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

Schouwenburg, M.S.

2 Hospital variation and the impact of postoperative complications on the use of perioperative chemo(radio)therapy in resectable gastric cancer. Results from the Dutch Upper GI Cancer Audit

Schouwenburg MG, Busweiler LAD, Beck N, Henneman D, Amodio S, van Berge Henegouwen MI, Cats A, van Hillegersberg R, van Sandick JW, Wijnhoven BPL, Wouters MWJ, Nieuwenhuijzen GAP; Dutch Upper GI Cancer Audit group

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ABSTRACT

Background: Dutch national guidelines on the diagnosis and treatment of gastric cancer recommend the use of perioperative chemotherapy in patients with resectable gastric cancer. However, adjuvant chemotherapy is often not administered. The aim of this study was to evaluate hospital variation on the probability to receive adjuvant chemotherapy and to identify associated factors with special attention to postoperative complications.

Methods: All patients who received neoadjuvant chemotherapy and underwent an elective surgical resection for stage IB-IVa (M0) gastric adenocarcinoma between 2011 and 2015 were identified from a national database (Dutch Upper GI Cancer Audit). A multivariable linear mixed model was used to evaluate case-mix adjusted hospital variation and to identify factors associated with adjuvant therapy. Results: Of all surgically treated gastric cancer patients who received neoadjuvant chemotherapy (n ¼ 882), 68% received adjuvant chemo(radio)therapy. After adjusting for case-mix and random variation, a large hospital variation in the administration rates for adjuvant was observed (OR range 0.31 e7.1). In multivariable analysis, weight loss, a poor health status and failure of neoadjuvant chemo-therapy completion were strongly associated with an increased likelihood of adjuvant therapy omission. Patients with severe postoperative complications had a threefold increased likelihood of adjuvant therapy omission (OR 3.07 95% CI 2.04e4.65).

Conclusion: Despite national guidelines, considerable hospital variation was observed in the probability of receiving adjuvant chemo(radio)therapy. Postoperative complications were strongly associated with adjuvant chemo(radio)therapy omission, underlining the need to further reduce perioperative morbidity in gastric cancer surgery.

INTRODUCTION

Surgery is the cornerstone of curative treatment for patients with gastric cancer. However, optimal surgical treatment provides long-term survival in only 20e30% of the patients [1,2] The high relapse rate has led to the utilization of perioperative treatment modalities, with adjuvant chemoradiotherapy being the preferred treatment in the United States [3] and perioperative chemotherapy in Europe [4,5]. Adjuvant chemotherapy is presumed to be an important component of perioperative chemotherapy, since several Asian studies showed a survival benefit with adjuvant chemotherapy regimens alone [6,7].

Dutch guidelines recommend perioperative chemotherapy containing the ECF (epirubicin, cisplatin and 5-fluorouracil) regimen for patients with resectable gastric cancer who are eligible in terms of physical condition and comorbidity [8]. Despite national guidelines, only half of the patients receive perioperative chemotherapy in Dutch clinical practice [9]. It remains to be elucidated whether this relates to low compliance with national guidelines or to the variation in frailty and comorbidities of the unselected patient population. Previous population-based studies confirmed that both patient and tumour characteristics influence the probability of receiving perioperative treatment, including a higher age, more comorbidity and a lower clinical tumour stage [9-12].

However, it is not well understood to what extent perioperative complications influence the probability of receiving adjuvant chemo(radio)therapy in patients who are considered eligible for multimodal treatment. Gastric surgery is associated with relatively high perioperative complication rates [13], which, by decreasing patient's condition, could have a major influence on the probability of receiving the adjuvant component of perioperative chemo(radio) therapy.

Furthermore, to what extent the use of guideline-recommended adjuvant chemo-(radio)therapy varies between hospitals is not fully elucidated.

The aim of this study was to evaluate hospital, patient, tumour and treatment factors that influence the utilization of the adjuvant component of the perioperative

chemo(radio)therapy regimen for surgically treated gastric cancer patients in the Netherlands.

METHODS

Since 2011, all patients with the intent of a resection for oesophageal or gastric cancer in the Netherlands are registered in the Dutch Upper Gastrointestinal Cancer Audit (DUCA) [14]. The DUCA was set up as a nationwide surgical quality improvement programme. The main objective of the audit is to report risk-adjusted process and outcome information to participating hospitals for internal quality improvement purposes.

Detailed information on patient- and disease-specific characteristics as well as information on the diagnostic process, treatment and perioperative outcome is collected prospectively. Data are compared with an external data registration, the Netherlands Cancer Registry (NCR), on completeness and accuracy. The NCR registers all newly diagnosed malignancies in the Netherlands [2]. The concordance of the DUCA registration with the data set of the NCR on a national level is very high, and has been estimated to be 98% of all gastric cancer resections in 2013 [14].

