteristic	Total-body CT n=84	Standard workup n=86	P-value
Mortality; n, % (95%CI)			
In-hospital mortality	n = 11 13.1% (7.3-22.1)	n = 21 24.4% (16.5-34.5)	0.059*
24-hour mortality	n = 4 4.8% (1.5-12.0)	n = 6 7.0% (3.0-14.7)	0.747†
Time intervals; minutes (IQR)			
Time to end of imaging	30 (18-42)	38 (28-57)	0.008‡
Time to diagnosis	45 (35-60)	57 (43-85)	0.008‡
Time at ED	59 (44-94)	82 (57-105)	0.033‡
Time to intervention	82 (62-121)	96 (62-135)	0.230‡
Complications; n, % (95%CI)	n = 39 46.4% (36.2-57.0)	n = 42 48.8% (38.6-59.2)	0.753*
Length of stay; days (IQR)			
Total hospital stay	23 (12-37)	21 (10-33)	0.612‡
ICU stay	6 (2-12)	6 (2-13)	0.861‡
Ventilation days	3 (1-9)	4 (1-8)	0.939‡

Data are number, % (95% confidence interval by modified Wald) or median (interquartile range).

* Chi^2 test; † Fisher's Exact Test; ‡ Mann-Whitney U test.

CI denotes confidence interval and ED denotes Emergency Department.


4

Indications for total body computed tomography in blunt trauma patients: a systematic review

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Abstract

Purpose

Total-body CT scanning (TBCT) could improve the initial inhospital evaluation of severe trauma patients. Indications for TBCT however differ between trauma centres, so more insight how to select patients that could benefit from TBCT is required. The aim of this review was to give an overview of currently used indications for total-body CT in trauma patients and to describe mortality and Injury Severity Scores of patient groups selected for TBCT.

Methods

A systematic review was performed by searching Medline and Embase databases. Studies evaluating or describing criteria for selection of patients with potentially severe injuries for TBCT during initial trauma care were included. In addition, studies comparing total-body CT during the initial assessment of injured patients with conventional imaging and selective CT in specific patient groups were included.

Results

Thirty eligible studies were identified. Three studies evaluated indications for TBCT in trauma with divergent methods. Combinations of compromised vital parameters, severe trauma mechanisms and clinical suspicion on severe injuries are often used indications; however clinical judgement is used as well. Studies describing TBCT indications selected patients in different ways and were difficult to compare regarding mortality and injury severity.

Conclusions

Indications for TBCT in trauma show a wide variety in structure and cut-off values for vital parameters and trauma mechanism dimensions. Consensus on indications for TBCT in trauma is lacking.

Introduction

The work-up of trauma patients by ATLS (Advanced Trauma Life Support) guidelines uses a step-up approach for diagnostic imaging. After conventional radiography of the chest and pelvis and focused assessment by sonography (FAST), selective computed tomography can be performed subsequently on indication.[1] Ongoing improvements in speed and accuracy of Computed Tomography (CT) and increased availability of CT scanners in or nearby the trauma room made immediate total-body CT (TBCT) feasible as a diagnostic tool in the initial assessment of trauma patients. Initial trauma care thus might be improved when total-body CT scan is incorporated in the initial assessment of a potentially multiple and severely injured patient.[2]

A disadvantage of TBCT scanning is increased radiation exposure for patients that appear to have minor injuries for which selective CT scanning on indication could be sufficient. For the overall group of trauma patients the proportion of patients receiving a high radation dose of >20mSv at the trauma room is increased.[3] For multitrauma patients the radiation dose is however comparable for the complete hospital admission.[4] In order to prevent excessive radiation exposure, the appropriate selection of patients for TBCT is essential.[3,5] The decision to perform an immediate TBCT is based on information obtained during the pre-hospital phase and the first inhospital assessment. Therefore, indications such as compromised vital parameters, clinical suspicion on severe injuries and high risk injury mechanisms are often used to select trauma patients that might benefit from immediate TBCT.

Justification for performing a TBCT is only possible in hindsight, when all diagnoses have been confirmed by radiologic imaging, interventions and the clinical course. Moreover, different outcome measures are used to justify TBCT, such as: classification as multiple or severely injured patient by anatomical scoring systems (e.g. Injury Severity Score) or certain high risk profiles for injuries.[6-8] In order to improve selection and guide future research on the proper indications for TBCT after major trauma a better insight in current indications is required. Therefore the aim of this review was 1) to give an overview of currently used indications for total-body CT in trauma patients and 2) to describe mortality and Injury Severity Scores of patient groups selected for TBCT.

Methods

For this systematic review the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) are used as a guideline.[9]

Inclusion and exclusion criteria

Studies evaluating or describing indications for TBCT during initial trauma care were included. In addition, studies comparing TBCT during the initial assessment of injured patients with conventional imaging and selective CT in specific patient groups were included. TBCT should at least comprise the following body regions: head, neck, thorax, abdomen and pelvis. For selection of studies no distinction was made between immediate TBCT and TBCT with preceding conventional radiologic imaging. Reviews, randomized and observational studies describing original data were eligible for inclusion. Study protocols, case reports and editorials were excluded. Literature in a language other than English or German was also excluded.

Search strategy

The Medline and Embase Library databases were searched for articles published between 1947 and July 2014. The search terms consisted of synonyms of 'total-body CT' combined with synonyms and words related to trauma and injury. The full search is presented in Appendix 2. The last search was performed in July 2014 and was conducted with the help of a clinical librarian. A cross-reference search was performed on the included articles.

Study selection and data extraction

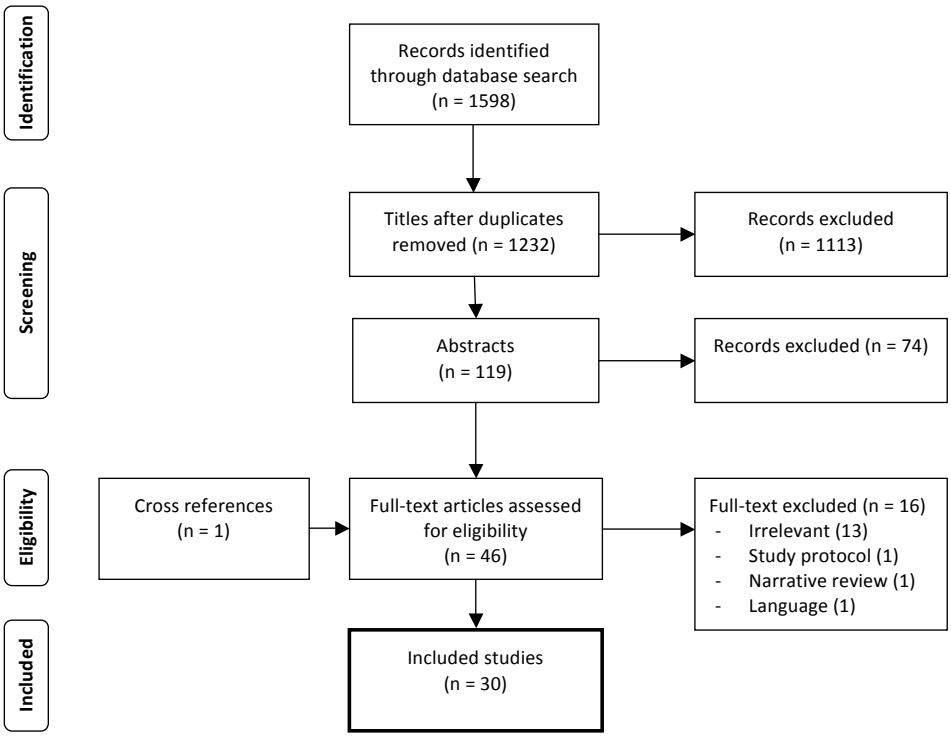
Two reviewers independently assessed titles and abstracts of all studies identified by the initial search and excluded irrelevant studies. Secondly, the full texts of the remaining eligible studies were assessed to determine whether they met the inclusion criteria. Any discrepancies in inclusion were resolved by discussion between the reviewers. In case no consensus was reached, this was solved by a third reviewer. The following data from each included paper was extracted: author, publication year, country, study design, inclusion criteria, sample size, Injury Severity Score (ISS), indications for TBCT, and outcome.

Results

Study selection

The Search identified 532 records from the Medline database and 1006 records from the Embase database. 366 duplicates were removed. 30 studies were included for data extraction (Figure 1). Included study designs were retrospective for 17 studies and prospective or observational for 10 studies. The remaining three were a randomized clinical trial, a case matched study and one questionnaire survey. Studies were published between 2003 and 2013, except for one, which was published in 1998.

Figure 1. Flowchart for the selection of studies



Studies on TBCT indications

For three included studies the main objective was to evaluate indications for TBCT in trauma patients. Wurmb et al.[8] assessed whether a triage scheme could appropriately select sedated and ventilated patients with severe trauma for TBCT scanning. This triage scheme used specific trauma mechanisms, compromised vital signs and clinically obvious injuries. An Injury Severity Score (ISS) of 16 or higher was used to define severe trauma. Sensitivity of this triage scheme for severe trauma was 96.7 % and positive predictive value was 69.4%.

Hsiao et al.[7] also used an anatomical definition of severe trauma to justify TBCT for patients that triggered trauma team activation and were CT scanned during the initial inhospital assessment. An Abbreviated Injury Score (AIS) of 2 or more in two or more body regions defined multi-regional injury. Clinical judgement had a sensitivity of 50% and a 32% positive predictive value for multi-region injury. Mean ISS was 17 (sd16) for patients that underwent TBCT. Multivariable logistic regression resulted in the following independent predictors for multi-region injury: full trauma team activation, GCS <9, fall >5m or pedal cyclist. The derived prediction model did not show an improvement for accuracy of selection when compared to decision by clinical judgement.

Babaud et al.[6] evaluated the French national triage criteria (10) (Vittel criteria) for detecting patients with at least one injury. Multivariable logistic regression within the patient group resulted in the following independent predictors for detection of an injury: GCS <13, penetrating trauma and resuscitation with >1000 mL colloids. For 15% of the patients selected by one or more Vittel criteria an unsuspected severe injury was detected by TBCT.

Characteristics of populations studied to assess the effect of TBCT

Seventeen studies reported their indications for TBCT in trauma. Sets of indications consisted of combinations of compromised vital parameters (15 studies), high risk trauma mechanisms (14 studies), clinical suspicion of severe injury (12 studies) and clinical judgement (2 studies). In eight other studies the decision to perform a TBCT was based only on clinical judgement or suspicion on severe or multiple injuries. Table 1 further shows the patient population, ISS, type of indications used for TBCT and the outcome measures for the included studies.

Table 2 shows that selection of multitrauma patients was often a result of the studydesign rather than selection of patients for TBCT by traumaleaders. Five retrospective studies enrolled patients with an ISS of 16 or higher.[2,11-14] Weninger et al.[15] included only patients with an ISS of 17 or higher and at least one body region with an AIS of 4 or higher. Rieger et al. (16) included patients with an ISS of 18 or higher. Two prospective studies included patients who triggered trauma team activation and reported a median ISS of 5 (IQR 1-14) and 13 (1-17) for patients who underwent TBCT based on clinical judgement.[17-18] Hsiao et al.[7] retrospectively selected patients receiving CT imaging during trauma assessment and reported a mean ISS of 17 (sd16) for patients with an indication for TBCT by clinical judgement. The remaining studies that described an indication by clinical judgement, retrospectively selected patients by ISS or bleeding control measures (Table 2).

In the appendix the described TBCT indications after trauma and cut-off values for vital parameters and trauma mechanism dimensions are presented from 30 included articles. These are categorized by vital parameters, clinical suspicious injuries, high risk trauma mechanism and contra-indications. For all included literature minor age and isolated penetrating injury were formulated as contra-indications for TBCT or indirectly formulated by including only adults and patients sustaining blunt trauma.

Discussion

In this systematic review of studies that evaluate or describe indications for TBCT in initial trauma care, we showed similarities and differences of these indications. There is a wide variety of eligibility criteria and outcome measures between studies (Table 2). Combinations of compromised vital parameters, severe trauma mechanisms and clinical suspicion on severe injuries are most often reported however clinical judgement

on expected severe and multiple injuries is described as well. Within these groups of indications there is a large variation in used parameters and cut-off values (Table 3). Because of this variety between sets of indications it is difficult to compare indications for TBCT between studies.

Differences in outcome measures for justification of TBCT in hindsight implicate a lack of consensus towards patient groups that rightfully received a TBCT during their trauma work-up. Anatomical scoring systems with different thresholds for ISS and AIS for body regions are used to justify the performance of TBCT or to select patients who might benefit from TBCT scanning.[7,8] Several retrospective studies on TBCT select patients by anatomical scoring systems and therefore suggest that patients above these thresholds could benefit from TBCT. Other outcome measures reflecting the severity or extent of injuries might be suitable as well, such as mortality, morbidity, ICU admittance, surgical and radiological interventions or detection of unsuspected injuries.

Not only parameters reflecting severe injury could justify TBCT. Decreased levels of consciousness could be considered an indication on itself since clinical indicators for imaging are unreliable owing to the lack of subjective input from the patient. Routine CT imaging for patients with unreliable physical examination is reported to reveal unsuspected findings in up to 38%, leading to treatment changes in 19-26%.[19,20] Furthermore one could hypothesize that TBCT might lead to early discharge for less severely injured patients when used to rule out injuries.[19] Since the probability of detecting injuries after major trauma during the clinical course of alert patients might be lowered after TBCT, the inhospital observation of the clinical course might be less valuable.

This review included only three studies for which the main objective was to evaluate indications for TBCT in trauma patients. Studies that described mortality and ISS already chose study eligibility criteria in order to select patients that might benefit from TBCT. Thereby, the wide variety of eligibility criteria made comparison of mortality and ISS of patient groups selected for TBCT less valuable. Besides limited comparability of methods, there was also a low availability of mortality and ISS for the included studies.

An anatomical scoring system such as ISS as indication for TBCT cannot be used in daily practice because the results are calculated after radiologic imaging is performed. As well as other outcome parameters reflecting severe injury, anatomical scoring systems could only be helpful as outcome measure for the evaluation of the indication for TBCT and not to define the indication for TBCT.

In this overview of TBCT indications we did not make a distinction between immediate TBCT and TBCT after conventional X-rays and sonography. Future prospective research on the indication for one or both strategies should consider this difference in its design. Furthermore, there was no distinction made regarding different imaging protocols. Contrast enhancement and body position were not described for included studies.

Table 1. Overview of included studies

Author, study year, country	Study design	Patients overall (TBCT)	ISS, median (IQR) TBCT / Control / overall	TBCT indications	Outcome
Sierink 2014,[14] The Netherlands	CM	304 (152)	18 (9-29) / 18 (8-29) / NA	VP, CSI	30d Mortality
Wada 2013,[21] Japan	RS	152 (132)	34 (25-45) / 41 (34-51) / NA	CJ	28d SMR (TRISS)
Sierink 2013,[4] The Netherlands	RS	301 (151)	22 (18-27) / 25 (17-29) / NA	VP, CSI	Radiation exposure
Huber-Wagner 2013,[11] Germany	RS	16719 (9233)	30 (12) / 28 (12) / 29 (12) *	Not defined	SMR (RISC)
Sedlic 2013,[13] Canada	RS	67 (67)	NA	VP, TM, CSI	SMR (TRISS)
Kimura 2013,[22] Japan	RS	5208 (1858)	26 (25-26) / 23 (23-24) / NA †	VP: GCS	SMR (TRISS)
Hsiao 2013,[7] Australia	RS	660 (98)	17 (16) / 5 (6) / NA*	CJ / PM: VP, TM, FTTA	Multi-region injured ‡
Asha 2012,[3] Australia	RS	1280 (624)	4 (2-10) / 4 (2-10) / 4 (2-10)	VP, TM/CJ, CSI	Radiation exposure / missed injuries
Babaud 2012,[6] France	PS	339 (189)	NA	VP, TM, CSI (Vittel)	Unsuspected injuries
Stengel 2012,[23] Germany	RS	982 (982)	25 (18-33)/ - / 25 (18-33)	VP, TM, CSI, CJ (DGU)	Missed injuries
Hutter 2011,[24] Germany	OS	1144 (608)	21 (9) / 28 (12) / NA *	VP, TM	Mortality
Gupta 2011,[17] USA	PS	701 (600)	5 (1-14) / 2 (1-5) / 5 (1-13)	CJ	Missed injuries
Smith 2011,[25] UK	OS	254 (138)	14 (11) / 7 (6) / NA * 13 (11) / 7 (9) / NA	TM	Change of treatment
Wurmb 2011,[26] Germany	RS	318 (163)	27 (17-41) / 24 (13-34) / NA	VP, TM, CSI (Nast-Kolb)	Time to surgery / Mortality
Smith 2012,[27] UK	Survey	245 hospitals	-	VP, TM, CSI, PMI, WS	-
Tillou 2009,[18] USA	PS	284	13 (1-17) / - / 13 (1-17)	CJ	Unsuspected injuries
Huber-Wagner 2009,[2] Germany	RS	4621 (1494)	32 (14) / 28 (12) / 30 (13)*	Not defined	SMR (TRISS / RISC)
Wurmb 2009,[28] Germany	RS	161 (82)	24 (11-33) / 22 (11-32) / NA	VP, TM, CSI (Nast-Kolb)	Time to diagnosis
Rieger, 2009,[16] Austria	RS	88	29 (10) / - / 29 (10) *	VP, TM, CSI (Nast-Kolb)	Time to diagnosis / missed injuries
Nguyen 2009,[29] Swiss	OS	90	NA	TM	Examination time
Wurmb 2007,[8] Germany	RS	120 (85)	NA / NA / 19 (3-75)	VP, TM, CSI (Nast-Kolb)	Polytrauma (ISS≥16)
Weninger 2007,[15] Austria	OS	370 (185)	27 (10) / 28 (12) / NA *	Not defined	Accuracy / Time to diagnosis
Prokop 2006,[12] Germany	RS	100	33 (12) / - / 33 (12) *	CJ	Examination time
Salim 2006,[19] USA	PS	1000	NA	Normal abdominal PE, and TM	Change of treatment
Sampson 2006,[30] UK	RS	296	NA	Not defined	(unsuspected) injuries

Wurmb 2005,[31] Germany	PC	120 (78)	NA	VP, TM, CSI (Nast-Kolb)	Examination time
Heyer 2005,[32] Germany	RCT	80	NA	CJ	Examination time / radiation exposure
Albrecht 2004,[33] Germany	RS	50	NA	CJ	Missed injuries
Self 2003,[20] USA	RC	457	NA	CJ	Change of treatment
Leidner 1998,[34] Sweden	PS	111	NA	CJ	Examination time / missed injuries

ISS: Injury Severity Score, IQR: interquartile ranges.

CM: case matched study, RS: retrospective study, PM: prediction model, OS: Observational study, PS: prospective study, RCT: randomized clinical trial.

VP: vital parameters, TM: trauma mechanism, CSI: clinical suspicious injury, CJ: clinical judgement, FTTA: full trauma team activation, PE physical examination, SMR: standardized mortality ratio.

* mean, sd; † mean, 95%CI; ‡ Multi -region injured defined by AIS ≥ 2 in ≥ 2 body regions (head/face, vertebral column, chest, abdomen/pelvis)

Table 2. Overview of reported mortality and polytrauma proportion in populations selected for TBCT studies

Author, study year, country	**Eligibility criteria** besides blunt trauma, adult and direct transfer	**Mortality (%)** TBCT / Control / overall	**Polytrauma**, ISS ≥ 16 (%) TBCT / Control / overall
Sierink 2014,[14] The Netherlands	≥ 1 VP or CSI	13.0 / 13.0 / 13.0 (30d)	63.2 / 63.2 / 63.2
Wada 2013,[21] Japan	Requiring bleeding control	18.1 / 80.0 / 26.3 (28d)	>75 / >75 / >75
Sierink 2013,[4] The Netherlands	ISS ≥ 16 and ≥ 1 VP or CSI	5.3 / 4.6 / 5.0 (30d)	100 (by protocol)
Huber-Wagner 2013,[11] Germany	ISS ≥ 16	17.4 / 21.4 / 19.2 (overall)	100 (by protocol)
Sedlic 2013,[13] Canada	TBCT performed, and ISS ≥ 16, and ≥ 1 VP, TM or CSI	14.9 / - / - (ND)	100 (by protocol)
Kimura 2013,[22] Japan	GCS 3-12, SBP>75mmHg	24 / 28 / 27 (ND)	NA
Hsiao 2013,[7] Australia	Trauma team activation and initial CT scan required	3.1 / 1.2 / 1.5 (ND)	51.5 / 16.5 / 21.7
Asha 2012,[3] Australia	Trauma team activation	NA	17.5 / 18.5 / 18.0
Babaud 2012,[6] France	≥ 1 Vittel criterion	NA	NA
Stengel 2012,[23] Germany	≥ 1 VP, TM or CSI, CJ	7.1 / - / 7.1 (ND)	36.7
Hutter 2011,[24] Germany	Admission to trauma center	15 / 8 / 13 (overall)	95.1 / 96.9 / 95.5
Gupta 2011,[17] USA	Trauma team activation after blunt trauma	NA	- / - / 20
Smith 2011,[25] UK	Suspicion on having multiple or serious injuries	4.7 (ND)	NA
Wurmb 2011,[26] Germany	(suspected) multiple trauma requiring emergency surgery	5.8 / 5.5 / 5.7 (30d)	87.1 / 71.6 / 84.4
Smith 2012,[27] UK	-	-	-
Tillou 2009,[18] USA	Trauma team activation after blunt trauma	NA	NA
Huber-Wagner 2009,[2] Germany	ISS ≥ 16	21 / 22 / 22 (overall)	100 (by protocol)
Wurmb 2009,[28] Germany	ISS ≥ 18	NA	100 (by protocol)
Rieger 2009,[16] Austria	Treatment in resuscitation area by trauma team	NA	67.0 / 58.2 / 62.7
Nguyen 2009,[29] Swiss	TBCT performed, and MVC or fall from > 3m	NA	NA
Wurmb 2007,[8] Germany	Sedated and ventilated trauma patients	NA	69.4 / 5.7 / 50.8
Weninger 2007,[15] Austria	ISS ≥ 17, and AIS ≥ 4 in ≥ 1 body region (head, thorax or abdomen), and survival until ICU admission	17 / 16 / 17	100 (by protocol)
Prokop 2006,[12] Germany	ISS >16 and TBCT performed	13 / - / 13	100 (by protocol)

Salim 2006,[19] USA	No visible evidence of chest or abdominal injury, and hemodynamically stable, and PE of abdomen normal or unevaluable because of depressed level of consciousness, and significant mechanism of injury	NA	NA
Sampson 2006,[30] UK	hemodynamically stable, and AIS ≥ 2 in ≥ 1 body region (head/neck, thorax, abdomen/pelvis, spine or extremities)	NA	NA
Wurmb 2005,[31] Germany	Treatment in resuscitation area by trauma team	NA	NA
Heyer 2005,[32] Germany	Suspected injury of ≥ 2 body regions of which ≥ 1 is life threatening, and ICU admission	NA	NA
Albrecht 2004,[33] Germany	Prehospital suspected polytrauma, and TBCT performed	NA	NA
Self 2003,[20] USA	Blunt head injury and TBCT performed	NA	NA
Leidner 1998,[34] Sweden	Hemodynamically stable, and clinical suspicion of multiple organ injuries or a trauma mechanism capable of producing major injury to multiple organ systems.	NA	NA

ISS: Injury Severity Score, VP: vital parameters, TM: trauma mechanism, CSI: clinical suspicious injury, CJ: clinical judgement, ND: not defined, NA: not available

Little is known of the predictive value of specific parameters within the sets of indications for severe and multiple injury. However, reduced Glasgow Coma Scale (GCS) after major trauma seems to be a valid indication for TBCT. Firstly, it is reported to independently predict multi-region injury and detection of injury in general. Secondly, the unreliability of the physical examination can result in unsuspected findings needing treatment. Decision for a cut-off value for GCS might depend on which goal one pursue; to select multiple and severely injured patients or reduction of missed injuries after major trauma.

Future research needs to prospectively determine the positive predictive value of separate TBCT indications for multiple and severely injured patients. Positive predictive values for TBCT indications are useful for determining the proportion of patients that were appropriately selected for TBCT and the concomitant radiation exposure could therefore be accepted. In order to determine the proportion of the multiple and severely injured patients selected for TBCT sensitivity of a set of indications has to be calculated. Emphasis on specific diagnostic tests changes when another type of outcome measure is chosen such as reduction of missed injuries.

The question remains, whether we should use fixed sets of indications for TBCT and if so how they should be defined. In the meantime one should be aware that selection of patients for TBCT by clinical judgement alone could result in relatively low ISS. Independently from which outcome measure chosen, one should carefully weigh the potential benefits of TBCT to an increased radiation exposure and potential increase of costs. The unsuspected findings and eventual shortening of hospital admission should outweigh the increased radiation exposure in order to make TBCT beneficial for the less severely injured patients.

Conclusion

Indications for TBCT in trauma show a wide variety in formulation and cut-off values for vital parameters and trauma mechanism dimensions. Combinations of compromised vital parameters, severe trauma mechanisms and clinical suspicion on severe injuries are often used. However, clinical judgement on expected severe and multiple injuries is used as well. Consensus on outcome measures for justification of TBCT should be obtained to guide further research on the appropriate indications for TBCT in trauma.

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Appendix

Overview of described TBCT indications after trauma and cut-off values for vital parameters and trauma mechanism dimensions

Type of indication	Subtype	Cut-off value
Vital Parameters	– Respiratory rate	≥/> 29/min or </≤ 10/min
	– O_2 Saturation	<90% / <85% for age >75yr
	– Pulse	≥ 120/min / <50/min
	– Systolic blood pressure	<80 / <90 / ≤100 / <100 for age > 65yr
	– Estimated exterior blood loss	≥ 500 ml
	– GCS	<9 / <10 / ≤ 13 / ≤ 14 for age >65yr
	– Abnormal pupillary reaction on site	
Trauma mechanism	– Fall	>3m / > 5m / >6m / unclear height
	– Motor vehicle (driver, passenger)	
	• Initial speed >65 kph (40 mph) / 35mph	
	• Combined velocitiy ≥ 50km/h	
	• High speed crash	
	• Major auto deformity >50 cm (20 in.)	
	• Intrusion into passenger compartment >30 cm (12 in.)	
	• Vehicle rollover	
	• head-on collision	
	• Ejection from vehicle / car	
	• Extrication time >20 min	
	• Entrapment > 30 minutes / trapped in car	
	• Crush injury to thorax/abdomen	
	• Death same passenger compartment	
	– Pedestrian struck	
	• By motor vehicle at any speed	
	• With significant impact >10 kph (5 mph)	
	• Thrown >10 ft or run over	
	– Bicyclist struck	
	• Hit by larger vehicles	
	• Hit by car	
	• With significant impact >10 kph (5 mph)	
	– Motorcyclist	
	• High speed crash	
	• Crash >30 kph (20 mph) / >50kph	
	• Separation from motorcycle	
	– Victim thrown or run over	
	– Crash against truck	
	– Technical rescue required / extrication	
	– Global assessment (vehicle deformation, estimated speed, no helmet, no seat belt)	
	– Major industrial accident	
	– Blast injury / explosion, buried person	

Type of indication	Subtype	Cut-off value
	– Significant assault – Assaulted with depressed level of consciousness – Torso crush injury – Unknown mechanism with abnormal vital parameters – Unknown mechanism	
Clinically suspicious injury	– Fractures of ≥ 2 (proximal) long bones – Flail chest, open chest, or multiple rib fractures – (unstable) pelvic fracture – Smashed pelvis – Open abdominal wound – Unstable vertebral fractures – Spinal cord injury / suspected spinal cord injury – Penetrating injuries to head, neck, chest, abdomen, groin,and extremities proximal to elbow and knee – Penetrating injury – Gunshot wound (including air rifle) – Stabwound – Combination trauma with burns >20 % of BSA – Severe burn, smoke inhalation – Amputation proximal to wrist and ankle – Crush injury proximal to wrist and ankle – Traumatic limb paralysis – Acute ischemia of a limb – Any evidence of airway obstruction or compromise – Multiple body region injuries	
Clinical judgement	– Suspected injury of ≥ 2 body regions of which ≥ 1 is life threatening – Suspicion of severe trauma by paramedics or emergency doctors on scene	
Other	– (modified) Early warning score – Requiring bleeding control measurement – Resuscitation prior to admission (assisted ventilation, colloid fluids >1L, catecholamines, inflated antishock trousers) – Predisposition , to be determined (Age>65 years, heart or coronary failure, respiratory failure, 2nd or 3rd trimester pregnancy, dyscrasia)	

Type of indication	Subtype	Cut-off value
Exclusion	– Minor age – pregnancy – Referred from another hospital – too unstable to undergo a CT scan and requires (cardiopulmonary) resuscitation or immediate operation – availability of CT scanner – clear identification of abnormalities by FAST and X-ray – focal / isolated trauma without potential multiple trauma or severe kinetic component as defined by Vittel criteria – Obesity >200kg	< 15, < 17, <18 years

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5

Refining the criteria for immediate total body CT after severe trauma

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European Radiology 2020

Abstract

Objectives

Initial trauma care could potentially be improved when conventional imaging and selective CT scanning is omitted and replaced by immediate total body CT (iTBCT) scanning. Because of the potentially increased radiation exposure by this diagnostic approach, proper selection of the severely injured patients is mandatory.

Methods

In the REACT-2 trial severe trauma patients were randomized to iTBCT or conventional imaging and selective CT based on predefined criteria regarding compromised vital parameters, clinical suspicion of severe injuries or high-risk trauma mechanisms in five trauma centers. By logistic regression analysis with backward selection on the 15 study inclusion criteria a revised set of criteria was derived and subsequently tested for prediction of severe injury and shifts in radiation exposure.

Results

In total, 1083 patients were enrolled with median ISS of 20 (IQR 9-29) and median GCS of 13 (IQR 3-15). Backward logistic regression resulted in a revised set consisting of nine original and one adjusted criteria. Positive predictive value improved from 76% (95% CI 74%-79%) to 82% (95% CI 80%-85%). Sensitivity decreased by 9% (95% CI 7%-11%). The area under the receiver operating characteristics curve remained equal and was 0.80 (95% CI 0.77-0.83); original set: 0.80 (95% CI 0.77-0.83). The revised set retains 8.78 mSv (95% CI 6.01-11.56) for 36% of the non-severely injured patients.

Conclusions

Selection criteria for iTBCT can be reduced from 15 to 10 clinically criteria. This improves the positive predictive value for severe injury and reduces radiation exposure for less severely injured patients.

Introduction

Improvements in speed and accuracy of computed tomography (CT) made immediate total body CT (iTBCT) feasible as a diagnostic tool in the primary care for severe trauma patients. Initial trauma care for severe trauma patients can be improved when the step-up approach of conventional imaging and selective CT is omitted and an iTBCT is performed instead. iTBCT scanning is safe, shortens the time to end of imaging and does not increase direct medical costs.[1] However, it has not been demonstrated to improve survival.[1] Because of the potentially increased radiation exposure by this diagnostic approach proper selection of severely injured patients is mandatory.[2-4] Criteria for total body CT in trauma vary across trauma centres and consensus is lacking.[5,6] Early identification of severely injured patients will reduce exposure to radiation by iTBCT in less severely injured patients.

The decision to perform an iTBCT is based on information obtained during the pre-hospital phase and during the in-hospital primary survey. Justification for performing an iTBCT is only possible in hindsight, when radiologic imaging, interventions and the clinical course have confirmed all diagnoses. The REACT-2 was a randomized controlled trial set up to determine the effect of iTBCT on mortality compared to conventional imaging and selective CT. Inclusion criteria of this multicenter randomized trial aimed to select severely injured patients benefitting most from iTBCT before imaging.[7]

The aim of the present analysis was to assess the discriminatory power of REACT-2 criteria for severely injured patients that could benefit from iTBCT during the primary assessment of trauma care. Furthermore, a revised set of criteria was derived and tested for discriminatory characteristics on detection of severe injury and shifts in radiation exposure compared to the original set of REACT-2 inclusion criteria.

Methods

Study design and patient selection

This study is a secondary analysis of the REACT-2 trail in which non-pregnant adult severe trauma patients were included in five trauma centers in the Netherlands and Switzerland between April 2011 to January 2014. Inclusion was based on predefined compromised vital parameters, clinical suspicion of specific severe injuries and high-risk trauma mechanisms. Patients were considered eligible when meeting one or more of the 15 inclusion criteria and none of the exclusion criteria as shown in table 6 in the appendix.

Patients were randomized to iTBCT or the standard work-up (STWU) that consists of conventional imaging with selective CT of specific body regions (i.e. head, neck, chest and/or abdomen and pelvis). Decision of eligibility by the trauma leader

as well as documentation of the concerning criteria by a trauma team member was performed before the start of radiologic imaging. After obtaining vital parameters, a physical examination and potentially life-saving interventions (*e.g.*, securing airway, chest tube placement, or hemorrhage control measures) the trauma team proceeded to CT scanning in the same or an adjacent trauma resuscitation room. CT scanning could be interrupted any moment when the patient should deteriorate and could be reached within seconds by trauma team members. iTBCT was performed without preceding conventional imaging and consisted of an unenhanced CT of the head and neck with arms alongside the trunk. The second part consisted of a contrast enhanced CT of chest, abdomen and pelvis. The preferred technique of the second part was split-bolus intravenous contrast imaging with the arms raised alongside the head.[8] Brain reconstruction was in axial planes with 5 mm head kernel and 1 mm bone kernel, cervical spine in 1 mm bone kernel in axial, sagittal, and coronal planes. Torso was reconstructed at 3 mm axial and coronal slices in soft and bone kernel. CT scanners at the participating sites were all 64-slice multidetector row CT scanners. Indication for selective CT of specific body regions was set by local protocols.

The design of the REACT-2 study has been previously described (ClinicalTrials.gov: NCT01523626) and published.[7] The REACT-2 study was approved by the medical ethics committees at all participating centers (AMC MEC 10/145).

Outcome

iTBCT was considered justified if a patient was classified as severely injured by in-hospital findings and clinical course. Definition of severe injury in the current study was met by presence of at least one of the following conditions:

- Injury Severity Score (ISS) ≥16;
- Requiring emergency surgery or emergency radiologic intervention;
- Direct admission to the Intensive Care Unit;
- In-hospital death.

Statistical analysis

Continuous data with a normal distribution are presented as means with standard deviation and non-normally distributed data are presented as medians with interquartile ranges. Independent sample t-tests and Mann-Whitney U tests were used to compare the parametric and non-parametric continuous data, respectively. The Chi-squared test was used to compare the categorical variables. A p-value of less than 0.05 was considered statistically significant.

To identify criteria that could select severely injured patients, we entered all REACT-2 inclusion criteria in backward stepwise multivariate logistic regression analysis on severe injury using $p < 0.05$ as criterion. These criteria are clinically useful and available early in the primary trauma assessment. Selection by univariate logistic regression analysis on single REACT-2 inclusion criteria before the multivariate analy-

sis was omitted since the criteria were defined in advance. Thereby, there were more events or non-events (i.e. status as severely injured patient or status as non-severely injured patient) present in the study population than 10-fold the 15 REACT-2 inclusion criteria, which allowed multivariate analysis of all criteria. When clinically appropriate the threshold values for vital parameters and trauma mechanism characteristics of specific criteria were retrospectively adjusted and included again in the regression analysis. Threshold value for pulse was increased by steps of 10 per minute, for systolic blood pressure (SBP) lowered by steps of 10 mmHg and for fall from height by steps of one meter. Positive predictive value (PPV), relative sensitivity and receiver operating characteristics (ROC) were used to compare the accuracy of the sets of criteria.

Numbers needed to iTBCT scan to perform one unnecessary iTBCT scan for a non-severely injured patient were compared between the sets of criteria; calculated by (1/(1-PPV)). Reduction of iTBCT scans for non-severely injured patients were calculated by subtraction of false positive rates (1-PPV). Shifts in radiation exposure were calculated by subtraction of the sum of all effective doses from all radiological examinations done in the trauma room. The radiation dose was estimated based on the dose catalogue of Mettler and colleagues.[9] Differences of the mean for radiation doses were presented with 95% CI. All statistical analyses were performed with SPSS version 24 (SPSS inc., Chicago, Illinois).

Results

In the REACT-2 trial 1083 patients were enrolled of which 541 (50.0%) underwent iTBCT as primary diagnostic modality. Within the entire group 785 patients (72.5%) eventually underwent TBCT during the primary assessment as they underwent an iTBCT or CT scans from head, neck, chest, abdomen and pelvis secondary to x-rays and ultrasound. Median age was 43 (IQR 27-59) and 76% of the patients were male. Median ISS was 20 (IQR 9-29) and median in-hospital Glasgow Coma Scale (GCS) was 13 (IQR 3-15). Baseline demographic and clinical characteristics are presented in Table 1.

There were 827 severely injured patients as defined by the combined outcome and therefore the original set of criteria has a PPV for severe injury of 76% (95% CI 74%-79%). Table 2 presents the prevalence within the enrolled population and the PPV for each separate criterion. Backward logistic regression analysis of the 15 original criteria resulted in selection of seven criteria shown in Table 3. After adjustment of threshold values for vital parameters and trauma mechanism characteristics the backward selection resulted in nine original and one adjusted criteria. Therefore five of the original criteria (respiratory rate ≥ 30/min or ≤ 10/min, pulse ≥ 120/min, ejection form a vehicle, death of occupant in same vehicle and severely injured patient in same vehicle) were not of additional value and can be omitted.