Patient selection

All patients who were planned to receive the standard perioperative chemo (radio) therapy and received neoadjuvant chemo-therapy and underwent a curative resection for primary gastric cancer between 2011 and 2015 were selected. A curative resection was defined as a curative macroscopically complete resection and no signs of metastatic disease at time of diagnosis and at surgery. Tumour stage was defined according to the seventh edition of the International Union Against Cancer tumour node metastasis (TNM) classification [15]. According to the 7th TNM classification, gastro-oesophageal junction (GEJ) tumours were classified as oesophageal tumours in the DUCA database and were therefore excluded from this study. Patients were considered not eligible for analyses when information was missing regarding the location of the tumour, date of birth, date of surgery, intent of surgery, treatment modalities received and the patient's vital status 30 days post-operatively and/or

at time of discharge. Patients with other treatment regimens, such as neoadjuvant chemo (radio)therapy alone or adjuvant chemo(radio)therapy alone, were excluded.

In order to investigate current hospital variation, hospitals that stopped performing gastric cancer surgery during the study period were excluded.
Patients were classified to the hospital of surgical treatment, since the hospital of diagnosis or the hospital of chemo(radio) therapy is not registered in the DUCA.
For this study, no ethical approval or informed consent was required under Dutch law.

Variables

The studied variables included patient characteristics (age, sex, weight loss before surgery, American Society of Anesthesiologists (ASA) classification, comorbidity according to the Charlson Co-morbidity Index (CCI) [16]), tumour characteristics (tumour site, clinical and pathological tumour stage, differentiation grade) and treatment characteristics (histologic regression after neoadjuvant therapy, radicality of resection, completion of neoadjuvant therapy, intraoperative complications and severe postoperative complications). Hospital stay was defined as days between date of surgery and date of discharge. Postoperative mortality was defined as death within 30 days from the date of surgery or during the initial hospital admission.

A severe postoperative complication was defined as a complication within 30 days with a Clavien-Dindo classification of grade III (requiring surgical, endoscopic or radiological intervention), grade IV (requiring intensive care (IC) management) or grade V (leading to death) [17] Complications were classified into non-surgical complications (e.g. pulmonary, cardiac, thromboembolic, neurologic, urologic complications) or surgical complications (e.g. anastomotic leakage, chylous leakage, haemorrhage, wound and intra-abdominal abscess, pancreatitis).

Treatment groups

Patients were grouped into two treatment categories: receipt of neoadjuvant chemotherapy component alone or receipt of the complete perioperative regimen. Perioperative therapy was defined as neoadjuvant chemotherapy (three cycles of ECF, ECC or EOX) and either adjuvant chemotherapy (three cycles of ECF/ECC or

EOX) or adjuvant chemoradiotherapy with cisplatin and capecitabine according to the CRITICS trial; a large randomized phase III trial evaluating the added value of adjuvant chemoradiotherapy after neoadjuvant chemotherapy that ran during the study period [18].

Statistical analysis

Patient, tumour and treatment characteristics between both treatment groups were compared using the chi-square test for categorical variables and the independent two-sample t-test for continuous variables.

To quantify the true hospital variation for the use of adjuvant chemo(radio)therapy, adjusting for case-mix factors (non-modifiable patient and tumour-specific risk factors that can influence the outcome) was required [19]. Available case-mix factors that can influence the use of adjuvant chemo(radio)therapy were entered in a multivariable linear mixed model: age, sex, weight loss before surgery, ASA classification, CCI, pathologic tumour and nodal stage, tumour location, histologic tumour regression and tumour differentiation. Missing items were included in the analysis as a separate category if exceeding 5%. To account for the hierarchical nature of patients nested within hospitals, the hospital was included as a random effect [19]. The case-mix and random effect adjusted log odds of adjuvant chemo(radio)therapy per hospital were individually presented with the hospital-specific 95% confidence intervals (CIs). The log odds could then be converted into an odds ratio (OR) by taking the exponential. The variation in use of adjuvant chemo(radio)therapy between hospitals was tested for statistical significance with the likelihood ratio test.

Secondly, a univariable and multivariable linear mixed model were used to quantify the association of patient, tumour and treatment factors with the omission of adjuvant chemo(radio) therapy. The multivariable analysis for adjuvant therapy omission was repeated to evaluate the association of surgical and non-surgical complications separately. As a sensitivity analysis, we also assessed the association of severe complications on adjuvant therapy in a younger (<70 years) and healthier (ASA classification I-II, minor weight loss of <5 kg) cohort of patients. Statistical significance was defined as a two-sided p value < .05. All analyses were performed in PASW Statistics version 20 (SPSS inc Chicago, IL, USA) and R version 3.2.2.

RESULTS

Use of perioperative chemo(radio)therapy

Between January 1st, 2011 and December 31st, 2015, 882 patients who received neo-adjuvant chemotherapy and underwent a curative resection for gastric cancer were registered in 24 hospitals (Figure 1). In total, 167 patients (18%) started with the neoadjuvant therapy but did not complete the regimen due to toxicity. Of the remaining, 280 patients only completed the neoadjuvant component (32%) and

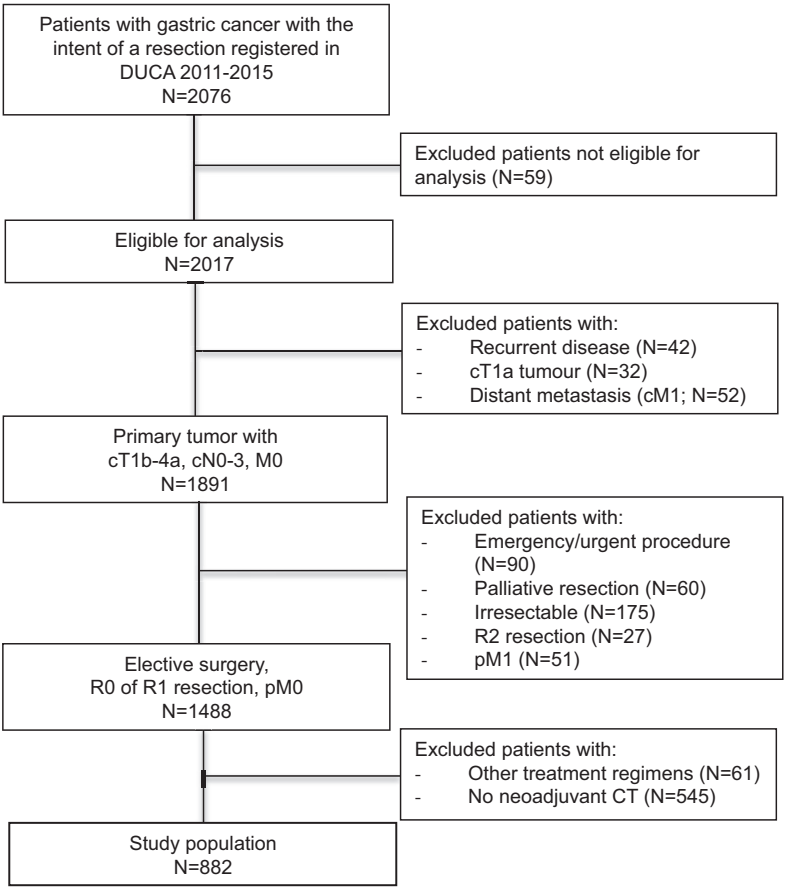

Figure 1. Study population. DUCA = Dutch Upper Gastro-Intestinal Cancer Audit, CT = chemotherapy.

602 patients (68%) received the whole perioperative chemo(radio)therapy regimen (Table 1). Patients with perioperative chemo (radio)therapy were younger, with less weight loss, less comorbidities, completed neoadjuvant chemotherapy more often, had a better tumour response to chemotherapy and experienced postoperative complications less frequently compared to patients with neoadjuvant chemotherapy alone. Sixteen patients (2%) died within the hospitalization or 30 days after surgery, all due to severe postoperative complications.

Table 1. Patient and tumour characteristics.

	Neoadjuvant CT only N=280 N (%)	Perioperative therapy[a] N=602 N (%)	*P*
Age, mean [range], years	67 [31-83]	63 [22-83]	<.001[b]
Age, years			
<60	56 (20)	206 (34)	<.001
60-69	109 (39)	225 (37)	
≥70	115 (41)	171 (28)	
Sex			
Male	175 (63)	395 (66)	.368
Female	105 (38)	207 (34)	
Weight loss			
0kg	62 (22)	172 (29)	.001
1-5kg	51 (18)	154 (26)	
6-10kg	75 (27)	134 (22)	
>10kg	45 (16)	52 (9)	
Unknown	47 (17)	90 (15)	
ASA classification			
ASA I	20 (7)	145 (24)	<.001
ASA II	178 (64)	353 (59)	
ASA III+	79 (28)	103 (17)	
Unknown	3 (1)	1 (0)	
Charlson Comorbidity Index			
Charlson 0	128 (46)	348 (58)	.001
Charlson 1	62 (22)	128 (21)	
Charlson 2+	90 (32)	126 (21)	