Table 1. Baseline demographic and clinical characteristics, n_{max} = 1083

Characteristic	**n***	
Age (years)	1083	43 (27-59)
Male sex, n (%)	1083	824 (76.1)
Blunt trauma, n (%)	1083	1064 (98.2)
Trauma mechanism blunt trauma, n (%)	1064	
Fall from height		348 (32.7)
MVC – patient as occupant		391 (36.7)
MVC – patient as cyclist		125 (11.7)
MVC – patient as pedestrian		74 (7.0)
Other		126 (11.8)
Pre-hospital vital parameters		
Respiratory rate (per minute)	640	16 (14-20)
Pulse (bpm)	948	89 (25)†
Systolic blood pressure (mmHg)	910	133 (31)†
GCS (points)	1061	14 (6-15)
Triage Revised Trauma Score	618	7.04 (5.03-7.84)
In-hospital vital parameters		
Respiratory rate (per minute)	669	16 (14-20)
Pulse (bpm)	1059	88 (22)†
Systolic blood pressure (mmHg)	1060	131 (27)†
Hypotensive at admission, n (%)	-	82 (7.7)
GCS (points)	1083	13 (3-15)
Revised Trauma Score	651	7.11 (4.09-7.84)
Total-body CT, n (%)	1083	785 (72.5)
Immediate total-body CT, n (%)	1083	553 (51.1)
Abbreviated Injury Scale ≥3, n (%)	1083	
Head		465 (42.9)
Chest		435 (40.2)
Abdomen		116 (10.7)
Extremities		304 (28.1)
Injury Severity Score (points)	1083	20 (9-29)
Multitrauma patients, n (%)‡	1083	693 (64.0)
TBI patients, n (%)‡	1083	329 (30.4)
TRISS, survival probability	618	0.94 (0.68-0.98)

Results of the population described in this table were published earlier [1]. All data are number (%) or median (interquartile range) unless otherwise specified.

* This column displays the number of patients that was analysed for each specific variable.

† Mean (SD).

‡ Multitrauma patients are defined as ISS ≥16. TBI patients are defined as GCS <9 at presentation and AIS Head ≥3.

MVC Motor Vehicle Collision, CT Computed Tomography, ISS Injury Severity Score, TBI Traumatic Brain Injury, TRISS Trauma and Injury Severity Score.

Table 4 shows that PPV of the newly formed set of criteria statistically significant increased to 82% (95% CI 80%-85%) compared to 76% (95% CI 74%-79%) of the original set. Sensitivity of the revised set within the originally formed population was statistically significant reduced by 9% (95% CI 7%-11%). Clinical characteristics including trauma scores comparing severely injured patients not selected by the revised set of criteria to selected severely injured patients are displayed in Table 8 in the Appendix. The area under the ROC curve remained equal and was 0.80 (95% CI 0.77-0.83) in the revised set compared to 0.80 (95% CI 0.77-0.83) for the original set as shown in figure 1 in the Appendix. Numbers of iTBCT scans needed to perform one unnecessary scan for a non-severely injured patient was statistically significant improved from 1 in 4.2 (95% CI 3.8-4.7) to 1 in 5.6 (95% CI 4.9-6.5). The number of unnecessary iTBCT scans was statistically significant decreased with 6% (95% CI 2%-10%).

Shifts in radiation exposure for the different sets of criteria are displayed separately for severely injured and non-severely injured patients in Table 5. With the use of the original criteria iTBCT adds 1.19 mSv (95% CI -0.13-2.51) for severely injured patients and 8.15 mSv (95% CI 5.91-10.39) for non-severely injured patients compared to the STWU. Within patients not selected for iTBCT by the revised criteria, the STWU retains 1.32 mSv (95% CI -2.71-5.35) for 9% of the severely injured patients and retains 8.78 mSv (95% CI 6.01-11.56) for 36% of the non-severely injured patients compared to iTBCT. Shifts in radiation exposure are displayed separately for age groups < 45 years and > 45 years in Tables 8 and 9 in the Appendix.

Discussion

By retrospective analysis of a prospectively formed cohort of severe trauma patients we derived a revised set of 10 criteria for iTBCT, shown in Table 6. The new set of criteria has an increased PPV for detecting severe injury. Hence, these criteria could reduce the number of patients screened by iTBCT who are less severely injured and who will not have an advantage of all their body regions scanned. The relative reduction of sensitivity compared to the original set could be restrained to 9%. This reduction of sensitivity leads to a relative increase of severely injured patients for whom screening by iTBCT will be retained and will have conventional imaging and selective CT scanning. Since there is no reduction of mortality after iTBCT for the trial population selected by the original criteria, the aim for a revised set of iTBCT criteria with higher PPV and lower sensitivity can be justified. Without loss of overall discriminative capacity for severe injuries we changed the set of criteria for iTBCT with emphasis on the reduction of radiation exposure for the less severely injured patient.

Quantification of the shifts in radiation exposure was performed separately for the less severely injured patients. For 36% of the less severely injured patient a significant reduction in radiation exposure could be demonstrated by use of the revised set of

Table 2. Predictive value of REACT-2 immediate total-body CT criteria for severe injuries, n=1083

	n	PPV, % (95% CI)	NPV, %* (95% CI)	Sens, %* (95% CI)	Spec, %* (95% CI)
Parameters at hospital arrival					
respiratory rate ≥ 30/min or ≤ 10/min	16	81 (62-100)	24 (21-26)	2 (1-2)	99 (98-100)
pulse ≥ 120/min	69	80 (70-89)	24 (21-27)	7 (5-8)	95 (92-97)
pulse ≥ 130/min †	49	88 (79-97)	24 (22-27)	5 (4-7)	98 (96-100)
pulse ≥ 140/min †	26	88 (63-76)	24 (21-27)	3 (2-4)	99 (98-100)
systolic blood pressure ≤ 100 mmHg	116	96 (92-99)	26 (23-29)	13 (11-16)	98 (96-100)
systolic blood pressure < 90 mmHg †	82	100 (100-100)	26 (23-28)	10 (8-12)	100 (100-100)
systolic blood pressure < 80 mmHg †	32	100 (100-100)	24 (22-27)	4 (3-5)	100 (100-100)
estimated exterior blood loss ≥ 500 ml	43	91 (82-99)	24 (22-27)	5 (3-6)	98 (97-100)
GCS ≤13 or abnormal pupillary reaction	485	93 (91-95)	37 (33-41)	55 (51-58)	87 (83-91)
GCS ≤ 8 †	437	99 (98-100)	39 (35-43)	52 (49-56)	98 (97-100)
GCS = 3 †	394	99 (99-100)	37 (33-41)	47 (44-51)	99 (98-100)
Clinical suspicions					
fractures from at least two long bones	90	89 (82-95)	25 (22-28)	10 (8-12)	96 (94-99)
flail chest, open chest or multiple rib fractures	114	83 (76-90)	25 (22-27)	12 (9-14)	93 (89-96)
severe abdominal injury	65	82 (72-91)	24 (21-27)	6 (5-8)	95 (93-98)
pelvic fracture	98	78 (69-86)	24 (21-27)	9 (7-11)	91 (88-95)
unstable vertebral fractures / spinal cord compression	69	68 (57-79)	23 (21-26)	6 (4-7)	91 (88-95)
Injury mechanisms					
fall from height (> 3 meters / > 10 feet)	319	62 (57-67)	18 (15-20)	24 (21-27)	53 (47-59)
fall from height (> 4 meters / > 13 feet) †	166	70 (64-77)	23 (20-25)	14 (12-17)	81 (76-86)
fall from height (> 5 meters / > 16 feet) †	126	71 (64-79)	23 (20-26)	11 (9-13)	86 (82-90)
fall from height (> 6 meters / > 20 feet) †	82	78 (69-87)	24 (21-26)	8 (6-10)	93 (90-96)
fall from height (> 7 meters / > 23 feet) †	60	87 (78-95)	24 (22-27)	6 (5-8)	97 (95-99)
fall from height (> 8 meters / > 26 feet) †	40	88 (77-98)	24 (22-27)	4 (3-6)	98 (96-100)

ejection from a vehicle	30	60 (42-78)	23 (21-26)	2 (1-3)	95 (93-98)
death of occupant in same vehicle	17	65 (42-87)	24 (21-26)	1 (1-2)	98 (96-100)
severely injured patient in same vehicle	18	78 (59-97)	24 (21-26)	2 (1-3)	98 (97-100)
wedged or trapped chest / abdomen	60	83 (74-93)	24 (21-27)	6 (4-8)	96 (94-99)

* Within the group of patients selected by the original criteria

† Retrospectively adjusted criteria

GCS Glasgow Coma Scale, PPV Positive Predictive Value, NPV Negative Predictive Value, Sens Sensitivity, Spec Specificity, CI Confidence Interval

Table 3. Predictive value of REACT-2 immediate total-body CT criteria for severe injuries, n=1083

				Backward selection of criteria			
		Univariate analysis		Original criteria		Adjusted criteria	
	n	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Parameters at hospital arrival							
respiratory rate ≥ 30/min or ≤ 10/min	16	1.35 (0.38-4.76)	0.644	-	-	-	-
pulse ≥ 120/min	69	1.23 (0.67-2.25)	0.499	-	-	-	-
*pulse ≥ 130/min **	49	2.29 (0.96-5.43)	0.061			-	-
*pulse ≥ 140/min **	26	2.41 (0.72-8.10)	0.154			-	-
pulse (continuous) †		1.02 (1.01-1.02)	< 0.001			-	-
systolic blood pressure ≤ 100 mmHg	116	7.78 (3.14-19.29)	< 0.001	5.71 (2.23-14.62)	< 0.001	5.72 (2.22-14.75)	< 0.001
*systolic blood pressure < 90 mmHg **	82	∞ (0 - ∞)	0.996				
*systolic blood pressure < 80 mmHg **	32	∞ (0 - ∞)	0.998				
systolic blood pressure (continuous) †		0.99 (0.98-0.99)	< 0.001				
estimated exterior blood loss ≥ 500 ml	43	3.12 (1.10-8.81)	0.032	3.29 (1.09-9.93)	0.035	3.70 (1.20-11.37)	0.023
GCS ≤13 or abnormal pupillary reaction	485	7.83 (5.32-11.52)	< 0.001	10.02 (6.69-15.00)	< 0.001	12.65 (8.23-19.45)	< 0.001
*GCS ≤ 8 **	437	69.24 (25.54-187.66)	< 0.001				
*GCS = 3 **	394	114.45 (28.28-463.28)	< 0.001				
GCS (continuous) †		0.69 (0.64-0.74)	< 0.001				
Clinical suspicions							
fractures from at least two long bones	90	2.64 (1.34-5.16)	0.005	4.08 (2.02-8.25)	< 0.001	4.94 (2.41-10.15)	< 0.001
flail chest, open chest or multiple rib fractures	114	1.62 (0.97-2.71)	0.066	2.81 (1.62-4.86)	< 0.001	3.27 (1.85-5.76)	< 0.001
severe abdominal injury	65	1.39 (0.73-2.65)	0.313	-	-	2.18 (1.07-4.42)	0.031
pelvic fracture	98	1.08 (0.66-1.77)	0.771	1.76 (1.03-3.01)	0.039	1.82 (1.05-3.14)	0.033
unstable vertebral fractures / spinal cord compression	69	0.64 (0.38-1.09)	0.098	-	-	1.87 (1.06-3.31)	0.032

Injury mechanisms							
fall from height (> 3 meters / > 10 feet)	319	0.35 (0.26-0.47)	< 0.001	-	-	-	-
*fall from height (> 4 meters / > 13 feet) **	166	0.70 (0.48-1.01)	0.054			1.64 (1.07-2.52)	0.022
*fall from height (> 5 meters / > 16 feet) **	126	0.75 (0.49-1.13)	0.167				
*fall from height (> 6 meters / > 20 feet) **	82	1.11 (0.65-1.91)	0.709				
*fall from height (> 7 meters / > 23 feet) **	60	2.08 (0.98-4.44)	0.058				
*fall from height (> 8 meters / > 26 feet) **	40	2.22 (0.86-5.72)	0.099				
fall from height (continuous) †		1.17 (1.06-1.29)	0.002				
ejection from a vehicle	30	0.45 (0.22-0.95)	0.037	-	-	-	-
death of occupant in same vehicle	17	0.56 (0.21-1.53)	0.261	-	-	-	-
severely injured patient in same vehicle	18	1.09 (0.35-3.33)	0.887	-	-	-	-
wedged or trapped chest / abdomen	60	2.71 (1.04-4.54)	0.038	2.11 (1.00-4.42)	0.049	2.57 (1.20-5.51)	0.015

* Retrospectively adjusted criteria

† Continuous data of regarding criterion used were possible

GCS Glasgow Coma Scale, OR Odds Ratio, CI Confidence Interval

Table 4. Characteristics of different sets of criteria for immediate total body CT

	PPV (95% CI)	Relative sensitivity* (95% CI)	ROC AUC (95% CI)	Numbers needed to overscan† (95% CI)	Decrease of unnecessary iTBCT scans‡ (95% CI)
Original criteria (n = 15)	76 % (74-79)	Reference	0.80 (0.77-0.83)	4.2 (3.8-4.7)	Reference
Selected original criteria (n = 7)	87 % (85-90)	80 % (77-83)	0.78 (0.75-0.81)	7.9 (6.7-9.8)	11 % (8-14)
Selected adjusted criteria (n = 10)	82 % (80-85)	91 % (89-93)	0.80 (0.77-0.83)	5.6 (4.9-6.5)	6 % (2-10)

* Relative sensitivity within the population preselected by the original criteria.

† Number of iTBCT scans to perform one unnecessary iTBCT for a non-severely injured patient.

‡ Percentage decrease of iTBCT scans for non-severely injured patients.

ROC Receiver Operating Characteristic AUC Area Under the Curve, PPV Positive Predictive Value, CI Confidence Interval

Table 5. Shifts in radiation exposure in different sets of criteria for immediate total body CT and standard work-up with selective CT, n= 1083.

	Original criteria (15)		**Selected criteria (7)**		**Selected and adjusted criteria (10)**	
	additional radiation exposure compared to STWU, mSv (95%CI)	*% of population*	*additional radiation exposure compared to STWU, mSv (95%CI)*	*% of population*	*additional radiation exposure compared to STWU, mSv (95%CI)*	*% of population*
Selected for iTBCT						
Severely injured	1.19 (-0.13 to 2.51)	76.4	2.05 (0.56 to 3.53)	60.9	1.17 (-0.23 to 2.57)	69.7
Non-severely injured	8.15 (5.91 to 10.39)	23.6	7.24 (3.07 to 11.41)	8.8	7.91 (4.77 to 11.05)	15.1
	additional radiation exposure compared to iTBCT, mSv (95%CI)		*additional radiation exposure compared to iTBCT, mSv (95%CI)*		*additional radiation exposure compared to iTBCT, mSv (95%CI)*	
Selected for STWU						
Severely injured	-	-	2.11 (-0.74 to 4.95)	15.4	-1.32 (-5.35 to 2.71)	6.7
Non-severely injured	-	-	-8.78 (-11.44 to -6.13)	14.9	-8.78 (-11.56 to -6.01)	8.5

iTBCT denotes immediate total body CT; STWU denotes standard work-up with selective CT

Table 6. Revised criteria for immediate total-body CT in trauma patients

Trauma patients with one of the following parameters at hospital arrival:
- systolic blood pressure <100 mmHg
- estimated exterior blood loss ≥500 ml
- Glasgow Coma Score ≤13 or abnormal pupillary reaction

AND / OR

Patients with a clinical suspicion of one of the following diagnoses:
- fractures from at least two long bones
- flail chest, open chest or multiple rib fractures
- severe abdominal injury
- pelvic fracture
- unstable vertebral fractures / spinal cord compression

AND / OR

Patients with one of the following injury mechanisms:
- fall from a height (>4 meters / >13 feet)
- wedged or trapped chest / abdomen

Contra indications:*

Trauma patients with one of the following characteristics:
- known age <18 years
- known pregnancy
- referred from another hospital
- clearly low-energy trauma with blunt injury mechanism
- any patient with a stab wound in one body region
- any patient who is judged to be too unstable to undergo a CT scan and requires (cardiopulmonary) resuscitation or immediate operation because death is imminent

* Contra indications for immediate total-body CT were not revised. These criteria are mentioned in this table to give a complete overview.

criteria. This effect was also present for patients of age < 45 years. The precise amounts of reduction in radiation exposure have to be interpreted in perspective of ongoing developments of low dose CT scanning.

Compromised vital parameters, clinical suspicion of severe injuries and high-risk mechanisms are widely used as criteria for TBCT in severe trauma.[5,6] The first report by Wurmb et al. on such a set of criteria for iTBCT described a PPV of 69% and sensitivity of 97% for ISS ≥ 16 in sedated and ventilated severe trauma patients. The difference in outcome measure and the selection of sedated and ventilated patients makes the results difficult to compare to our study.[10] Hsiao et al. reported 32% PPV and 50% sensitivity of criteria for TBCT by clinical judgment for the presence of multi-region injury defined by an Abbreviated Injury Score (AIS) of ≥2 in two or more body regions. After retrospective identification of predictors for multi-region injury a prediction model was made that did not show improvement for the area under the ROC curve compared to indication by clinical judgment.[11]

Hemodynamically compromised patients could benefit from trauma screening by iTBCT. Wada et al. reported reduced mortality for patients receiving TBCT before emergency bleeding control measurements in a retrospective study in two trauma centers.[12] Reduction in mortality in trauma patients requiring emergency bleeding control interventions by iTBCT could not be confirmed in the REACT-2 population. However, a potentially clinically relevant absolute risk reduction of 11.2% (95% CI -0.3 to 22.7%) in comparison with the STWU was observed.[13] Huber-Wagner et al. reported reduced mortality in severe trauma patients in moderate (SBP 90-110 mmHg) or severe (SBP <90 mmHg) shock when receiving TBCT during the resuscitation in a retrospective multicenter study.[14] In the present study compromised blood pressure (SBP < 100 mmHg) is an independent predictor for severe injury and is therefore a valid indication for iTBCT. It is recommendable to only perform CT scanning on hemodynamically compromised patients in the trauma resuscitation room or the adjacent room and the trauma team has direct access to the patient and has options for potential life-saving interventions any moment.

Patients with a compromised GCS could benefit from trauma screening by TBCT. Kimura et al. reported reduced mortality in patients with moderate to severe consciousness disturbance (GCS 3-12) in a retrospective multicenter study.[15] Furthermore, decreased levels of consciousness could be considered an indication on itself since several clinical indicators for imaging are unreliable owing to the lack of subjective input from the patient when screening for injuries. Routine CT imaging for patients with unreliable physical examination is reported to reveal unsuspected findings in up to 38%, leading to treatment changes in 19-26%.[16,17] Our study found GCS ≤13 or abnormal pupillary reaction an independent predictor for severe injury and further supports a compromised GCS to be a valid indication for iTBCT after severe trauma.

Besides vital parameters that indicate a hemodynamically or neurologically compromised status also clinical suspicions of specific injuries and high-risk trauma

mechanisms that independently predict patients to be severely injured in our study. Although these criteria are prone to interpretation differences, we would recommend adopting these criteria in iTBCT indication schemes. During mass casualty accidents overruling the iTBCT indication scheme has to be considered.[18,19] Furthermore, there should be awareness for the increase of incidental findings by TBCT compared to the STWU during implementation or refining of iTBCT indications schemes.[20,21]

Limitations and strengths

The main limitation of this study is the lack of information of patients who were not selected by the original REACT-2 criteria for eligibility of screening by iTBCT. This study could therefore only report the relative reduction of the sensitivity by the revised set compared to the original set of criteria. If proportions of severely injured patients in the group not selected by the original criteria were available the absolute sensitivity, specificity and negative predictive value could have been calculated. The proposed revised set of iTBCT criteria should be prospectively validated in another cohort of patients.