Table 1. Patient and tumour characteristics (*continued*)

	Neoadjuvant CT only N=280 N (%)	Perioperative therapy[a] N=602 N (%)	*P*
Clinical tumour stage[c]			
I	41 (15)	99 (16)	.062
II	117 (42)	271 (45)	
III	35 (13)	52 (9)	
Unknown	87 (31)	180 (30)	
Pathological tumour stage[c]			
I	69 (25)	151 (25)	0.003
II	73 (26)	200 (33)	
III	90 (32)	207 (34)	
Unknown	48 (18)	44 (7)	
Site of tumour			.346
Fundus	31 (11)	52 (9)	
Corpus	93 (33)	214 (36)	
Antrum / pylorus	116 (41)	260 (43)	
Whole stomach	19 (7)	40 (7)	
Other	4 (1)	15 (3)	
Unknown	17 (6)	21 (4)	
Histologic regression			
None	88 (31)	146 (24)	<.001
Partial/complete	107 (38)	351 (58)	
Unknown	85 (30)	105 (17)	
Differentiation grade			
Well/moderately	89 (32)	162 (27)	.034
Poorly/Undifferentiated	157 (56)	327 (54)	
Unknown	34 (12)	113 (19)	
Radical resection			
R0	246 (88)	545 (91)	.282
R1	32 (11)	50 (8)	
Unknown	2 (1)	7 (1)	

Table 1. Patient and tumour characteristics (*continued*)

	Neoadjuvant CT only N=280 N (%)	Perioperative therapy[a] N=602 N (%)	*P*
Neoadjuvant therapy completed[d]			
No	111 (40)	56 (9)	<.001
Yes	166 (59)	543 (90)	
Unknown	3 (1)	3 (1)	
Intraoperative complications			
No	263 (94)	581 (97)	.079
Yes	17 (6)	21 (4)	
Postoperative complications[e]			
No	151 (54)	428 (71)	<.001
Yes, grade I-II	24 (9)	62 (10)	
Yes, grade III-V	105 (38)	112 (19)	
Surgical	35 (7)	34 (6)	
Non-surgical	28 (13)	43 (7)	
Surgical and non-surgical	33 (16)	19 (3)	
Unknown	9 (4)	16 (3)	
Postoperative mortality			
No	264 (94)	602 (100)	<.001
Yes	16 (6)	0 (0)	
Hospital stay (median), days	10	8	<.001[b]

ASA=American Society of Anesthesiologists; CT=chemotherapy.

[a]Neoadjuvant chemotherapy combined with adjuvant chemo(radio)therapy

[b]Analysis performed independent two-sample t-test

[c] Tumour Node Metastasis system (7th edition)

[d] More than 80% of cycles were completed

[e] Classified according to Clavien-Dindo classification. Postoperative complications of grade III or higher are considered severe.

Hospital variation in the use of adjuvant chemo(radio)therapy

Unadjusted hospital variation in the administration of adjuvant chemo(radio)therapy ranged from 9% to 94%. A likelihood ratio test showed that the variability between hospitals for use of adjuvant chemo(radio)therapy was statistically significant (p value < .01). After adjustment for case-mix variables and fitting a random effect model, still considerable variation remained (Figure 2). Three hospitals administered

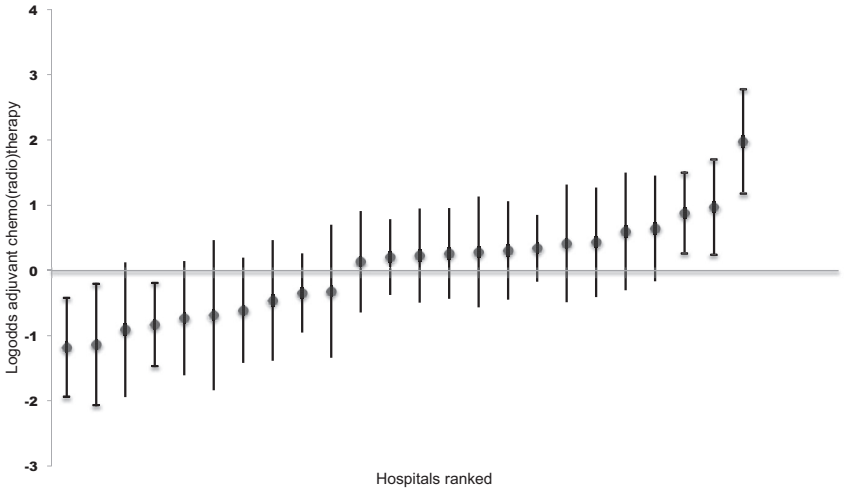

Figure 2. Hospital variation on the administration adjuvant chemo(radio)therapy on the log odds scale. Every hospital is presented as a dot with hospital specific 95% confidence interval, adjusted for case-mix with random-effects models. The zero-line represents the national average. Hospitals with an outcome less than 0 and marked with a dash (-) are negative outliers and have administered significantly less than average. Hospitals with an outcome above 0 and marked with a dash (-) are positive outliers and have administered significantly more than average.

significantly less neoadjuvant chemotherapy (negative outliers) and three hospitals administered significantly more chemotherapy (positive outliers) compared to the national average (range on log odds scale is -1.37-1.36, meaning a range on the odds scale of 0.31-7.2). Hence, in the hospital with the highest administration rate, patients were seven times more likely to receive adjuvant chemo(radio)therapy compared to the national average, irrespective of patient- and tumour-specific risk factors. In the hospital with the lowest administration rate, adjuvant chemo(radio)therapy was three times more likely to be omitted compared to the national average.

Effect of patient, tumour and treatment risk factors on adjuvant chemo(radio)therapy omission

Multivariable analysis showed that women, patients with severe weight loss, a higher ASA classification, failure of neoadjuvant chemotherapy completion and postoperative severe complications were most strongly associated with an increased likelihood of the omission of adjuvant chemo (radio)therapy (Table 2).

Table 2. Univariable and multivariable linear mixed model of patient, tumour and treatment factors associated with the omission of adjuvant chemo(radio)therapy.

Factor	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age				
<60	ref		ref	
60-69	**2.78 (1.23-2.69)**	**<.001**	1.42 (0.87-2.30)	.208
>/= 70	**2.47 (1.70-3.61)**	**<.001**	**1.80 (1.10-3.01)**	**.036**
Sex				
Male	ref		ref	
Female	1.15 (0.85-1.54)	.368	**1.50 (1.02-2.22)**	**.036**
Weight loss				
0kg	ref		ref	
1-5kg	0.92 (0.60-1.41)	.699	1.06 (0.62-1.82)	.967
6-10kg	1.56 (1.04-2.32)	.33	1.57 (0.93-2.65)	.125
>10kg	**2.40 (1.47-3.93)**	**.001**	**2.31 (1.22-4.38)**	**.030**
Unknown	1.45 (0.92-2.29)	.112	1.47 (0.81-2.67)	.338
ASA classification				
ASA I	ref		ref	
ASA II	**3.66 (2.22-6.03)**	**<.001**	**2.04 (1.12-3.72)**	**.021**
ASA III+	**5.56 (3.20-9.66)**	**<.001**	**2.82 (1.41-5.66)**	**.005**
Charlson score				
Charlson 0	ref		ref	
Charlson 1	1.31 (0.91-1.90)	.139	1.01 (0.63-1.61)	.838
Charlson 2+	**1.94 (1.39-2.72)**	**<.001**	1.39 (0.88-2.19)	.101
Pathological tumour stage[a]				
I	ref		ref	
II	0.80 (0.54-1.18)	.260	**0.53 (0.32-0.87)**	**.012**
III	0.95 (0.65-1.39)	.796	**0.48 (0.28-0.83)**	**.008**
Unknown	**2.39 (1.45-3.93)**	**.001**	0.70 (0.34-1.43)	.322
Site of tumour				
Corpus	ref		ref	
Fundus	1.37 (0.83-2.28)	.222	1.73 (0.89-3.35)	.115
Antrum/pylorus	1.02 (0.74-1.42)	.875	0.90 (0.58-1.38)	.898
Whole stomach	1.09 (0.601-1.99)	.771	1.21 (0.54-2.71)	.545
Unknown	1.34 (0.74-2.42)	.329	1.23 (0.56-2.67)	.661

Table 2. Univariable and multivariable linear mixed model of patient, tumour and treatment factors associated with the omission of adjuvant chemo(radio)therapy (*continued*)