The definition of multitrauma and multi-region injured patients is subject of debate. Several cut-off values for ISS or AIS are used with eventual involvement of vital parameters proposed.[22] As a part of the combined outcome measure of this study we chose ISS ≥16 to justify iTBCT in hindsight for patients with multiple relevant injuries (AIS ≥3 in two or more body regions or AIS ≥3 in one body region and AIS ≥2 in two or more body regions) and patients with a severe injury of at least one body region (AIS ≥4). Hsiao et al. chose AIS ≥2 in two regions as the anatomical outcome measure to justify TBCT.[11] In our opinion TBCT for patients with eventually AIS of 2 in two body regions is not justified. On the contrary, the screening of a patient with a severe injury in only one body region could be justified since there is a higher probability of concomitant injury, which should be quickly excluded with high accuracy.

An alternative approach for refining the criteria for iTBCT criteria is to determine its discriminative power for selection of patients who would otherwise receive equal or even higher radiation exposure by selective CT scanning compared to the radiation exposure of iTBCT. This particularly reflects the judgment of the trauma team leader for the necessity of CT scans of specific body regions which does not necessarily correlates with selection of severely injured patients.[23] Therefore the radiation exposure by the diagnostic approach with selective CT scans was not eligible as outcome measure for revision of the iTBCT criteria.

Strength of this multicenter study is the assessment of prospectively observed criteria for iTBCT in a large trial population. Previous studies assessed retrospectively observed TBCT criteria or were performed in a single center setting. The combined clinical outcome parameter is suitable to define severely injured patients and patients that need fast and detailed diagnostics when an immediate intervention or ICU treatment is indicated. The addition of immediate surgery to the combined outcome

measure is supported by reports of potential time and survival benefit for patients receiving emergency surgery.[12,24] The revised set of criteria will reduce the exposure to radiation for less severely injured patients without loss of discriminative capacity for severe injury. Thereby the revision led to a simplification, which implies easier application during primary trauma care.

Conclusion

This study presents a revised set of 10 clinically criteria for iTBCT with a high predictive value for severe injury and therefore reduces radiation for the less severely injured patients for iTBCT. The criteria selected as predictors in this study should be prospectively validated in another cohort of patients for whom screening by iTBCT is considered after severe trauma.

Collaborators

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Appendix

Figure 1. Receiver operating characteristic (ROC) curves for severe injury of the original criteria, selected criteria and the selected adjusted criteria

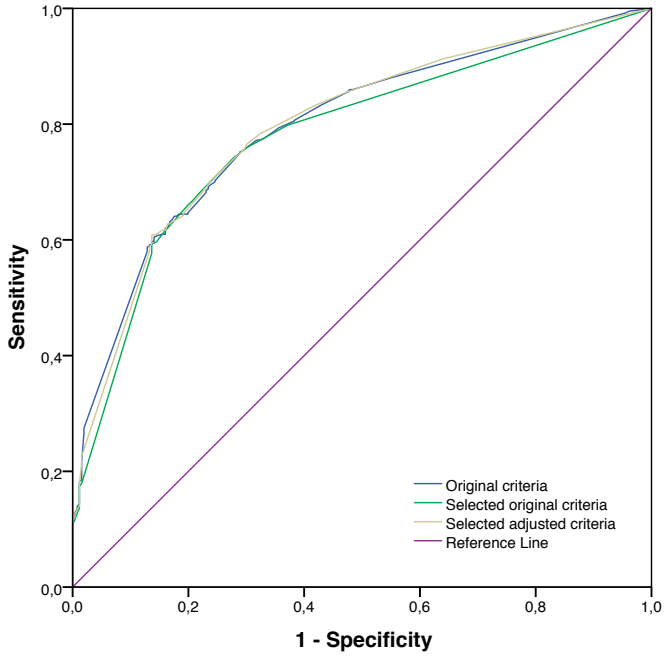

Table 7. Original indications for immediate total-body CT in trauma patients used in REACT-2 trial

Trauma patients with one of the following parameters at hospital arrival:
- respiratory rate ≥30/min or ≤10/min
- pulse ≥120/min
- systolic blood pressure ≤100 mmHg
- estimated exterior blood loss ≥500 ml
- Glasgow Coma Score ≤13 or abnormal pupillary reaction

AND / OR

Patients with a clinical suspicion of one of the following diagnoses:
- fractures from at least two long bones
- flail chest, open chest or multiple rib fractures
- severe abdominal injury
- pelvic fracture
- unstable vertebral fractures / spinal cord compression

AND / OR

Patients with one of the following injury mechanisms:
- fall from a height (>3 meters / >10 feet)
- ejection from a vehicle
- death of occupant in same vehicle
- severely injured patient in same vehicle
- wedged or trapped chest / abdomen

Contra indications

Trauma patients with one of the following characteristics were excluded:
- known age <18 years
- known pregnancy
- referred from another hospital
- clearly low-energy trauma with blunt injury mechanism
- any patient with a stab wound in one body region
- any patient who is judged to be too unstable to undergo a CT scan and requires (cardiopulmonary) resuscitation or immediate operation because death is imminent

Table 8. Clinical characteristics for severely injured patients not selected by the revised set of criteria (n=75) in comparison to selected severely injured patients (n=752).

Characteristic	Not selected (n) vs. selected (n)*	Not selected (n=75)	Selected (n=752)	P-value
Age (years)	75 vs. 752	47 (30-59)	43 (26-60)	0.279†
Male sex, n (%)	75 vs. 752	60 (80.0)	571 (75.9)	0.429‡
Blunt trauma, n (%)	75 vs. 752	71 (94.7)	741 (98.5)	0.039‡
Abbreviated Injury Scale ≥3, n (%)	75 vs. 752			
Head		37 (49.3)	415 (55.2)	0.332‡
Chest		33 (44.0)	388 (51.6)	0.210‡
Abdomen		9 (12.0)	107 (14.2)	0.596§
Extremities		19 (25.3)	253 (33.6)	0.144‡
Injury Severity Score (points)	75 vs. 752	22 (17-29)	25 (17-34)	0.009†
Polytrauma patients, n (%)‖	75 vs. 752	60 (80.0)	633 (84.2)	0.349‡
TRISS, survival probability	31 vs. 459	0.94 (0.85-0.98)	0.88 (0.51-0.97)	0.031†
In-hospital mortality, n (%)	75 vs. 752	10 (13.3)	161 (21.4)	0.133§
Length of stay (days)				
Total hospital stay	75 vs. 752	11 (4-19)	11 (4-22)	0.124†
ICU stay	75 vs. 752	1 (0-2)	1 (0-5)	0.249†
Ventilation days	75 vs. 752	0 (0-1)	1 (0-3)	0.059†

All data are number (%) or median (interquartile range) unless otherwise specified.

* This column displays the number of patients that was analysed for each specific variable.

† Mann-Whitney U test; ‡Chi² test; §Fisher's Exact Test.

‖Polytrauma patients are defined as ISS ≥16. Traumatic Brain Injury (TBI) patients are defined as GCS <9 at presentation and AIS Head ≥3.

TRISS denotes Trauma and Injury Severity Score.

Table 9. Shifts in radiation exposure in different sets of criteria for immediate total body CT and standard work-up with selective CT for patients of age < 45 years, n= 562.

	Original criteria (15)		**Selected criteria (7)**		**Selected and adjusted criteria (10)**	
	additional radiation exposure compared to STWU, mSv (95%CI)	*% of population*	*additional radiation exposure compared to STWU, mSv (95%CI)*	*% of population*	*additional radiation exposure compared to STWU, mSv (95%CI)*	*% of population*
Selected for iTBCT						
Severely injured	0.66 (-0.35 to 2.66)	75.6	2.29 (0.11 to 4.47)	61.2	1.00 (-1.09 to 3.09)	70.3
Non-severely injured	9.87 (6.92 to 12.82)	24.4	9.31 (3.21 to 15.41)	8.9	9.52 (5.30 to 13.74)	15.7
	additional radiation exposure compared to iTBCT, mSv (95%CI)		*additional radiation exposure compared to iTBCT, mSv (95%CI)*		*additional radiation exposure compared to iTBCT, mSv (95%CI)*	
Selected for STWU						
Severely injured	-	-	6.18 (1.38 to 10.98)	14.4	3.82 (-3.69 to 11.32)	5.3
Non-severely injured	-	-	-10.35 (-13.50 to -7.20)	15.5	-10.21 (-13.40 to -7.03)	8.7

iTBCT denotes immediate total body CT; STWU denotes standard work-up with selective CT

Table 10. Shifts in radiation exposure in different sets of criteria for immediate total body CT and standard work-up with selective CT for patients of age > 45 years, n= 521.

	Original criteria (15)		**Selected criteria (7)**		**Selected and adjusted criteria (10)**	
	additional radiation exposure compared to STWU, mSv *(95%CI)*	% of population	*additional radiation exposure compared* to STWU, mSv *(95%CI)*	% of population	*additional radiation exposure compared* to STWU, mSv *(95%CI)*	% of population
Selected for iTBC						
Severely injured	1.57 (-0.11 to 3.26)	77.2	1.65 (-0.36 to 3.66)	60.7	1.20 (-0.62 to 3.03)	69.1
Non-severely injured	6.25 (2.80 to 9.71)	22.8	4.66 (0.27 to 9.05)	8.6	6.12 (1.62 to 10.61)	14.6
	additional radiation exposure compared to iTBCT, mSv (95%CI)		*additional radiation exposure compared to iTBCT, mSv (95%CI)*		*additional radiation exposure compared to iTBCT, mSv (95%CI)*	
Selected for STWU						
Severely injured	-	-	-1.34 (-4.20 to 1.52)	16.5	-4.66 (-8.81 to 0.51)	8.1
Non-severely injured	-	-	-7.00 (-11.43 to 2.57)	14.2	-6.92 (-11.69 to 2.14)	8.3

iTBCT denotes immediate total body CT; STWU denotes standard work-up with selective CT


6

High rates of clinically relevant incidental findings by total-body CT scanning in trauma patients; results of the REACT-2 trial

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Abstract

Objectives

To determine whether there is a difference in frequency and clinical relevance of incidental findings detected by total-body computed tomography scanning (TBCT) compared to those by the standard work-up (STWU) with selective computed tomography (CT) scanning.

Methods

Trauma patients from five trauma centers were randomized between April 2011 and January 2014 to TBCT imaging or STWU consisting of conventional imaging with selective CT scanning. Incidental findings were divided in three categories: 1) Major finding, may cause mortality, 2) Moderate finding, may cause morbidity and 3) Minor finding, hardly relevant. Generalized estimating equation was applied to assess differences in incidental findings.

Results

In total 1083 patients were enrolled of which 541 patients (49.9%) were randomized for TBCT and 542 patients (50.1%) for STWU. Major findings were detected in 23 patients (4.3%) in the TBCT group compared to 9 patients (1.7%) in the STWU group (Adjusted rate ratio 2.851; 95%CI 1.337-6.077; $p<0.007$). Findings of moderate relevance were detected in 120 patients (22.2%) in the TBCT group compared to 86 patients (15.9%) in the STWU group (Adjusted rate ratio 1.421; 95%CI 1.088-1.854; $p<0.010$).

Conclusions

Compared to selective CT scanning more patients with clinically relevant incidental findings can be expected by TBCT scanning.

Introduction

Total-body computed tomography scanning (TBCT) is often used during the primary assessment of patients after severe trauma. Instead of selective computed tomography (CT) scanning of specific body regions, trauma teams routinely perform CT scans of the head, neck, thorax, abdomen and pelvis for trauma patients who could benefit from TBCT scanning. A potential disadvantage compared to the selective approach is the increased radiation exposure of TBCT scanning.[1,2] Since TBCT does not evidently decrease mortality in the general trauma population indication setting is important and a subject of debate.[3] Another consideration when performing TBCT is the increase of non-trauma related radiologic findings. These concomitant incidental findings should be prioritized with respect to potential life threatening injuries and might require additional follow-up and treatment. Incidental findings could bring forth the advantage of earlier diagnosis of malignancy or vascular disease. On the contrary, when clinical significance is absent incidental findings could also result in unnecessary investigations and concerns for the patient and extra health care costs.

Previous studies reported detection of incidental findings in 32% to 43% of trauma patients screened in trauma centers with selective CT scanning.[4,5] Studies on TBCT scanning reported incidental findings in 45% to 53% of trauma patients.[6-8] Direct comparison of frequency and relevance of incidental findings between trauma screening by TBCT scanning and the standard work-up with selective CT scanning in trauma patients is lacking. A difference in the frequency of relevant incidental findings can therefore only be assumed.

The aim of this study is to determine whether incidental findings detected by TBCT scanning, differ in frequency and relevance, from those detected by conventional imaging supplemented with selective CT in patients with severe trauma.

Methods

Study design and patient selection

This study was a secondary analysis of patients selected for the multicenter randomized controlled REACT-2 trial, of which the study protocol and main results were published previously.[3,9] In short, in the REACT-2 trial adult trauma patients, with compromised vital parameters, clinical suspicion of specific severe injuries or high-risk trauma mechanisms were randomized to undergo either an immediate TBCT scan or standard radiological work-up (STWU). The inclusion and exclusion criteria are listed in the Appendix. Patients were included between April 2011 and January 2014 in four level 1 trauma centers in The Netherlands and one in Switzerland. Informed consent was temporarily waived during the initial presentation in the trauma room. At the earliest opportunity after the trauma work-up information was given and informed con-

sent requested to the patient or legal representative. The study was approved by the medical ethics committees at all participating centers (AMC MEC 10/145).

The randomization process was performed by the trauma team immediately after the primary assessment of the patient. TBCT scanning was performed without conventional imaging or sonography in adv ance and consisted of a non-enhanced CT scan of the head and neck with arms alongside the trunk and followed by a contrast enhanced CT scan of the chest, abdomen and pelvis. The preferred technique for the second scan was split-bolus intravenous contrast imaging after raising the arms if possible.[10] STWU consisted of x-rays of the chest and pelvis, a focused assessment with sonography in trauma (FAST) and CT scans from specific body regions if indicated. Indications for selective CT scanning were predefined according to local protocols. These indications are listed in the appendix. CT-scanners were located in the trauma room or in an adjacent room and were all 64-slice multidetector row CT-scanners.

Data collection

Radiological images were interpreted by the radiology resident and subsequently a senior radiologist experienced in trauma imaging. Although focusing on traumatic injuries, this 'double-reading system' minimizes the number of missed findings.[11] All findings were described in the radiological reports, which are accessible through the computerized hospital databases of participating centers. Any available previous radiologic imaging of the same patient was also reviewed to confirm the findings to be new. In addition, trauma room report, interventional and pathology reports, and discharge letters were reviewed. For follow-up data all available in-hospital files were searched when relevant with a minimum of 6 months and maximum of 2 years after admission to the trauma resuscitation room.

Definitions and categorization of incidental findings

The clinical relevance of an incidental finding was subdivided into three subcategories being 1) Major finding, may cause mortality, 2) Moderate finding, may cause morbidity and 3) Minor finding, hardly relevant and no follow-up needed. The findings and corresponding relevance were scored based on the latest information on the finding. A list of incidental findings that could be expected, was formulated before data acquisition and derived from earlier reports on this subject.[4-8,12,13] Some incidental findings were added to more than one relevance category because the clinical importance of the same type of finding varied widely. For these specific findings, size-, age- or complexity specific cut-off values have been added to their description (e.g. simple vs. complicated renal cyst). Findings that already had been described previously, as well as traumatic lesions, were excluded. Degenerative joint diseases, common atherosclerotic vessel disease, enostosis, sinusitis, age-related cerebral atrophy and signs of earlier operations or old cerebral hematoma/infarction have also been excluded as incidental findings, in accordance with previous literature.[4,8,14]

For pulmonary nodules and renal cysts, classification was performed in accordance with the Fleischner society pulmonary nodule recommendations and Bosniak renal cyst classification.[15,16] With respect to the Fleischner recommendations, patients requiring follow-up within 6 months were defined as major findings, follow-up between 6 and 12 months as moderate findings and minor if no follow-up was needed. Bosniak class 1 corresponds to minor findings, class 2 to moderate findings and classes 2F and over to major findings. In the case of any abnormal lymph nodes, asymptomatic findings were classified as minor, unless the nodes were >10 mm in size, in which case these were labeled as moderate. Lymphadenopathy of major relevance indicates suspected lethal findings such as a suspected (non-)Hodgkin-lymphoma. If the nodular size was not reported, classification was performed by the reviewers of this study according to follow-up advice or further descriptions from the reporting radiologist.
Multitrauma patients were defined as patients with an Injury Severity Score ≥16. Traumatic Brain Injury (TBI) patients were defined as patients with GCS <9 (Glasgow Coma Scale) at presentation and AIS Head ≥3 (Abbreviated Injury Scale).

Statistical analysis

Continuous data with a normal distribution is presented as means with standard deviation and the non-normally distributed data is presented as medians with interquartile ranges. Independent sample t-tests and Mann-Whitney U Tests were used to compare the parametric and non-parametric continuous data respectively. Generalized estimating equation (GEE) was applied to assess differences in incidental findings between TBCT and STWU. The Kolmogorov-Smirnov test was used to confirm Poisson distributed numbers of major and moderate incidental findings. The total number of incidental findings as well as the number of minor incidental findings seemed negative binomially distributed which was confirmed by a non-significant Chi-squared test of goodness of fit of observed and theoretical data, the latter generated with the 'rnegbin' function in R. The results are reported as rate ratios of incidental findings with TBCT versus STWU, corrected for age, sex and center. The Chi-squared test was used to compare categorical variables when categories consisted of at least 10 cases, otherwise Fisher's exact test was used. A p-value below 0.05 was considered to reflect statistical significance. Statistical analysis was performed with SPSS version 23 (SPSS inc., Chicago, Illinois).

Results

Baseline characteristics of the study population are shown in Table 1. In total 1083 patients were enrolled of which 541 patients were randomized for TBCT (n=49.9%). Median age was 42 years (IQR 27-59) in the TBCT group and 45 years (IQR 26-59) in the STWU group (p=0.746). The groups are comparable for all baseline characteristics

Table 1. Baseline demographic and clinical characteristics of patients*

Characteristic	Total-body CT (n=541)	Standard work-up (n=542)
Age (years)	42 (27-59)	45 (26-59)
Male sex, n (%)	413 (76.3)	411 (75.8)
Blunt trauma, n (%)	530 (98.0)	534 (98.5)
Trauma mechanism blunt trauma, n (%)		
Fall from height	170 (32.1)	178 (33.3)
MVC – patient as occupant	201 (37.9)	190 (35.6)
MVC – patient as cyclist	65 (12.3)	60 (11.2)
MVC – patient as pedestrian	29 (5.5)	45 (8.4)
Other	65 (12.3)	61 (11.4)
Comorbidity, n (%)		
ASA I or II	495 (95.7)	501 (96.2)
ASA III, IV or V	22 (4.3)	20 (3.8)
CT performed at ED, n (%)*		
Head	539 (99.6)	483 (89.1)
Neck	535 (98.9)	480 (88.6)
Chest	529 (97.8)	315 (58.1)
Abdomen / pelvis	528 (97.6)	278 (51.3)
Abbreviated Injury Scale ≥3, n (%)		
Head	247 (45.7)	218 (40.2)
Chest	229 (42.3)	206 (38.0)
Abdomen / pelvic content	49 (9.1)	67 (12.4)
Pelvis and extremities	150 (27.7)	154 (28.4)
Injury Severity Score (points)	20 (10-29)	19 (9-29)
Multitrauma patients, n (%)*†	362 (66.9)	331 (61.1)
TBI patients, n (%)†	178 (32.9)	151 (27.9)

* Results in this table were published earlier.[3] P>0.05 for all between-group comparisons except for CT performed (p<0.001 for all body regions) and multitrauma patients (p=0.045). All data are number (%) or median (interquartile range).