Factor	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Differentiation				
Good/medium	ref		ref	
Bad/none	1.14 (0.83-1.58)	.411	0.92 (0.60-1.42)	.980
Unknown	**0.63 (0.41-0.96)**	**.032**	0.69 (0.38-1.27)	.367
Histologic regression				
Partial/complete	ref		ref	
None	**1.98 (1.41-2.78)**	**<.001**	**1.68 (1.05-2.69)**	**.023**
Unknown	**2.66 (1.96-3.8)**	**<.001**	**2.13 (1.26-3.58)**	**.003**
Radical resection				
R0	ref		ref	
R1	1.42 (0.89-2.27)	1.44	1.36 (0.70-2.66)	.481
Neoadjuvant therapy completed[b]				
Yes	ref		ref	
No	**6.48 (4.5-9.34)**	**<.001**	**6.55 (4.14-10.35)**	**<.001**
Intraoperative complications				
No	ref		ref	
Yes	1.79 (0.93-3.45)	.082	1.82 (0.77-4.30)	.179
Severe postoperative complications				
No	ref		ref	
Grade I-II	1.1 (0.67-1.82)	.72	1.36 (0.73-2.53)	.439
Grade >III	**2.66 (1.92-3.68)**	**<.001**	**3.07 (2.04-4.65)**	**<.001**

Bold printed numbers are statistically significant ($p<0.05$).

ASA=American Society of Anesthesiologists, CI=confidence interval.

[e] Tumour Node Metastasis system (7th edition)

[b] More than 80% of cycles were completed

Severe postoperative complications increased the likelihood of adjuvant treatment omission more than threefold (OR 3.07; 95% CI2.04-4.65). Additional multivariable analysis showed that severe surgical complications displayed a greater effect on the probability of the omission of adjuvant chemo(radio)therapy than severe non-surgical complications (OR 3.42 95% CI 1.93-6.04 vs 1.85 95% CI 1.02-3.37). Patients with a combination of both severe surgical and severe non-surgical complications had

the highest likelihood of adjuvant chemo(radio)therapy omission (OR5.54 95%CI 2.77- 11.07).
After further selecting a younger cohort of patients with less comorbidities and weight loss (<70 years, ASA I-II, weight loss <5 kg; N = 267), 81% received adjuvant chemotherapy and 20% experienced a severe postoperative complication. After adjustment, an increase in the likelihood of adjuvant treatment omission following severe postoperative complications was also found in this subgroup (OR 2.45 95% CI 1.15-5.25).

DISCUSSION

This population-based study shows that after completing the neoadjuvant therapy, only 68% of surgically treated gastric cancer patients receive the adjuvant chemo(radio)therapy component of the perioperative chemo(radio)therapy regimen. Furthermore, a significant hospital variation is observed in the probability of receiving adjuvant treatment, with postoperative severe surgical complications having a major impact.

Similar compliance rates of adjuvant chemo(radio)therapy were observed in this study as those shown in the MAGIC trial (68% vs 65%, respectively) [4]. The ACTS-GC and CLASSIC trial evaluated the effect on survival of adjuvant chemotherapy alone and reported comparable compliance rates of 67% [6,7]. This indicates the difficulty of delivering the adjuvant component following gastric surgery, even in selected patient populations. Apparently, the treating physicians and/or patients are reluctant to administer the adjuvant component in older and frail patients because of perceived toxicity of the regimen in the trials and uncertainty on long-term harms and benefits. These results show the need for specific guidelines that are more tailored to individual patients and subgroups.

Considerable hospital variation was observed with regard to the use of adjuvant chemo(radio)therapy, even after adjustment for case-mix factors and random variation. In hospitals with the lowest administration rates, adjuvant chemo(radio) therapy was three times more likely to be omitted compared to the national average,

suggesting that underuse of adjuvant chemotherapy is not merely a reflection of the age or comorbidity burden, but it may also reflect other (hospital specific) factors. Previous studies demonstrated that consultation of a medical oncologist [10] and a dedicated multi-disciplinary team meeting [11] are independently associated with higher rates of adjuvant chemo(radio)therapy receipt, which underlines the importance of the decisional process.

The effect of hospital variation in adjuvant chemotherapy use on overall survival has not been studied yet. A recent Dutch study on gastric cancer patients demonstrated significant hospital variation in the probability to receive potential curative surgical treatment [20]. Patients diagnosed in hospitals with a lower probability of undergoing surgical treatment had a worse overall survival [20]. Future studies are needed to explore whether a lower hospital probability of chemotherapy use is also associated with poorer survival.

A very strong effect of severe postoperative complications on the probability to omit adjuvant chemo(radio)therapy was demonstrated, which increased more than threefold compared to patients who had no complications. This has also been reported for other oncologic procedures with high perioperative morbidity rates, including procedures for colorectal and pancreatic cancer [21e24]. A recent retrospective multicentre US study in resectable gastric cancer patients showed that the combination of experiencing postoperative complications and not subsequently receiving adjuvant chemo(radio)therapy increased the long-term overall mortality twofold [25].