† Multitrauma patients are defined as ISS ≥16. Traumatic Brain Injury (TBI) patients are defined as GCS <9 (Glasgow Coma Scale) at presentation and AIS Head ≥3 (Abbreviated Injury Scale).

MVC Motor Vehicle Collision, ASA American Society of Anaesthesiologists, ED Emergency Department.

except for the number of multitrauma patients; TBCT n= 362 (66.9%) vs. STWU n= 331 (61.1%), p=0.045. Median ISS was not different between groups; TBCT 20 (IQR 10-29) vs. STWU 19 (9-29), p=0.405.

In total 441 incidental findings were found in 233 of the patients (42.9%) randomized for TBCT compared to 290 findings in 167 of the patients (32.5%) randomized for the STWU (adjusted rate ratio 1.531; 95% Confidence Interval [95%CI] 1.274-1.840; p<0.001), as shown in Table 2. Major findings were detected in 23 patients (4.3%) in the TBCT group compared to 9 patients (1.7%) in the STWU group (adjusted rate ratio 2.851; 95%CI 1.337-6.077; p<0.007). Moderate findings were detected in 120 patients (22.2%) compared to 86 patients (15.9%) in the groups randomized for TBCT and STWU respectively (adjusted rate ratio 1.421; 95%CI 1.088-1.854; p<0.010).

Table 2. Trauma patients with incidental findings

Characteristic	Total-body CT (n=541)	Standard work-up (n=542)	Rate ratio (95%CI)	p	Adjusted rate ratio* (95%CI)	p
Patients with incidental findings, n (%)	232 (42.9)	176 (32.5)	1.524 (1.251-1.856)	< 0.001†	1.531 (1.274-1.840)	< 0.001†
Major relevance	23 (4.3)	9 (1.7)	2.672 (1.243-5.744)	0.012‡	2.851 (1.337-6.077)	0.007‡
Moderate relevance	120 (22.2)	86 (15.9)	1.394 (1.051-1.849)	0.021‡	1.421 (1.088-1.854)	0.010‡
Minor relevance	172 (31.8)	129 (23.8)	1.551 (1.240-1.940)	< 0.001†	1.536 (1.238-1.905)	< 0.001†

*Adjusted for age, sex and center; † Wald test with assumption of negative binomial distribution, ‡ Wald test with assumption of Poisson distribution
95%CI = 95% Confidence Interval

Table 3. Characteristics of incidental findings

Characteristic	Total-body CT	Standard work-up	p*
Incidental findings, n	441	290	
Body region, n (%)			0.786
Head	56 (12.7)	39 (13.4)	
Neck	26 (5.9)	22 (7.6)	
Thorax	65 (14.7)	47 (16.2)	
Abdomen / pelvis	292 (66.2)	180 (62.1)	
Extremities	2 (0.5)	2 (0.7)	
Organ system, n (%)			0.696
Renoadrenal	112 (25.4)	75 (25.9)	
Hepato-biliary	92 (20.9)	64 (22.1)	
Respiratory	55 (12.5)	27 (9.3)	
Reticulo-endothelial	49 (11.1)	33 (11.4)	
Neurological	33 (7.5)	25 (8.6)	
Endocrinological	27 (6.1)	21 (7.2)	
Gastro-intestinal	27 (6.1)	11 (3.8)	
Urethrogenital	18 (4.1)	15 (5.2)	
Cardiovascular	16 (3.6)	15 (5.2)	
Musculoskeletal	11 (2.5)	4 (1.4)	
Cutaneous	1 (0.2)	0 (0)	
Neoplasm			0.456
Confirmed	20 (4.5)	10 (3.4)	
Suspected	29 (6.6)	14 (4.8)	

* Chi^2 for distribution over categories

Table 3 shows comparisons of the distribution of the incidental findings over clinical categories between the two groups. Distribution over categories of relevance, body regions, organ systems or neoplasms was similar between the imaging groups. Table 2 and 3 in the appendix show the follow-up and medical documentation of incidental findings per category of relevance. These characteristics were comparable between the imaging groups, however follow-up rates were low and documentation of incidental findings was poor in both groups. In the discharge letters 39.3% of the major findings and 13.8% of the moderate findings were mentioned.

The complete list of all findings arranged by body region and relevance is presented in table 4 in the Appendix. Simple renal and hepatic cysts were most commonly found of all incidental findings for patients in both imaging groups. The suspicious pulmonary nodule was the most described potentially lethal finding (n=6). Of all findings of moderate relevance gallstones and hepatic steatosis were most frequently described. One in every twenty-four incidental findings was a pathologically confirmed neoplasm (4.1%).

Discussion

This study shows that in TBCT imaging, it is more likely to detect an incidental finding than during the standard work-up with selective CT scanning. In every category of clinical relevance, the TBCT scan detects significantly more findings. The incidental findings do not differ in distribution over body regions or tissue types, although the largest difference comes from the abdominal region. We could not demonstrate a significant difference in follow-up, which could be explained by low follow-up rates in general and poor documentation of incidental findings and their management in trauma patients. Trauma teams using TBCT scanning should be aware of an increase of relevant incidental findings and should pay special attention to reporting and management of these additional findings.

In the present study, incidental findings were found in 43% of patients undergoing TBCT scanning of which 42% may cause serious morbidity. Similar results were reported in previous studies on incidental findings in TBCT scans for initial trauma evaluation. These studies however did not make a direct comparison to incidental findings found by selective CT scanning. The study by Hofstetter et al. found incidental findings in 50% of their patients and 29% of the findings may require follow-up.[7] In another study by Barett et al. findings were detected in 53% of all patients by TBCT and 59% of these findings required urgent follow-up.[6] Sierink et al. recently found incidental findings in 45% of all patients and reported 31% of the findings may require follow-up.[8] Thus, with the present study included, the percentage of trauma patients with incidental findings detected by TBCT ranges from 43% to 53%. Of these findings 29% to 59% have clinical relevance, however definition of clinical relevance will be interpreted differently.

Considering future diagnostic work-up, the separate and detailed inclusion of moderate and major findings in the trauma room report's conclusion may help communicate these findings to the general practitioner and other treating physicians. Poor documentation could result in lack of further diagnostic work-up or treatment in other institutes; a structural problem also described in previous reports on CT in trauma and emergency imaging.[4,5,13,17-20] Thereby, complete and clear documentation might save costs in the long-term by eliminating repeated work-up for incidental findings. Future research should aim to appoint effective methods to grant proper reporting and management of incidental findings in trauma patients.

Limitations and strengths

The categorization of incidental findings in three relevance groups is subjective to personal interpretation as there is no consensus guideline. Discrepancies between previous studies show that specific findings are not always categorized in the same category of clinical relevance. To minimize the effect of interpretation, the categorization of expected incidental findings was done before data acquisition in concordance with

previous literature and under supervision of an experienced radiologist. The particular type of classification that was used in this study closely resembled those of previous studies.[4,6-8,14]

Secondly, the documentation of incidental findings in the radiology reports could be incomplete. The amount of incidental findings may have been influenced by the acute setting of trauma care, and therefore findings of minor or moderate interest may not have been reported at all since they seemed irrelevant during primary trauma care. However, the risk for underestimation is decreased by the double-reading system. On the other hand, the rate of unknown findings might be overestimated because previous imaging of the patient might not be available during formulation of the radiology report.

Thirdly, the follow-up is probably underestimated by reporting issues as well. Follow-up was done between 6 months and 2 years after first trauma presentation and only within the in-hospital documentation of the trauma centers where the patient was initially presented. Subsequently, some patients with e.g. pulmonary nodules would receive their first follow-up after 1 year or in a different hospital. Furthermore, it is possible that the finding was discussed and an expectative approach was preferred, but not reported in the patient files.

This study, that investigated the frequency and clinical relevance of incidental findings in trauma, is the first that directly compared TBCT scanning with conventional imaging supplemented with selective CT. Additional strengths include the international multicenter setting, large comparable patient groups and its randomization setting. Lastly, the list of expected incidental findings assisted in adequate prospective categorization.

Conclusion

When using TBCT scanning instead of selective CT scanning in primary trauma care more clinically relevant incidental findings can be expected. Data did not show a significantly higher workload through follow-up, however documentation on follow-up is suboptimal. When evaluating trauma patients with TBCT scanning, extra alertness towards detection, documentation and follow-up of relevant incidental findings is warranted.

Collaborators

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Appendix

Indications for immediate total-body CT in trauma patients used in REACT-2 trial

Trauma patients with one of the following parameters at hospital arrival:
- respiratory rate ≥30/min or ≤10/min
- pulse ≥120/min
- systolic blood pressure ≤100 mmHg
- estimated exterior blood loss ≥500 ml
- Glasgow Coma Score ≤13
- abnormal pupillary reaction

OR

Patients with a clinical suspicion of one of the following diagnoses:
- fractures from at least two long bones
- flail chest, open chest or multiple rib fractures
- severe abdominal injury
- pelvic fracture
- unstable vertebral fractures / spinal cord compression

OR

Patients with one of the following injury mechanisms:
- fall from a height (>3 meters / >10 feet)
- ejection from a vehicle
- death of occupant in same vehicle
- severely injured patient in same vehicle
- wedged or trapped chest / abdomen

Contra indications

Trauma patients with one of the following characteristics will be excluded:
- known age <18 years
- known pregnancy
- referred from another hospital
- clearly low-energy trauma with blunt injury mechanism
- any patient with a stab wound in one body region
- any patient who is judged to be too unstable to undergo a CT scan and requires (cardiopulmonary) resuscitation or immediate operation because death is imminent

Table 1. Indications for Selective CT scanning after conventional imaging

CT-brain
A patient with trauma of the head and with at least:
➔ **1 major criterion:**
- EMV ≤13
- loss of consciousness >30 minutes
- haemodynamically unstable
- age ≥60 years
- high-risk trauma
- vomiting
- posttraumatic seizure
- coagulopathy risk factors (primary or by medication)
- focal neurological deficit
- >1 point decline in EMV after 1 hour
- posttraumatic amnesia >4 hours
- clinical suspicion for skull base or facial fractures

➔ **and/or at least 2 minor criteria:**
- age between 40-60 years
- posttraumatic loss of consciousness
- posttraumatic amnesia 2-4 hours
- externally facial injuries without signs of fractures
- 1 point decline in EMV after 1 hour

CT of the cervical spine
1. Always when CT-brain is performed
2. In all patients unless they meet all the Nexus criteria:
   - no posterior midline cervical spine tenderness
   - no focal neurological deficit
   - a normal level of alertness
   - no evidence of intoxication
   - no painful distracting injuries

X-cervical spine
Never indicated. If Nexus deviant: cervical-CT.

Chest CT (with iv contrast)
1. Chest gunshot wound with suspicion of transmediastinal route
2. Acute aortic injury
3. Abnormal mediastinum seen at chest radiography.
   - mediastinal widening
   - pleural cap ('apical cap')
   - aorta arc unclear enclosed
   - left main bronchus removed downwards
   - deviated trachea or esophagus
   - filled aortopulmonary window
   - widened paraspinal line
   - widened paratracheal line right
4. Relative indications:
   - type and severity of trauma
   - fractures of costa 1 or 2
   - thoracic spine fracture
   - posterior sternoclavicular luxation
   - hesitation about the existence of pneumothorax / pneumomediastinum or pneumopericardium
   - fractures of the clavicle and shoulder

Abdominal CT (with iv contrast)
1. Penetrating injuries in abdomen, chest and/or flank
2. Deficits found with FAST
   - intra-abdominal free fluid
   - suspicion organ injury
   - suspicion retroperitoneal injury
3. Dislocated pelvic ring fracture and/or dislocated acetabulum fracture
4. Clinical suspicion of intraabdominal injury at physical examination
5. Subjective judgment of severity of injury by trauma leader
   - combined thoracic and pelvic injury
   - 'seatbelt sign'
   - chance fracture

X-thoracic and lumbar spine
Not indicated when chest or abdominal CT is performed (reconstructions can be made)
1. Complaints of the thoracic and lumbar spine
2. Tenderness of the thoracic and lumbar spine in the midline
3. Loss of consciousness
4. Deficits in peripheral neurologic examination
5. Painful distracting injuries

Pelvic CT (with iv contrast)
1. All pelvic ring and acetabulum fractures unless conventional imaging is sufficient for adequate diagnosis and treatment
2. After reposition of hip luxation with suspicion of femoral head fractures and/or acetabulum fracture.
   When CT-abdomen is performed, CT-pelvis is not necessary.

Retrograde urethrogram
1. Male patient with severe pelvic injury (type B and C)
2. Bleeding from the meatus, perineal injury or injury of the outer genital organs
3. Penetrating abdominal injury
4. In women only selectively after inspection

Imaging of the extremities
When fractures/dislocations are suspected: conventional imaging and selective CT.

Table 2. Follow-up for incidental findings

Characteristic	Total-body CT	Standard work-up	p*
Incidental finding of *major* relevance, n	24	9	0.129‡
Follow-up, n(%)	12 (50.0)	5 (55.6)	
No follow-up, n(%)	9 (37.5)	0 (0.0)	
Deceased in-hospital, n(%)*	3 (12.5)	4 (44.4)	
Incidental finding of *moderate* relevance, n	160	115	0.141†
Follow-up, n(%)	10 (6.3)	13 (11.3)	
No follow-up, n(%)	126 (78.8)	86 (74.8)	
Deceased in-hospital, n(%)*	24 (15.0)	16 (13.9)	
Incidental finding of *minor* relevance, n	257	166	0.735†
Follow-up, n(%)	1 (0.4)	1 (0.6)	
No follow-up, n(%)	227 (88.3)	141 (84.9)	
Deceased in-hospital, n(%)*	29 (11.3)	24 (14.5)	

* Incidental findings in patients deceased in-hospital were excluded from this analysis

† Chi2, ‡ Fisher's exact

Table 3. Documentation of incidental findings

Characteristic	Total-body CT	Standard work-up	p
Incidental finding of *major* relevance, n	24	9	
Trauma letter, n(%)	10 (41.7)	5 (55.6)	0.697†
Discharge letter, n(%)	10 (41.7)	3 (33.3)	0.999†
Incidental finding of *moderate* relevance, n	160	115	0.816*
Trauma letter, n(%)	31 (19.4)	21 (18.3)	**0.455***
Discharge letter, n(%)	20 (12.5)	18 (15.7)	
Incidental finding of *minor* relevance, n	257	166	
Trauma letter, n(%)	11 (4.3)	9 (5.4)	0.642†
Discharge letter, n(%)	13 (5.1)	6 (3.6)	0.632†

* Chi^2, † Fisher's exact

Table 4. List of incidental findings in 1083 trauma patients categorized by body region and clinical relevance.

Location			Frequency	Percentage
Head	Major			
		mass, brain	4	0.5%
	Moderate			
		aneurysm, brain, <5.5cm	1	0.1%
		cranial osteoma	5	0.7%
		leukoaraiosis <50 years	2	0.3%
	Minor			
		retention cyst	27	3.7%
		leukoaraiosis >50 years	25	3.4%
		brain calcification	16	2.2%
		arachnoid cyst	10	1.4%
		brain cyst	2	0.3%
		cisterna magna, large	1	0.1%
		colloid cyst	1	0.1%
		parotid stone	1	0.1%
Neck	Major			
		-		
	Moderate			
		thyroid nodule	22	3.0%
		cervical lymphadenopathy	3	0.4%
		thyroid lesion	6	0.8%
		goitre / struma	5	0.7%
		mass, thyroid	1	0.1%
		esophageal hyperplasia	1	0.1%
		thyroid cyst, complicated	1	0.1%
	Minor			
		cervical lymphadenopathy	5	0.7%
		thyroid calcification	2	0.3%
		thyroid cyst, simple	1	0.1%
Thorax	Major			
		pulmonary nodule, tumorous aspect	6	0.8%
		mass, breast	1	0.1%
		penetrating aortic ulcer	1	0.1%
		pulmonary lesion, tumorous aspect	1	0.1%
		thoracic lymphadenopathy	1	0.1%
	Moderate			
		Cardiomegaly	10	1.4%
		pulmonary nodule, relevant	6	0.8%
		COPD	3	0.4%

Location			Frequency	Percentage
		aneurysm, thoracic, <5,5cm	1	0.1%
		atelectasis	2	0.3%
		gynecomastia	1	0.1%
		heart valve calcification	1	0.1%
		intrathoracic struma	1	0.1%
		mammary nodule	1	0.1%
		pleural fluid	1	0.1%
		pleural plaques	3	0.4%
		pleural thickening	1	0.1%
		pulmonary consolidation	4	0.5%
		pulmonary lesion, relevant	2	0.3%
		sternal hemangioma	1	0.1%
		thoracic lymphadenopathy	5	0.7%
	Minor			
		thymus remainder	20	2.7%
		pulmonary nodule, small aspecific	13	1.8%
		azygos lobe	1	0.1%
		congenital vascular anomalies	3	0.4%
		pericardial cyst	2	0.3%
		pericardial effusion	1	0.1%
		pulmonary cyst, simple	7	1.0%
		pulmonary granuloma	6	0.8%
		sebaceous cyst	1	0.1%
		thoracic lymphadenopathy	8	1.1%
Abdomen/Pelvis	Major			
		aneurysm, abdominal, >5.5cm	1	0.1%
		dissection, abdominal	1	0.1%
		mass, adrenal	6	0.8%
		mass, bladder	1	0.1%
		mass, hepatic	1	0.1%
		mass, pararectal	1	0.1%
		mass, para-splenic	1	0.1%
		mass, renal	4	0.5%
		pancreatic lesion, complicated	1	0.1%
		penetrating aortic ulcer	1	0.1%
	Moderate			
		gallstone	27	3.7%
		hepatic steatosis	25	3.4%
		hepatic nodule, relevant	12	1.6%
		renal cyst, complicated	12	1.6%
		renal stone	12	1.6%
		abdominal aortic aneurysm, <5.5cm	1	0.1%
		abdominal aortic stenosis	1	0.1%
		abdominal lymphadenopathy	5	0.7%

Location		Frequency	Percentage
	adrenal hyperplasia	5	0.7%
	adrenal hypertrophy	1	0.1%
	adrenal lesion, relevant	6	0.8%
	adrenal nodule, relevant	5	0.7%
	aneurysm, abdominal, <5.5cm	4	0.5%
	cryptochordism	3	0.4%
	cutaneous nodule, relevant	1	0.1%
	diaphragmatic hernia	3	0.4%
	hepatic cyst, complicated	4	0.5%
	hepatic lesion, relevant	6	0.8%
	hernia inguinalis	1	0.1%
	hernia umbilicalis	1	0.1%
	horseshoe kidney	3	0.4%
	hydrocele testis	1	0.1%
	hydronephrosis	4	0.5%
	monokidney	1	0.1%
	pancreatic atrophy	7	1.0%
	pancreatic calcification	3	0.4%
	pancreatic cyst	3	0.4%
	pancreatic steatosis	2	0.3%
	pneumaturia	1	0.1%
	porcelain gallbladder	1	0.1%
	prostatic hypertrophy	8	1.1%
	renal atrophy	2	0.3%
	renal lesion, complicated	1	0.1%
	Riedel's hepatic lobe	1	0.1%
	splenic lesion, relevant	2	0.3%
	suspected fibromuscular dysplasia	1	0.1%
	vesical calculus	1	0.1%
Minor			
	renal cyst, simple	97	13.3%
	hepatic cyst, simple	50	6.8%
	diverticulosis	35	4.8%
	spleen, accessory	20	2.7%
	hepatic lesion, simple	11	1.5%
	abdominal lymphadenopathy	6	0.8%
	adrenal cyst, simple	2	0.3%
	adrenal lesion, simple	4	0.5%
	adrenal nodule, simple	3	0.4%
	bladder diverticulum	3	0.4%
	corpus luteum cyst	1	0.1%
	duplex collecting system	1	0.1%
	fluid in rectouterine pouch	3	0.4%
	intestinal malrotation	1	0.1%
	ovarian cyst, <5cm	3	0.4%

Location			Frequency	Percentage
		prostatic calcification	10	1.4%
		renal calcification	1	0.1%
		renal cortex, thinning	2	0.3%
		renal ectopia	1	0.1%
		renal lesion, simple	3	0.4%
		splenic cyst, simple	4	0.5%
		urachal cyst	1	0.1%
		uterine calcification	4	0.5%
		uterine fibroid	1	0.1%
Extremities	Major			
		-		
	Moderate			
		bone lytic lesion	2	0.3%
	Minor			
		bone cyst, simple	1	0.1%
		bone lesion, simple	1	0.1%

7

Early detection of severe injuries after major trauma by immediate total-body CT scouts

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Abstract

Introduction

Evaluation of immediate total-body CT (iTBCT) scouts during primary trauma care could be clinically relevant for early detection and treatment of specific major injuries. The aim of this study was to determine the diagnostic usefulness of TBCT scouts in detecting life-threatening chest and pelvic injuries.

Methods

All patients who underwent an iTBCT during their primary trauma assessment in one trauma center between April 2011 and November 2014 were retrospectively included. Two experienced trauma surgeons and two emergency radiologists evaluated iTBCT scouts with structured questionnaires. Inter-observer agreement and diagnostic properties were calculated for endotracheal tube position and identification of pneumo- and/or hemothorax and pelvic fractures. Diagnostic properties of iTBCT scouts for indication for chest tube placement and pelvic binder application were calculated in comparison to decision based on iTBCT.

Results

In total 220 patients with a median age of 37 years (IQR 26-59) were selected with a median Injury Severity Score of 18 (IQR 9-27). There was moderate to substantial inter-observer agreement and low false positive rates for pneumo- and/or hemothorax and for severe pelvic fractures by iTBCT scouts. For 19.8% to 22.5% of the endotracheal intubated patients trauma surgeons stated that repositioning of the tube was indicated. Positive predictive value and sensitivity were respectively 100% (95%CI 52%-100%) and 50% (95%CI 22%-78%) for decisions on chest tube placement by trauma surgeon 1 and 67% (95%CI 13%-98%) and 22% (95%CI 4%-60%) for decisions by trauma surgeon 2. Only in one of 14 patients the pelvic binder was applied after iTBCT acquisition.

Conclusions

iTBCT scouts can be useful for early detection of pneumo- and/or hemothorax and severe pelvic fractures. Decision for chest tube placement based on iTBCT scouts alone is not recommended.

Introduction

Improvements in speed and accuracy of Computed Tomography (CT) made immediate Total Body CT (iTBCT) feasible as a diagnostic tool in the primary care for severe trauma patients. Initial trauma care for severe trauma patients can be improved when the step-up approach of conventional imaging and selective CT is omitted and an iTBCT is performed instead. iTBCT scanning is safe, shortens the time to end of imaging and does not increase direct medical costs. However, it has not been demonstrated to improve survival for patients with severe trauma.[1]

After positioning the patient the first step in obtaining a CT is acquisition of a scout. CT scouts are primarily used for the planning of scanning the body regions of interest. Additionally, it is essential for good functioning of dose modulation techniques and thus can contribute to the reduction of radiation exposure. Scout images provide an immediate overview of the body that resembles conventional radiography and could give diagnostic information while awaiting further CT scan acquisition. Assessment of CT scouts has been reported to add value to detection of musculoskeletal findings by CT only.[2-4] Several studies suggest the use of CT scouts to rule out vertebral fractures, with sensitivity ranging from 70-98.7% and specificity 99.7-100%.[5-7] However, little is known about the possibilities of detection of chest or pelvic injury by CT scouts.

Evaluation of iTBCT scouts while the trauma team waits for the complete iTBCT could be clinically relevant for early detection and associated early treatment of specific major injuries. Trauma surgeons than could decide to interrupt the acquisition of the TBCT for intervention or could perform an intervention immediately after iTBCT acquisition without prior interpretation of the other CT images. The aim of this study was to determine the diagnostic properties of iTBCT scouts for 1) detecting life-threatening chest and pelvic injuries, and 2) indications for chest tube placement and pelvic binder application in trauma patients.

Methods

Study design and patient population

The study was a retrospective cohort study on all consecutive patients who underwent an iTBCT during their primary trauma assessment in one trauma center between April 22, 2011 and November 1, 2014. After obtaining vital parameters, a physical examination and potential life-saving interventions (*e.g.*, securing airway, chest tube placement, or hemorrhage control measures) the trauma team proceeded to CT scanning in the same or adjacent trauma resuscitation room. Prior conventional imaging (*i.e.*, chest / pelvic radiographs and focused assessment by sonography in trauma) was omitted. iTBCT scouts consisted of a lateral scout of the head and cervical spine, and an anteroposterior scout of chest, abdomen and pelvis. Two experienced trauma

surgeons (VJ and IB) and two experienced emergency radiologists (LB and SK) evaluated the anonymized images (DICOM standard, extracted from PACS) from the iTBCT scouts independently from each other and blinded for iTBCT outcome. Findings were reported using a structured web-based questionnaire for each case. The clinical reports and radiology reports of the iTBCT performed consecutively after the scout and AIS (Abbreviated Injury Score) were used as reference standard for these findings.

The structured questionnaires provided the observers with the following patient information: age, sex, trauma mechanism, in-hospital vital parameters (respiratory rate, blood pressure, pulse, Glasgow coma scale), and pre-hospital interventions (endotracheal intubation, placement of chest tube or pelvic binder). For every case the observer answered if the following major findings were present: endotracheal tube mal-placement, hemothorax or pneumothorax or a pelvic fracture. As an alternative the observer could state the quality of the imaging was insufficient to recognize these findings. When a major finding was recognized the observer had to answer if endotracheal tube repositioning, chest tube placement or application of a pelvic binder was indicated. For every case a list of other relevant findings could be checked and a free text field was available to describe other findings. Finally the observer could state if the iTBCT scout was of inferior quality and if so, for which reason. The local medical research ethics committee decided that the study was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO).

Statistical analysis

Continuous data with a normal distribution are presented as means with standard deviation and non-normally distributed data are presented as medians with interquartile ranges. To measure the inter-observer agreement on presence of endotracheal tube mal-placement, hemo- or pneumothorax and pelvic fractures Fleiss' kappa were calculated for all 4 observers and Cohen's kappa for coupled observers. Observers were coupled by profession and in simulated teams (4 combinations of two trauma surgeons and two radiologists). Fleiss' and Cohen's kappa values were interpreted according to the categorical rating of Landis and Koch: poor agreement < 0; slight agreement, 0.00-0.20; fair agreement, 0.21-0.40; moderate agreement, 0.41-0.60; substantial agreement, 0.61-0.80; and almost perfect agreement, 0.81-1.00.[8]

The sensitivity, specificity, positive predictive value and negative predictive value for diagnosis of hemo- and/or pneumothorax and pelvic fractures with an Abbreviated Injury Scale (AIS) ≥3 by iTBCT scout were calculated in comparison to the Abbreviated Injury Scores derived from iTBCT reports. The sensitivity, specificity, positive predictive value and negative predictive value for the decision to perform an intervention based on the iTBCT scout were calculated in comparison to the actual interventions performed on iTBCT results. Interventions consisted of placement of a chest tube for pneumo- or hemothorax or application of a pelvic binder for unstable pelvic fractures. Confidence intervals for diagnostic test characteristics were calculated using Wilson procedure with correction for continuity.[9]

The rate of other potential relevant findings on iTBCT scouts is presented in the appendix. Reasons for inferior quality scouts are listed in the appendix as well. Statistical analyses were performed with SPSS version 24 (IBM Corp., Armonk, NY; 2016). Binomial confidence intervals were calculated using vassarstats.net. Analyses for pooling data and confidence intervals of pooled data were performed with MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; 2018).

Results

In this study 220 patients with a median age of 37 years (IQR 26-59) were included. Most of them sustained blunt trauma (95.0%). Median Injury Severity Score (ISS) was 18 (IQR 9-27). In all 220 patients iTBCT was indicated and performed. In 17 patients (7.7 %) chest radiographs were done before iTBCT; pelvic radiographs in 3 patients (1.4 %) and FAST in 6 patients (2.7 %). Endotracheal intubation was performed in 102 patients (46.4%) before arrival in the trauma room or before iTBCT scanning. Chest tubes were placed in 30 patients (13.6%). In 12 patients (40.0%) chest tubes were placed before iTBCT scanning. Pelvic binders were placed in 14 patients (6.4%). Only one of these pelvic binders was applied after iTBCT scanning. See Table 1 for demographic and clinical characteristics.

Table 1. Demographic and clinical characteristics.

Characteristic	**(n=220)**
Age (years)	37 (26-59)
Male sex, n (%)	168 (76.4)
Blunt trauma, n (%)	209 (95.0)
Pre-hospital / trauma room interventions, n (%)	
Endotracheal intubation	102 (46.4)
Chest tube placement	30 (13.6)
- Before TBCT	12 (40.0)
- After TBCT	18 (60.0)
Pelvic binder placement	14 (6.4)
- Before TBCT	13 (92.9)
- After TBCT	1 (7.1)
Pneumo- and/or hemothorax, n (%)	48 (21.8)
Pelvic fracture AIS ≥3, n (%)	22 (10.0)
AIS ≥3, n (%)	
Head	90 (40.9)
Chest	75 (34.1)
Abdomen	20 (9.1)
Extremities	55 (25.0)
Injury Severity Score (points)	18 (9-27)
Polytrauma patients, n (%)*	129 (58.6)

Data are number (%) or median (interquartile range).

AIS denotes Abbreviated Injury Scale.

* Polytrauma patients are defined as ISS ≥16.

Inter-observer variability of findings on iTBCT scouts is shown in Table 2. For the evaluability of endotracheal tube position there was poor, respectively slight agreement between radiologists and within simulated teams (K -0.03, 95% CI -0.05 – 0.00 and K 0.13, 95% CI 0.03 – 0.23). For diagnosing pneumo- and / or hemothorax on iTBCT scouts there was moderate agreement between radiologists (K 0.57, 95% CI 0.35-0.79) and substantial agreement within simulated teams (K 0.61, 95% CI 0.49 – 0.73). For diagnosing pelvic fractures on iTBCT scouts there was substantial agreement between radiologists and within simulated teams (K 0.73, 95% CI 0.57 – 0.90 and K 0.64, 95% CI 0.46 – 0.81).

Sensitivity for radiologist agreement on pneumo- and / or hemothorax by iTBCT scout was 26% (95% CI 13% – 44%) and 21% (95% CI 15% – 29%) for agreement in simulated teams. Positive predictive value was 100% (95% CI 63% – 100%) for agreement between radiologists and 93% (95% CI 78% – 99%) for agreement in simulated teams. Sensitivity for radiologist agreement on severe pelvic fractures (AIS ≥3) by TBCT scout was 53% (95% CI 29% – 75%) and 56% (95% CI 43% – 68%) for agreement in simulated teams. Positive predictive value was 71% (95% CI 42% – 90%) for agreement between radiologists and 73% (95% CI 59% – 85%) for agreement in simulated teams. See Table 3 for diagnostic properties for findings by iTBCT scouts.

Within the endotracheal intubated patients for whom the position of the tube was evaluable by iTBCT scout for 19.8% to 22.5% of the patients trauma surgeons stated that repositioning of the tube was indicated. Within the observed pneumo- or hemothorax for 8.9% to 18.9% of the patients the trauma surgeons were confident to decide for chest tube placement. See Table 4 for decisions for interventions by trauma surgeons based on iTBCT scouts.

Table 5 shows the predictive value of iTBCT scouts for the indication of chest tubes compared to the actual chest tube placement performed after iTBCT scanning. Positive predictive value was 100% (95% CI 52% – 100%) within 6 decisions for chest tube placement by trauma surgeon 1 and 67% (95% CI 13% – 98%) within 3 decisions for chest tube placement by trauma surgeon 2. Sensitivity of TBCT scout for chest tube indication was 50% (95% CI 22% – 78%) and 22% (95% CI 4 % – 60 %) within patients for whom pneumo- or hemothorax was detected by iTBCT scout assessment. Calculation of diagnostic properties of iTBCT scouts for the indication of pelvic binders was omitted because there was only one pelvic binder applied after iTBCT acquisition.

Discussion

The results of this study suggest that iTBCT scouts can be used for early detection of pneumo- and or hemothorax and pelvic fractures with moderate to substantial inter-observer agreement and low false positives compared to diagnosis by iTBCT. Our data could not support decisions for chest tube placement neither for pelvic binder

Table 2. Inter-observer variability of findings by iTBCT scouts.

		All observers (4)		**Radiologists (2)**		**Trauma surgeons (2)**		**Simulated teams (4x2)**	
Characteristic	n	Kappa* (95% CI)	Absolute agreement (%)	Kappa† (95% CI)	Absolute agreement (%)	Kappa† (95% CI)	Absolute agreement (%)	Pooled Kappa† (95% CI)	Mean absolute agreement (%)
Endotracheal tube position	102	0.22 (0.15-0.30)	76.5	-0.03 (-0.05-0.00)	94.1	0.58 (0.37-0.79)	88.2	0.13 (0.03-0.23)	83.9
Pneumo- or hemothorax	208	0.57 (0.52-0.63)	91.3	0.57 (0.35-0.79)	94.2	0.42 (0.13-0.71)	95.2	0.61 (0.49-0.73)	95.7
Pelvic fracture	220	0.63 (0.57-0.68)	90.5	0.73 (0.57-0.90)	95.9	0.50 (0.27-0.73)	93.6	0.64 (0.46-0.81)	94.8

Data are Kappa values (95% Confidence Interval) and proportions. Not intubated patients were excluded for analysis on evaluability of endotracheal tube position (n=118). Patients with chest tubes placed before TBCT were excluded for analysis on Hemo- or pneumothorax (n=12).

* Fleiss' kappa; † Cohen's kappa

CI denotes Confidence interval.

Table 3. Diagnostic properties for findings by iTBCT scouts.

		Sensitivity (%)		**Specificity (%)**		**PPV (%)**		**NPV (%)**	
	n		95% CI		95% CI		95% CI		95% CI
Pneumo- and / or hemothorax									
All observers	190	**14**	(5 – 33)	**100**	(97 – 100)	**100**	(40 – 100)	**87**	(81 – 91)
Both radiologists	196	**26**	(13 – 44)	**100**	(97 – 100)	**100**	(63 – 100)	**86**	(80 – 91)
Both trauma surgeons	198	**13**	(4 – 31)	**100**	(97 – 100)	**100**	(40 – 100)	**86**	(80 – 90)
Simulated teams		**21**	(15 – 29)	**100**	(99 – 100)	**93**	(78 – 99)	**86**	(83 – 88)
Pelvic fracture AIS ≥3									
All observers	199	**40**	(17 – 67)	**99**	(97 – 100)	**86**	(42 – 99)	**95**	(91 – 98)
Both radiologists	211	**53**	(29 – 75)	**98**	(94 – 99)	**71**	(42 – 90)	**95**	(91 – 98)
Both trauma surgeons	206	**39**	(18 – 64)	**99**	(97 – 100)	**88**	(47 – 99)	**94**	(90 – 97)
Simulated teams		**56**	(43 – 68)	**98**	(97 – 99)	**73**	(59 – 85)	**95**	(93 – 96)

CI denotes confidence interval and AIS denotes Abbreviated Injury Scale.
Patients with chest tubes placed before TBCT were excluded (n=12).

Table 5. Decision for chest tube by TBCT scout vs. actual decision by iTBCT.

		Sensitivity (%)		**Specificity (%)**		**PPV (%)**		**NPV (%)**	
	n		95% CI		95% CI		95% CI		95% CI
Trauma surgeon 1	36	**50**	(22-78)	**100**	(83-100)	**100**	(52-100)	**80**	(61-92)
Trauma surgeon 2	44	**22**	(4-60)	**97**	(83-100)	**67**	(13-98)	**83**	(67-92)

CI denotes confidence interval.
Patients with chest tubes placed before TBCT were excluded (n=12), another patient was excluded for this analysis since an infaust prognosis made the trauma team stop treatment directly after the TBCT

Table 4. Indication for interventions by trauma surgeons based on iTBCT scouts.

		Indicated		Unclear		Not indicated	
	n	n	%	n	%	n	%
ETT repositioning							
Trauma surgeon 1	81	16	19.8	0	0.0	65	80.2
Trauma surgeon 2	89	20	22.5	1	1.1	68	76.4
Indication chest tube							
Trauma surgeon 1	37	7	18.9	25	67.6	5	13.5
Trauma surgeon 2	45	4	8.9	33	73.3	8	17.8

Data are number (%).
ETT denotes endotracheal tube.

application based on iTBCT scouts alone. Indication for chest tube placement remains often unclear on scouts and in only few cases trauma surgeons feel confident to act based only on the scouts. Low sensitivity for these findings implicates iTBCT scout could not be used for exclusion of pneumo- and or hemothorax and pelvic fractures. Furthermore, clinical signs should be imminent and in accordance to scout findings to support early intervention before complete CT scan acquisition.

To our knowledge this is the first study to investigate the diagnostic value of iTBCT scouts for major chest and pelvis injuries. If used for the detection of life-threatening injuries, the TBCT scout could be compared to a Lodox statscan, a low-dose x-ray of the total body.[10-12] Yang et al. performed a review on total body x-rays in acute medical emergencies. Injuries studied were pneumothorax, pelvic fractures and spine fractures. Overall sensitivity ranged from 62% to 73%, and specificity from 99% to 100% compared with CT for the evaluation of polytrauma patients. Sensitivity for pneumo- and or hemothorax ranged from 53.6% to 79.2% and specificity ranged from 99.3 % to 100.0 %. Sensitivity for pelvic fractures ranged from 64.4% to 85.7% and specificity ranged from 99.0% – 100.0%.[13] When comparing this to the results of this study, diagnostic properties for iTBCT scout seem inferior to the properties of the Lodox statscan. This might be explained by differences in resolution, the primary diagnostic purpose of the Lodox statscan and a potential learning curve for imaging assessment.