Optimal treatment comprises not merely the administration, but also a timely start after surgery and completion of all planned cycles of chemotherapy. Two recent Asian studies on timing of adjuvant chemotherapy in resectable gastric cancer showed that delayed treatment after 8 weeks was associated with worse survival outcomes [26,27]. They also demonstrated that the occurrence of postoperative surgical complications was the strongest factor related to this delay. Like our study, this indicates that complications following gastric cancer surgery not only affect short-term outcomes, but also influence long-term survival. This phenomenon might be related to the omission or delay of adjuvant treatment.

Gastric cancer surgery is complex and has a relatively high incidence of postoperative complications. This study showed that the effect of surgical complications on the omission of adjuvant chemotherapy is much stronger than that of non-surgical complications (OR 3.4 vs 1.9, respectively). Even among the healthier and younger patient cohort, severe complications were common (20%) with an over twofold increased likelihood of adjuvant chemo(-radio)therapy omission. Many efforts aimed to improve the outcome of gastric cancer surgery have been made, such as the centralization and the initiation of clinical audits [28]. Despite these efforts, severe complication rates remain high, ranging from 20% to 35% in Western countries [13,29].

This study has several strengths and limitations. The strength of this study is the population-based and prospective nature of the audit, including all Dutch hospitals with a 98% national coverage of all gastric cancer resections. It therefore reflects daily practice and is highly representative of the Dutch population. However, the DUCA has its focus on the quality of surgical treatment and short-term outcomes of care. Therefore, detailed information on the chemotherapy regimen, the number of received cycles, dosage, toxicity, reasons for not receiving chemotherapy and long-term follow-up is not registered. A multidisciplinary extension of the audit, including participation of medical oncologists, pathologists, gastroenterologists and radiation oncologists and merging DUCA data with survival data of the National Cancer Registry may offer a better understanding of the decision-making process and treatment patterns for multimodal therapy and ultimately the impact on long-term survival.

Furthermore, the DUCA does not register the hospital of diagnosis, and actual referral patterns could therefore not be revealed. Since centralization of surgical treatment of gastric cancer in the Netherlands has been introduced in 2013 with a minimum requirement of 20 resections per hospital annually, an increasing number of patients are referred for surgery from another hospital. However, perioperative treatment is not centralized and the hospital variation as shown in this study might thus also be related to the variation in decision-making on (neo)adjuvant treatment in hospitals of diagnosis.

These findings broaden our understanding of decision-making in the use of adjuvant chemotherapy for gastric cancer in daily clinical practice. In addition to the well-known patient and tumour factors associated with its use, the occurrence of post-operative surgical complications also has a major effect on adjuvant chemo(radio) therapy omission and might eventually affect long-term survival. Further efforts should therefore be made to decrease the incidence of complications and to improve recognition and management of perioperative morbidity to reduce omission of adjuvant treatment.

REFERENCES

1. Dassen AE, Lemmens VEPP, Van De Poll-franse LV, Creemers GJ. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007 : a population-based study in The Netherlands. Eur J Cancer 2010;46:1101e10. https://doi.org/10.1016/j.ejca.2010.02.013.
2. Netherlands cancer Registry. Available from. www.cijfersoverkanker.nl. [Accessed 31 July 2016].
3. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junc-tion. N Engl J Med 2001;345:725e30. https://doi.org/10.1056/NEJMoa010187.
4. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11e20. https:// doi.org/10.1056/NEJMoa055531.
5. Ychou M, Boige V, Pignon JP, Conroy T, Bouch O, Lebreton G, et al. Perioper-ative chemotherapy compared with surgery alone for resectable gastro-esophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715e21. https://doi.org/10.1200/JCO.2010.33.0597.
6. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007 Nov 1; 357(18):1810e20.
7. Bang Y, Kim Y, Yang H, Chung HC, Park Y, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315e21. https:// doi.org/10.1016/S0140-6736(11)61873-4.
8. Dutch guideline for gastric cancer. Available from. www.oncoline.nl. [Accessed 17 December 2015].
9. Trip AK, Stiekema J, Visser O, Dikken JL, Cats A, Boot H, et al. Recent trends and predictors of multimodality treatment for oesophageal, oesophagogastric junction, and gastric cancer: a Dutch cohort-study. Acta Oncol (Madr) 2015: 1e9. https://doi.org/10.3109/0284186X.2015.1009638.
10. Snyder RA, Penson DF, Ni S, Koyama T, Merchant NB. Trends in the use of evidence-based therapy for resectable gastric cancer. J Surg Oncol 2014;110: 285e90. https://doi.org/10.1002/jso.23635.
11. Bouvier AM, Crehange G, Azelie C, Cheynel N, Jouve JL, Bedenne L, et al. Adjuvant treatments for gastric cancer: from practice guidelines to clinical practice. Dig Liver Dis 2014;46: 72e5. https://doi.org/10.1016/j.dld.2013.07. 003.
12. Sherman KL, Merkow RP, Bilimoria KY, Wang CE, Mulcahy MF, Benson AB, et al. Treatment trends and predictors of adjuvant and neoadjuvant therapy for gastric adenocarcinoma in the United States. Ann Surg Oncol 2013;20: 362e70. https://doi.org/10.1245/s10434-012-2552-7.

13. Papenfuss WA, Kukar M, Oxenberg J, Attwood K, Nurkin S, Malhotra U, et al. Morbidity and mortality associated with gastrectomy for gastric cancer. Ann Surg Oncol 2014;21:3008e14. https://doi.org/10.1245/s10434-014-3664-z.
14. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, Henneman D, van Grieken NCT, Wouters MWJM, et al. Early outcomes from the Dutch upper gastrointestinal cancer audit. Br J Surg 2016;103:1855e63. https://doi.org/ 10.1002/bjs.10486.
15. Edge SB, Compton CC. The American Joint Committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471e4. https://doi.org/10.1245/s10434-010-0985-4.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373e83. https://doi.org/10.1016/0021-9681(87)90171-8.
17. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. Ann Surg 2004; 240:205e13. https://doi.org/10.1097/01.sla.0000133083. 54934.ae.
18. Dikken JL, van Sandick JW, Maurits Swellengrebel H, Lind PA, Putter H, Jansen EP, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). BMC Cancer 2011;11:329. https://doi.org/ 10.1186/1471-2407-11-329.
19. Osborne NH, Ko CY, Upchurch GR, Dimick JB. The impact of adjusting for reliability on hospital quality rankings in vascular surgery. J Vasc Surg 2011;53:1e5. https://doi.org/10.1016/j.jvs.2010.08.031.
20. Van Putten M, Verhoeven RHA, Van Sandick JW, Plukker JTM, Lemmens VEPP, Wijnhoven BPL, et al. Hospital of diagnosis and probability of having surgical treatment for resectable gastric cancer. Br J Surg 2016;103:233e41. https:// doi.org/10.1002/bjs.10054.
21. Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg 2014;260:372e7. https://doi.org/ 10.1097/SLA.0000000000000378.
22. Merkow RP, Bentrem DJ, Mulcahy MF, Chung JW, Abbott DE, Kmiecik TE, et al. Effect of postoperative complications on adjuvant chemotherapy use for stage III colon cancer. Ann Surg 2013;258:847e53. https://doi.org/10.1097/ SLA.0000000000000312.
23. Malietzis G, Mughal A, Currie AC, Anyamene N, Kennedy RH, Athanasiou T, et al. Factors implicated for delay of adjuvant chemotherapy in colorectal cancer: a meta-analysis of observational studies. Ann Surg Oncol 2015;22: 3793e802. https://doi.org/10.1245/s10434-015-4479-2.
24. Hendren S, Birkmeyer JD, Yin H, Banerjee M, Sonnenday C, Morris AM. Sur-gical complications are associated with omission of chemotherapy for stage III colorectal cancer. Dis Colon Rectum 2010;53:1587e93. https://doi.org/ 10.1007/DCR.0b013e3181f2f202.
25. Jin LX, Sanford DE, Squires MH, Moses LE, Yan Y, Poultsides GA, et al. Inter-action of postoperative morbidity and receipt of adjuvant therapy on long-term survival after resection for gastric adenocarcinoma: results from the U.S. Gastric cancer collaborative. Ann Surg Oncol 2016;23:2398e408. https:// doi.org/10.1245/s10434-016-5121-7.

26. Park HS, Jung M, Kim HS, Kim H, An JY, Cheong J, et al. Proper timing of adjuvant chemotherapy affects survival in patients with stage 2 and 3 gastric cancer. Ann Surg Oncol 2015: 224e31. https://doi.org/10.1245/s10434-014-3949-2.
27. Kaito A, Kinoshita T, Shitara K, Shibasaki H, Nishida T. Timing of initiation of adjuvant chemotherapy for gastric cancer : a case-matched comparison study of laparoscopic vs. open surgery. Eur J Surg Oncol 2017;43:801e7. https:// doi.org/10.1016/j.ejso.2017.01.008.
28. Dikken JL, Cats A, Verheij M, Van De Velde CJH. Randomized trials and quality assurance in gastric cancer surgery. J Surg Oncol 2013;107:298e305. https:// doi.org/10.1002/jso.23080.
29. Groene O, Lecturer S. National gastric cancer audit 2015 annual report. 2015

Part II

Assuring quality in precision medicine