To add value to the primary trauma assessment iTBCT scouts should have high positive predictive value for indication of interventions to ensure a low false positive rate leading to futile interventions. In case of high false positive rates for interventions it is preferable to wait for the results of the iTBCT scan that follow relatively shortly.

Limitations

Several characteristics of the scout assessments did not fit current practice. The format (DICOM) of the scout and the screen on which it is presented outdo those currently available before and during iTBCT acquisition. The time pressure and demanding environment that one may experience during acute trauma care was not present dur-

ing the assessments of the observers. These characteristics could decrease the actual diagnostic properties of the iTBCT scout.

Diagnostic properties of CT scouts might improve when made for diagnostic purposes instead of determination of the borders of the body regions of interest. Enhancing the quality for diagnostic purposes could consume extra time, increase radiation exposure and should therefore only be performed when it results in early treatment, which could not be demonstrated so far. A potential learning curve for scout assessment could have affected the results and underestimate the diagnostic properties as trauma surgeons and radiologists have not been trained for scout assessments.

Time intervals were not recorded in the present study. In the REACT-2 trial time to start imaging was 14 minutes (IQR 9-19) for iTBCT and 6 minutes (IQR 4-10) for the standard work-up (STWU); i.e.: chest and pelvic x-ray, FAST and selective CT scanning (unpublished REACT-2 data). Obtaining a chest and pelvic x-ray is faster than obtaining a CT scout. However, the iTBCT scout is already part of the acquisition of the iTBCT scan that provides definitive diagnosis in 50 minutes (38-68) after trauma room arrival compared to 58 minutes (42-78) for the standard work-up (p=0.001).[1]

It is recommendable to only perform immediate TBCT scanning on patients with suspected severe injuries in the trauma resuscitation room or in the adjacent room and the trauma team has direct access to the patient and has options for potential life-saving interventions any moment. In this study iTBCT was performed in the trauma resuscitation room or in the adjacent trauma resuscitation room and therefore the results of the present study will not apply to trauma centers without CT scanner in or adjacent to the trauma resuscitation room.

The structured questionnaire and internal control of the findings by iTBCT reports made the study design suitable for testing the concept of early diagnosis and treatment based on iTBCT scouts during the initial trauma assessment. The relatively low number of cases in which trauma surgeons were confident to place chest tubes after iTBCT scout assessment implies a larger study population is needed. Furthermore, a clinically relevant improvement might not be expected when iTBCT scout is of limited diagnostic value for only few patients when iTBCT results follow shortly.

Conclusion

Immediate total-body CT scouts can be useful for early detection of pneumo- and or hemothorax and severe pelvic fractures. However, further research is needed to support decisions for chest tube placement and pelvic binder application based on TBCT scouts alone. At present it is preferable to wait for the results of the iTBCT scan that follow relatively shortly before decisions on interventions are made.

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Appendix

Table 1. Relevant findings on TBCT scout documented additional to the structured questionnaire, n (%).

Characteristic	(n=220)
Head	
Skull fracture	3 (1.4)
Thorax	
Lung contusion	72 (32.7)
Multiple rib fractures	43 (19.5)
Subcutaneous emphysema	18 (8.2)
Pneumomediastinum	6 (2.7)
Suspicion of diaphragmatic rupture	3 (1.4)
Signs of aspiration	2 (0.9)
Lung oedema	1 (0.5)
Abdomen	
Distended stomach (indication for nasogastric tube)	36 (16.4)
Spine	
Cervical vertebrae fracture	4 (1.8)
Thoracic vertebrae fracture	6 (2.7)
Upper extremities	
Clavicle fracture	16 (7.3)
Other fracture	5 (2.3)
Contra-indication elevation of upper extremities	25 (11.4)
Lower extremities	
Femur fracture	24 (10.9)
Crural fracture	2 (0.9)
Hip dislocation	1 (0.5)
Other	
Bullet in situ	4 (1.8)

Table 2. Reasons for inferior quality TBCT scouts, n (%).

Characteristic	(n=220)
Scan related	
Partial imaging	10 (4.5)
Poor image quality (resolution/stripes)	6 (2.7)
Patient related	
External objects belonging to patient	8 (3.6)
Medical equipment	5 (2.3)
Upper extremities	5 (2.3)
Movement during scanning	4 (1.8)
Spine board	3 (1.4)
Adiposity	2 (0.9)
In situ material	1 (0.5)

Summary

This thesis has focused on the consequences of immediate total-body CT (iTBCT) scanning in comparison to the standard work-up (STWU) and the indication for iTBCT scanning after severe trauma in a large randomized controlled trial. Next to the effect on clinical outcomes, the effect on clinically relevant time intervals, radiation exposure and health economics effects were evaluated. These effects were also evaluated specifically for patients in need for emergency bleeding control interventions. The criteria for iTBCT were reconsidered in order to select the more severely injured patients and reduce the chance on unnecessary radiation exposure for the less severely injured patients.

In **Chapter 1** we compared in-hospital mortality in trauma patients after iTBCT scanning to the STWU in a multicenter randomized trial. Trauma patients with compromised vital parameters, clinical suspicion of life-threatening injuries or severe injury mechanisms were eligible. Secondary endpoints were radiation exposure, clinically relevant time intervals, missed injuries and hospital costs. The in-hospital mortality rate was not statistically different between groups (iTBCT 15.9% vs. STWU 15.7%, P=0.923). Subgroup analyses in polytrauma patients also did not reveal a significant difference between groups (iTBCT 22.4% vs. standard 24.8%, P=0.457). Imaging time in the trauma room (30 min vs. 37 min, P<0.001) was decreased in iTBCT patients. Substantially more patients in the STWU group received a lower effective radiation dose (21.0mSv [IQR=20.9-25.2] versus 20.6mSv [IQR=11.8-27.6], P<0.001). iTBCT was safe, shortened the imaging time and did not increase the hospital costs. On the other hand, iTBCT did not improve survival, and most patients in the STWU group received a lower radiation dose.

In **Chapter 2** the cost-effectiveness of iTBCT scanning is compared with the STWU during the initial trauma evaluation. Hospital health care costs and health outcomes were determined in the REACT-2 population for the first six months following trauma. A total of 928 Dutch patients with complete clinical follow-up were included. Mean costs of hospital care were €25,809 (95% bcaCI: €22,617 to €29,137) for the iTBCT group (N=456) and €26,155 (95% bcaCI: €23,050 to €29,344) for the standard work-up group, saving €346 (95% bcaCI: -€4,987 to €4,328; P=0.876). The percentages of patients alive at six months were similar. The difference in percentages of patients alive without serious morbidity was 61.6% in the iTBCT group versus 66.7% in the standard work-up group (difference 5.1%, P=0.104). The probability of iTBCT being cost-effective in keeping patients alive remained below 0.56 in the whole group, but was higher in multitrauma patients (0.8-0.9) and in patients with traumatic brain injury (over 0.9). From a

hospital health care provider perspective, iTBCT scanning should economically be the diagnostic strategy of first choice in multitrauma or traumatic brain injury patients.

Fast and detailed diagnostics could be especially beneficial for trauma patients in need of emergency bleeding control interventions. In **Chapter 3** we assessed whether an initial trauma assessment with iTBCT is associated with lower mortality in patients requiring emergency bleeding control interventions. In the REACT-2 trial 1083 patients were enrolled of which 172 (15.9%) underwent emergency bleeding control interventions following their initial trauma assessment. Within these 172 patients 85 (49.4%) underwent iTBCT as primary diagnostic modality during the initial trauma assessment. Reduction of mortality in trauma patients requiring emergency bleeding control interventions by iTBCT could not be demonstrated in this study; 12.9 % (95% CI 7.2%-21.9%) in the iTBCT group compared to 24.1 % (95% CI 16.3%-34.2%) in the STWU group (p=0.059). However, a potentially clinically relevant absolute risk reduction of 11.2% (95% CI -0.3% to 22.7%) in comparison with STWU was observed. Time to bleeding control intervention was not reduced significantly; 82 min (IQR 57-121) vs. 98 min (IQR 62-147), p=0.108.

Since we could not demonstrate a reduction in mortality and because of a relatively low inclusion rate of polytrauma patients in the REACT-2 trial we had to reconsider which patients could benefit from TBCT and how to select these patients. **Chapter 4** gives an overview of currently used criteria for total-body CT in trauma patients and describes mortality and Injury Severity Scores of patient groups selected for TBCT. A systematic review was performed by searching Medline and Embase databases. Studies evaluating or describing criteria for selection of patients with potentially severe injuries for TBCT during initial trauma care were included. In addition, studies comparing total-body CT during the initial assessment of injured patients with conventional imaging and selective CT in specific patient groups were included. Thirty eligible studies were identified. Three studies evaluated criteria for TBCT in trauma with divergent methods. Combinations of compromised vital parameters, severe trauma mechanisms and clinical suspicion on severe injuries are often used criteria; however clinical judgement is used as well. Studies describing criteria for TBCT selected patients in different ways and were difficult to compare regarding mortality and injury severity. Criteria for TBCT in trauma show a wide variety in structure and cut-off values for vital parameters and trauma mechanism dimensions. This study showed that consensus on criteria for TBCT in trauma is lacking.

In **Chapter 5** we aimed to refine the criteria for immediate total-body CT after severe trauma by using the prospectively gathered criteria for iTBCT of the REACT-2 patients. By logistic regression analysis with backward selection on the 15 study inclusion crite-

ria a revised set of criteria was derived and subsequently tested for prediction of severe injury by comparing positive predictive value (PPV), sensitivity and receiver operating characteristics (ROC). Backward logistic regression resulted in a revised set consisting of nine original study inclusion criteria and one adjusted criteria. PPV improved from 76% (95% CI 74%-79%) to 82% (95% CI 80%-85%). Sensitivity decreased by 9% (95% CI 7%-11%). The area under the ROC curve remained equal and was 0.80 (95% CI 0.77-0.83) for the revised set compared to 0.80 (95% CI 0.77-0.83) for the original set. The revised set retains 8.78 mSv (95% CI 6.01-11.56) for 36% of the non-severely injured patients. The selection criteria for iTBCT can be reduced from 15 to 10 clinical criteria.

In **Chapter 6** we aimed to confirm and quantify the expected increase of incidental findings by iTBCT compared to the STWU. Secondly, we tested whether this increase was also present within different categories of clinical relevance and divided them in three categories: 1) Major finding, may cause mortality, 2) Moderate finding, may cause morbidity and 3) Minor finding, hardly relevant. Generalized estimating equations were applied to assess differences in incidental findings.
Immediate total-body CT scanning resulted in more patients with incidental findings and 1.5 times more incidental findings. This increase in incidental findings was detected in every category of clinical relevance. Major findings were detected in 23 patients (4.3%) in the iTBCT group compared to 9 patients (1.7%) in the STWU group (Adjusted rate ratio 2.851; 95% CI 1.337-6.077; $p<0.007$). Findings of moderate relevance were detected in 120 patients (22.2%) in the iTBCT group compared to 86 patients (15.9%) in the STWU group (Adjusted rate ratio 1.421; 95% CI 1.088-1.854; $p<0.010$). When using iTBCT scanning instead of selective CT scanning in primary trauma care more clinically relevant incidental findings can be expected. Data did not show a significantly higher workload through follow-up, however documentation on follow-up is suboptimal. When evaluating trauma patients with iTBCT scanning, extra alertness towards detection, documentation and follow-up of relevant incidental findings is warranted.

In **Chapter 7** we explored the diagnostic usefulness of iTBCT scouts in detecting life-threatening chest and pelvic injuries. All patients who underwent an iTBCT during their primary trauma assessment in one trauma center were retrospectively included. Two experienced trauma surgeons and two emergency radiologists evaluated iTBCT scouts with structured questionnaires. Inter-observer agreement and diagnostic properties were calculated for endotracheal tube position and identification of pneumothorax and/or hemothorax and pelvic fractures. Diagnostic properties of iTBCT scouts for indication for chest tube placement and pelvic binder application were calculated in comparison to decision based on iTBCT. In total 220 patients with a median age of 37 years (P_{25}-P_{75} 26-59) were selected with a median Injury Severity Score of 18 (P_{25}-P_{75} 9-27). There was moderate to substantial inter-observer agreement and low false positive rates for pneumothorax and/or hemothorax and for severe pelvic fractures

by iTBCT scouts. Positive predictive value and sensitivity were respectively 100% (95% CI 61%-100%) and 50% (95% CI 25%-75%) for decisions on chest tube placement by trauma surgeon 1 and 67% (95% CI 21%-94%) and 22% (95% CI 6%-55%) for decisions by trauma surgeon 2. In conclusion iTBCT scouts can be useful for early detection of pneumothorax and/or hemothorax and severe pelvic fractures. However, the decision for chest tube placement based on iTBCT scouts alone is not recommended.

General discussion and future perspectives

Immediate total-body CT (iTBCT) is far beyond its first introduction in trauma care and has irreversibly claimed its position in the initial assessment of major trauma patients in international trauma centers. iTBCT is safe to perform during the initial assessment, even for patients with multiple life-threatening injuries. The reduction in mortality for the general trauma population could not be demonstrated in this thesis. However, for specific subgroups there could be a clinically relevant mortality reduction with iTBCT although not yet demonstrated to be statistically significant.

The potential beneficial effect of iTBCT on mortality or morbidity could be assumed for patients requiring bleeding control interventions and patients with traumatic brain injury (TBI) since both groups benefit from fast decision making and goal directed treatment. Furthermore, decreased levels of consciousness could be considered an indication on itself, since clinical indicators for imaging are unreliable owing to the lack of subjective input from the patient during the trauma work-up. Future research should focus on confirmation of potential survival benefit and reduction of morbidity for bleeding patients and TBI patients by iTBCT.

Since iTBCT is safe, fast and potentially reduces mortality and morbidity for specific subgroups we should not undo the widespread use of iTBCT during the initial assessment of major trauma patients. However, we should refine its further use carefully.

The main challenge within the topic of iTBCT today, is to decide which patients will benefit most likely from iTBCT and how to select these patients in order to reduce radiation exposure for the less severely injured patients. In order to determine the selection criteria one should define the outcome to justify the iTBCT in hindsight. This definition should reflect the severely injured patient. However, the definition of a severely injured patient is still under debate as well.[1] Clinical criteria that are available before imaging and are predictive for severe injury are useful as criteria for iTBCT. Injury Severity Score (ISS) becomes available after all injuries are known and is therefore not suitable as criterion for iTBCT. Since imaging during the initial trauma assessment after severe trauma has a screening character we should not strive for selection of 100% severely injured patients; Ideally the criteria for scanning have a high positive predictive value for selection of severely injured patients in order to reduce radiation exposure for the less severely injured patients. Meanwhile, the trade-off for sensitivity should be considered carefully in order to reduce false negative selection, i.e. withholding a severely injured patient a potentially life-saving iTBCT. Especially if future research could confirm a benefit for patients with internal bleeding or TBI we should not allow for too much reduction of sensitivity of iTBCT criteria for severe injury. Future

research should validate and/or revise existing sets of clinical criteria for selection of severely injured patients for iTBCT.

Radiation exposure is an important issue in the relatively young trauma population that forces the trauma team to be selective with decisions on iTBCT.[2,3] This should work in two directions since less severely injured patients receive more radiation when screened with iTBCT and severely injured patients might receive more radiation when they are screened with STWU since the cumulative exposure of separate examinations could exceed an iTBCT. Ongoing improvements in software algorithms for CT image calculation have the potential to further reduce radiation exposure by CT. With faster calculation times iterative reconstruction is also possible during the initial trauma care and produces more accurate images with the use of less radiation compared to filtered back projection.[4] Future research that aims to reduce radiation exposure for patients during initial trauma care should focus on refining criteria for iTBCT, contrast protocols and improvement of software algorithms for CT image calculation.

Several points should be considered when implementing iTBCT in a trauma center during the initial trauma assessment. Firstly, TBCT can be incorporated into the trauma resuscitation workflow in different ways. The REACT-2 trial investigated the immediate TBCT as first diagnostic modality without preceding X-rays and Focused Assessment with Sonography in Trauma (FAST). In specific cases, aberrant vital parameters could for example make one decide to confirm or rule out severe chest injury first by chest X-ray, before proceeding to TBCT. On the contrary, a relatively stable patient could appear severely injured after X-rays and ultrasound and a secondary TBCT is warranted. Decision schemes for these different workflows should be elaborated and clearly formulated. For successful incorporation of TBCT into the workflow of trauma resuscitation clear practice management guidelines on conditions to perform a TBCT should be formulated. The final decision on which imaging strategy is used remains with the trauma team leader depending on patient's vital parameters and clinical suspicion on injuries.

When implementing iTBCT in a trauma center the location of the CT scanner has to be chosen carefully,[5,6] especially when TBCT is performed immediately without prior X-rays or ultrasound. As described in the REACT-2 trial protocol CT scanner placement in the trauma resuscitation room or in the adjacent room is recommended. Performing life-saving interventions (i.e. endotracheal tube placement, chest tube placement, pelvic binder application) should be possible also at the CT scanning location after only interrupting the scanning process, sliding the patient out of the CT-gantry and without further transport. This recommendation has yet to be confirmed and accepted by guidelines. Next to the location of examination, the location of treatment is an opportunity for improvement in trauma care. Incorporation of angiographic embolization equipment into the operating room gives the team the possibility to transfer from

the trauma resuscitation room before a definitive treatment plan is made and also to combine or switch easily between different treatment modalities in the same location (Hybrid operation room; also called Multifunctional Image-Guided Therapy (MIGTS) suite or Resuscitation with Angiographic Percutaneous Techniques and Operative Resuscitation (RAPTOR) suite).[7,8] Another possibility to proceed rapidly with surgery and/or angiographic embolization after diagnosis is to incorporate the location of treatment into the trauma resuscitation room (Hybrid emergency room).[9] Early diagnosis by CT is then followed by earlier treatment without the need for further transport. The potential mortality reduction of these multifunctional rooms has yet to be confirmed. Patients should be carefully selected before assessment and/or treatment in these multifunctional rooms because fast diagnostics or angiographic embolization might not be available for other severely injured patients if another patient occupies the multifunctional room.

During the REACT-2 trial protocol violations decreased as the trauma teams gained experience with iTBCT scanning indicating trauma teams should be trained and mentored during the introduction of iTBCT in their trauma center. The change in workflow with iTBCT has specific consequences for all trauma team members. For example, the radiologist should perform an ABCD prioritized assessment of the iTBCT images and give an ABCD prioritized feedback to other trauma team members especially because iTBCT is the first vital imaging available. Early preparing for CT scanning could give pressure on fast airway control and obtaining intravenous access.[10]

In a setting where logistic requirements are met and trauma teams consist of trained members, the REACT-2 trial confirmed that even hemodynamically compromised patients can safely undergo iTBCT as primary diagnostic modality. Generalizability of the iTBCT literature to non Level 1 trauma centers might be limited. Leaving out prior X-rays or ultrasound is inadvisable when the CT scanner is not placed inside the trauma resuscitation room or in the adjacent room. As long as severe injuries still has to be ruled out there should be the possibility for immediate life saving interventions. Future research could focus on criteria for safe omission of prior X-rays or ultrasound in non Level 1 trauma centers and criteria for secondary TBCT. In preparation for mass casualty accidents a different imaging strategy has to be considered. Whether CT should be avoided as part of a minimal acceptable care strategy or iTBCT could be used for quick assessment should be further investigated.[11,12]

From a health care economic point of view there is no argument to prefer iTBCT above STWU or vice versa in the general trauma population. However, iTBCT scanning should economically be the diagnostic strategy of choice for multitrauma or traumatic brain injury patients in trauma centers. The investment to make the CT scanner available in or next to the trauma resuscitation room remains to be considered for trauma centers individually.

iTBCT brings an increase of incidental findings and an increase in relevant incidental findings. This effect should not be taken into account for the decision to make an iTBCT, however there should be special attention for administration and follow-up of these findings when performing an iTBCT. Different trauma centers describe poor handling of incidental findings.[13,14] To warrant proper handling of incidental findings by imaging during the initial trauma care new methods should be introduced and evaluated. The responsibility to handle these findings should be assigned to a physician concerned with the definitive treatment and incidental findings could be part of discharge and/or transfer checklists.

Performing a multicenter randomized controlled trial in the acute setting might be considered challenging on itself. The REACT-2 trial was an ambitious multicenter RCT with some specific challenges. Firstly, incorporating research into the demanding acute setting of the initial trauma assessment is challenging for correct patient selection and might add to the chances of trial protocol violations. Data was collected at different sites during different phases of healthcare and across different (para)medical disciplines. An adjusted informed consent procedure gave the opportunity to include patients in the acute care setting without prior consultation of the patient or family. Since the medical research ethics committee obliged the trial staff to obtain informed consent within the next working day a tactful, empathic however convincing approach was needed to help the patient or family to decide on study participation.

Dedicated research nurses and committed local investigators are key to enroll patients in to the trial with as few protocol violations as possible, a minimal number of missed inclusions, properly obtained informed consents, and efficient data completion in different centers. Because of this successful collaboration between trauma centers we succeeded in performing a multicenter RCT in which severely injured patients were prospectively enrolled during their initial trauma assessment. The REACT-2 trial proves the feasibility of a multicenter RCT, which focuses on the initial assessment of patients after severe trauma. Next to giving valuable information on iTBCT this multidisciplinary multi trauma center collaboration generated a valuable data set of 1083 patients after severe trauma that can be used for exploring or answering other research questions. This collaboration also gave the opportunity of sharing health care costs made for patients after severe trauma. Furthermore, the REACT-2 trial could be used as an example for collaborative multicenter grant requests for RCTs in major trauma that is the worldwide leading cause of death for the younger population.

The REACT-2 trial helped shifting the boundaries of CT scanning even further and changing the CT scanner from the 'tunnel of death' into a 'tunnel of life' that should be considered immediately and especially for those who are potentially severely injured and not in need of immediate resuscitative interventions.

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Nederlandse samenvatting

De focus van dit proefschrift ligt op het effect van een directe total-body CT scan (iTBCT) in vergelijking met de standaard work-up (conventionele beeldvorming met selectieve CT) en de indicatie voor een directe total-body CT scan na ernstig trauma in een grote gerandomiseerde studie uitgevoerd in 5 traumacentra. Naast klinische uitkomsten, werden klinisch relevante tijdsintervallen, stralingsbelasting en gezondheid economische effecten geëvalueerd. Deze uitkomsten werden ook specifiek geëvalueerd voor patiënten die spoedinterventies voor bloedingen ondergingen. De criteria voor de directe total-body CT werden heroverwogen om de meer ernstig gewonde patiënten te selecteren en de kans op onnodige stralingsbelasting voor de minder ernstig gewonde patiënten te verkleinen.

In **hoofdstuk 1** wordt de mortaliteit bij traumapatiënten na de iTBCT vergeleken met de standard work-up (STWU) in een multicenter gerandomiseerde studie. Traumapatiënten met afwijkende vitale parameters, klinische verdenking op specifieke levensbedreigende verwondingen of ernstige trauma mechanismen werden geïncludeerd. Secundaire eindpunten waren stralingsbelasting, klinisch relevante tijdsintervallen, gemiste verwondingen en ziekenhuiskosten. De mortaliteit tijdens de ziekenhuisopname was niet statistisch verschillend tussen de groepen (iTBCT 15,9% versus STWU 15,7%, P = 0,923). Subgroepanalyses bij polytraumapatiënten lieten ook geen significant verschil tussen de groepen zien (iTBCT 22,4% versus STWU 24,8%, P = 0,456). De tijd die nodig was om de beeldvorming te verrichten op de traumakamer was korter bij iTBCT-patiënten (30 min versus 37 min, P <0,001). Aanzienlijk meer patiënten in de STWU-groep hadden een lagere effectieve stralingsdosis (21,0mSv [IQR = 20,9-25,2] versus 20.6mSv [IQR = 11,8-27,6], P <0,001). De iTBCT is veilig, verkort de beeldvormingstijd en verhoogt de ziekenhuiskosten niet. De overleving verbeterde echter niet en de meeste patiënten in de STWU-groep werden blootgesteld aan een lagere stralingsdosis.

In **hoofdstuk 2** wordt de kosteneffectiviteit van de iTBCT vergeleken met de STWU tijdens de initiële trauma opvang. Gezondheidszorgkosten en gezondheidsuitkomsten werden bepaald in de REACT-2-populatie gedurende de eerste zes maanden na het trauma. In totaal werden de resultaten van 928 in Nederland geincludeerde patiënten met een volledige follow-up geanalyseerd. De gemiddelde kosten van de ziekenhuiszorg waren € 25.809 (95% bcaCI: € 22.617 tot € 29.137) voor de iTBCT-groep (N = 456) en € 26.155 (95% bcaCI: € 23.050 tot € 29.344) voor de STWU groep met daarmee een besparing van € 346 (95% bcaCI: € 4.987 tot € 4.328; P = 0,887). De percentages patiënten die na zes maanden in leven waren, waren vergelijkbaar in beide groepen. Het verschil in percentages van patiënten zonder serieuze morbiditeit was

61,6% in de iTBCT-groep versus 66,7% in de standaard opwerkgroep (verschil 5,1%, P = 0,104). De waarschijnlijkheid dat iTBCT kosteneffectief zou zijn om patiënten in leven te houden, bleef lager dan 0,56 in de hele groep, maar was hoger bij multitraumapatiënten (0,8-0,9) en bij patiënten met traumatisch hersenletsel (meer dan 0,9). Vanuit het perspectief van een ziekenhuisgezondheidszorgverlener zou een iTBCT scan economisch de diagnostische strategie van eerste keuze moeten zijn bij multitrauma patiënten en patiënten met traumatisch hersenletsel.

Snelle en gedetailleerde diagnostiek zou met name nuttig kunnen zijn voor traumapatiënten met een indicatie voor spoedinterventies bij ernstige bloedingen. In **hoofdstuk 3** hebben we onderzocht of een traumaopvang met iTBCT wordt geassocieerd met een lagere mortaliteit bij patiënten die een spoedinterventie voor bloedingen moeten ondergaan. In de REACT-2-studie werden 1083 patiënten geïncludeerd, waarvan 172 (15,9%) na hun primaire trauma opvang een spoedinterventie voor een ernstige bloeding ondergingen. Binnen deze 172 patiënten kregen 85 (49,4%) iTBCT als primaire diagnostische modaliteit tijdens de trauma opvang. Een mortaliteitsreductie door iTBCT bij traumapatiënten die spoedinterventies voor ernstige bloedingen ondergingen, kon in dit onderzoek niet worden aangetoond; 12,9% (95% BI 7,2%-21,9%) in de iTBCT-groep vergeleken met 24,1% (95% BI 16,3%-34,2%) in de STWU-groep (p = 0,059). Er werd wel een potentieel klinisch relevante absolute risicoreductie van 11,2% (95% BI -0,3% tot 22,7%) in vergelijking met de STWU groep waargenomen. Het tijdsinterval tot aan deze spoedinterventies was niet significant korter; 82 min (IQR 57-121) versus 98 min (IQR 62-147), p = 0,108.

Omdat we geen mortaliteitsreductie konden aantonen en vanwege de relatief lage inclusieaantallen van polytraumapatiënten in de REACT-2-studie, is de vraag welke patiënten baat zouden kunnen hebben bij TBCT en hoe deze patiënten het beste geselecteerd kunnen worden. **Hoofdstuk 4** geeft een overzicht van de huidige criteria voor de total-body CT bij traumapatiënten en beschrijft de mortaliteit en traumascores voor patiënten welke geselecteerd worden voor een TBCT. Een systematische zoektocht werd uitgevoerd in Medline en Embase. Studies die de criteria voor TBCT onderzochten en/of beschreven werden opgenomen. Daarbij werden studies opgenomen waarin TBCT tijdens de initiële opvang van gewonde patiënten met conventionele beeldvorming en selectieve CT in specifieke patiëntengroepen werd vergeleken. Dertig geschikte studies werden geïdentificeerd. Drie studies onderzochten specifiek de criteria voor TBCT bij traumapatiënten met uiteenlopende methoden. Combinaties van afwijkende vitale parameters, ernstige traumamechanismen en klinische verdenking op ernstig letsel werden vaak als criteria gebruikt. Het klinisch oordeel van de traumaleider voor de indicatiestelling voor TBCT werd ook beschreven. Studies die criteria beschrijven voor TBCT waren door hun diversiteit aan methoden

moeilijk met elkaar te vergelijken met betrekking tot mortaliteit en traumascores. Criteria voor TBCT bij trauma tonen een grote variëteit in structuur en grenswaarden voor vitale parameters en beschrijvingen van het traumamechanisme. De studie laat zien dat er geen consensus is over de criteria voor TBCT bij traumapatiënten.

In **hoofdstuk 5** reviseren we de criteria voor de directe TBCT na ernstig trauma met behulp van de prospectief verzamelde criteria voor iTBCT van de REACT-2-patiënten. Met behulp van logistische regressieanalyse met achterwaartse selectie op de 15 studie-inclusiecriteria werd een gereviseerde set criteria afgeleid en vervolgens getest op de voorspellende waarde van ernstig letsel door de positieve voorspellende waarde (PPV), sensitiviteit en receiver operating characteristics (ROC) te vergelijken. Achterwaartse logistische regressie resulteerde in een gereviseerde set bestaande uit negen originele en één aangepaste criteria. PPV verbeterde van 76% (95% BI 74% -79%) tot 82% (95% BI 80%-85%). Sensitiviteit daalde met 9% (95% BI 7%-11%). Het gebied onder de ROC-curve bleef gelijk en was 0,80 (95% BI 0,77-0,83) voor de gereviseerde set in vergelijking met 0,80 (95% BI 0,77-0,83) voor de originele set. De gereviseerde set geeft een reductie van de stralingsbelasting van 8,78 mSv (95% BI 6,01-11,56) voor 36% van de niet-ernstig gewonde patiënten. De criteria voor iTBCT kunnen worden verlaagd van 15 tot 10 klinische criteria.

In **hoofdstuk 6** hebben we de verwachte toename van toevalsbevindingen door TBCT ten opzichte van de STWU bevestigd en gekwantificeerd. Daarbij hebben we aangetoond dat deze toename ook aanwezig was in verschillende categorieën van klinische relevantie. De toevalsbevindingen werden in drie categorieën onderverdeeld: 1) Belangrijke bevinding, kan mortaliteit veroorzaken, 2) Matige belangrijke bevinding, kan morbiditeit veroorzaken en 3) Minimaal belangrijke bevinding, nauwelijks relevant. Generalized estimating equation werd toegepast om verschillen in toevalsbevindingen te beoordelen. iTBCT resulteerde in meer patiënten met toevalsbevindingen en 1,5 keer meer toevalsbevindingen. Deze toename van toevalsbevindingen wordt waargenomen in elke categorie van klinische relevantie. Belangrijke bevindingen werden gedetecteerd bij 23 patiënten (4,3%) in de TBCT-groep vergeleken met 9 patiënten (1,7%) in de STWU-groep (adjusted rate ratio 2,851; 95% BI 1,337-6,077; p <0,007). Bevindingen van matige relevantie werden waargenomen bij 120 patiënten (22,2%) in de TBCT-groep vergeleken met 86 patiënten (15,9%) in de STWU-groep (adjusted rate ratio 1,421; 95% BI 1,088-1,854; p <0,010). Bij gebruik van iTBCT in plaats van selectieve CT tijdens de trauma opvang zijn meer klinisch relevante toevalsbevindingen te verwachten. Onze data toonde geen significant hogere werklast door follow-up, echter was de documentatie over de follow-up suboptimaal. Bij de beoordeling van traumapatiënten met iTBCT is extra alertheid op het waarnemen, documentatie en follow-up van relevante toevalsbevindingen van belang.

In **hoofdstuk 7** onderzoeken we het diagnostische nut van iTBCT-scouts bij het detecteren van levensbedreigende thorax- en bekkenletsels. Twee ervaren traumachirurgen en twee radiologen beoordeelden de iTBCT-scouts van 220 patiënten met behulp van gestructureerde vragenlijsten. De overeenkomst tussen waarnemers en diagnostische eigenschappen werden berekend voor de positie van de endotracheale buis en identificatie van pneumo- en / of hematothorax en bekkenfracturen. Diagnostische eigenschappen van iTBCT-scouts voor indicatie voor plaatsing van de thorax drain en toepassing van het bekkenband werden berekend in vergelijking met de beslissing op basis van iTBCT. Er was een matige tot substantiële overeenkomst tussen waarnemers en lage fout-positieve waarden voor pneumo- en / of hematothorax en voor ernstige bekkenfracturen door iTBCT-scouts. Positieve voorspellende waarde en gevoeligheid waren respectievelijk 100% (95% BI 61%-100%) en 50% (95% BI 25%-75%) voor beslissingen over plaatsing van de borstbuis door traumachirurg 1 en 67% (95% BI 21 %-94%) en 22% (95% BI 6%-55%) voor beslissingen van traumachirurg 2. Concluderend kunnen iTBCT-scouts nuttig zijn voor vroege detectie van pneumo- en / of hematothorax en ernstige bekkenfracturen. Echter, de indicatiestelling voor de plaatsing van een thoraxdrain op basis van alleen iTBCT-scouts wordt niet aanbevolen.

PhD portfolio

Name PhD student:	Kaij Treskes
PhD period:	March 2013 - June 2020
Name PhD supervisor:	Prof. dr. J.C. Goslings

	Year	Workload (ECTS)
General Courses		
Basic course in legislation and organization for clinical researchers	2013	0.9
Practical biostatistics	2013	1.1
Advanced biostatistics	2015	2.1
Clinical epidemiology	2013-2014	1.2
Searching for a systematic review	2013	0.1
Scientific writing	2014	1.5
Career development	2015	0.8
Specific courses		
Evidence based surgery	2014	0.5
Seminars, workshops and master classes		
Weekly surgical department seminars	2013-2015	3
Journal club	2013-2014	2
Prehospital research workshop, Falck foundation	2014	0.25
Oral presentations		
NVT symposium NVvH chirurgendagen, Veldhoven. *Immediate total-body CT scanning versus conventional imaging and selective CT scanning in severe trauma patients: A randomized controlled trial (REACT-2 trial).*	2017	0.5
NVT Traumadagen, Amsterdam *Trauma surgery by general surgeons: Still an option for proximal femoral fractures?*	2015	0.5
NVT Traumadagen, Amsterdam *High rates of clinically relevant incidental findings by total-body CT scanning in trauma patients. (presented by Stijn Bos)*	2015	0.5
NVT Traumadagen, Amsterdam *Limited value of laboratory results after major trauma. (presented by Peter van Schie)*	2015	0.5
European Congress of Trauma and Emergency Surgery, Amsterdam. *Immediate total-body CT scanning versus conventional imaging and selective CT scanning in severe trauma patients: A randomized controlled trial (REACT-2 trial).*	2015	0.5

	Year	Workload (ECTS)
(Inter)national conferences		
NVT Traumadagen, Amsterdam	2015	0.25
NVT Traumadagen, Amsterdam	2014	0.25
NVT Traumadagen, Amsterdam	2013	0.25
European Congress of Trauma and Emergency Surgery, Amsterdam.	2015	0.25
European Congress of Trauma and Emergency Surgery, Lyon	2013	0.25
NVvH Chirurgendagen Veldhoven	2013	0.25
Supervising		
Guido Clerx, research nurse REACT-2	2013-2015	2
Teaching		
Stijn Bos, medical student *High rates of clinically relevant incidental findings by total-body CT scanning in trauma patients*	2013-2015	1
Marjolein Russchen, medical student *Early detection of severe injuries after major trauma by TBCT scouts*	2014-2015	1
Peter van Schie, medical student *Limited value of laboratory results after major trauma.*	2014-2015	1
Mathilde Tol, medical student *Trauma surgery by general surgeons: Still an option for proximal femoral fractures?*	2014-2015	1
Sophie Uittenbogaard, medical student *The effect of hospital volume and surgeon volume on outcome after surgery for proximal femoral fractures.*	2014-2015	1

List of publications

This PhD thesis

Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial.
Sierink JC, Treskes K, Edwards MJ, Beuker BJ, den Hartog D, Hohmann J, Dijkgraaf MG, Luitse JS, Beenen LF, Hollmann MW, Goslings JC; REACT-2 study group.
Lancet. 2016;388(10045):673-83.

Cost-effectiveness of immediate total-body CT after severe trauma
Treskes K, *Sierink JC, Goslings JC, Edwards MJ, Beuker BJ, van Lieshout E, Hohmann J, Luitse JS, Saltzherr TP, Hollman MW, S van Dieren, Dijkgraaf MG; REACT-2 study group.*
Submitted

Emergency Bleeding Control Interventions After Immediate Total-Body CT Scans in Trauma Patients.
Treskes K, *Saltzherr TP, Edwards MJR, Beuker BJA, Den Hartog D, Hohmann J, Luitse JS, Beenen LFM, Hollmann MW, Dijkgraaf MGW, Goslings JC; REACT-2 study group.*
World J Surg. 2019;43(2):490-6.

Indications for total-body computed tomography in blunt trauma patients: a systematic review.
Treskes K, *Saltzherr TP, Luitse JS, Beenen LF, Goslings JC.*
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Injury. 2020;51(1):15-9.

Other publications

Trauma surgery by general surgeons: Still an option for proximal femoral fractures?
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Curriculum Vitae

Kaij Treskes werd geboren op 4 juli 1985 in Amsterdam, alwaar hij op het Ignatius Gymnasium zijn VWO doorliep. Vanaf 2003 studeerde hij Geneeskunde aan de Vrije Universiteit van Amsterdam, waarna hij zijn artsexamen behaalde in juli 2011. Hij werkte vervolgens als arts-assistent bij de afdeling chirurgie van Tergooiziekenhuizen te Hilversum en Blaricum. In 2013 startte hij, onder begeleiding van prof. dr. J.C. Goslings met het onderzoek dat heeft geleid tot dit proefschrift. In 2016 heeft hij als arts-assistent bij de afdeling chirurgie van het Academisch Medisch Centrum Amsterdam gewerkt. Per januari 2017 is hij zijn opleiding tot traumachirurg begonnen in Gelre ziekenhuizen te Apeldoorn en Zutphen, welke hij per maart 2019 heeft voortgezet in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Kaij heeft samen met Nienke van den Akker twee dochters, Rosalien en Elisa.