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Translation of IDEA trial results into clinical practice: Analysis of the implementation of a new guideline for colon cancer

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Abstract

The IDEA trial showed no clinical relevant differences in efficacy between 3 and 6 months of oxaliplatin-based adjuvant chemotherapy (ACT) in colon cancer (CC), while toxicity was substantially lower in the 3 months regimen. Therefore, in 2017 the Dutch colorectal cancer guideline was revised and currently recommends 3 months of oxaliplatin-based ACT. Furthermore, the definition of high-risk stage II CC was restricted to pT4 tumors. We analyzed changes in ACT between 2015 and 2019. From the Netherlands Cancer Registry all 16 721 patients ≥18 years with resected high-risk stage II and stage III CC during 2015 to 2019 were selected. Differences in patient and treatment characteristics were analyzed per calendar year according to stage and age. Mean duration of oxaliplatin-based ACT decreased from 18.6 (±8.0) to 9.5 (±3.8) weeks between 2015 and 2019. In patients receiving ACT (n = 8170), the proportion treated with oxaliplatin increased from 74% to 83%. The proportion of patients receiving ACT was stable, 61% to 69% in stage III and 26% to 29% in pT4 stage II. ACT in previous high-risk pT3N0 disease decreased from 15% to 3%. Use of oxaliplatin increased from 27% to 49% in patients aged ≥75 years. The revised guideline was rapidly implemented and led to an increase in oxaliplatin-based ACT in the elderly and increased guideline-adherence in high-risk stage II CC.

KEYWORDS
adjuvant chemotherapy, cancer registry, colon cancer, guideline

What's new?

Results from the 2017 International Duration Evaluation of Adjuvant Chemotherapy Collaboration (IDEA) trial support the use of adjuvant chemotherapy (ACT) for 3 months in stage II and III colon cancer patients. Our study examined the impact of the incorporation of IDEA trial results into colon cancer treatment guidelines in the Netherlands. Analyses of Netherlands Cancer Registry data show that rapid guideline implementation shortened ACT duration, increased oxaliplatin-based ACT in elderly patients, and increased guideline-adherence in stage II disease. Shorter treatment duration can reduce toxicity and costs. The findings highlight the value of rapid translation of scientific insights into clinical care.

1 | INTRODUCTION

Adjuvant chemotherapy (ACT) after surgical resection in patients with stage III colon cancer (CC) is standard of care since pivotal trials showed a significant reduction of disease recurrence and mortality.[1-3] Initially, the efficacy of ACT was demonstrated with fluoropyrimidine monotherapy for a duration of 12 months.[4] Subsequently, a duration of 6 months proved to be equally effective.[5] The addition of oxaliplatin further increased the benefit of ACT.[3,6] Since 2004, duration of oxaliplatin-based ACT was established at 6 months with an estimated gain in 5-year DFS of 9% to 22%, depending on T- and N-stage subclassification.[7] In stage II CC the possible benefit of ACT is less certain with conflicting results in different trials. Small survival benefits (<5% gain in 10-year OS[8]) are likely due to low recurrence rates.[9-11] Although there is a lack of robust data regarding its benefit, international guidelines recommend administration of ACT for high-risk stage II CC patients.[12] However, there is no global consensus on high-risk factors in stage II CC resulting in discordant guidelines.[13-15]

Addition of oxaliplatin to fluoropyrimidine monotherapy also increases toxicity, mainly sensory peripheral neuropathy, which is cumulative and sometimes severe and irreversible. Therefore, a strategy to reduce toxicity, without unacceptably compromising outcomes, was subject of studies that evaluated shortening of ACT duration. The International Duration Evaluation of Adjuvant Chemotherapy Collaboration (IDEA) phase 3 randomized controlled trial (RCT) with a noninferiority design investigated 3 vs 6 months of fluoropyrimidine in combination with oxaliplatin.[16] Although the endpoint of noninferiority marginally missed statistical significance, the clinically not relevant difference in OS results supported the use of 3 months of adjuvant capecitabine plus oxaliplatin (CAPOX) or 5-FU plus oxaliplatin (FOLFOX) for most patients with stage III CC. In addition, there was a substantial reduction of toxicities, inconveniences, and costs associated with a shorter duration of treatment.

In 2017, results of IDEA were published and based on these results the Dutch guideline was revised in the same year.[16-20] The new guideline recommended 3 months of combination ACT, with a preference for CAPOX, in patients with high-risk stage II and stage III CC. For patients in whom fluoropyrimidine monotherapy is indicated, 6 months of treatment remained the recommended duration of treatment.

The definition of high-risk stage II CC has been the subject of debate for decades. Ten years of follow-up of the landmark MOSAIC trial did not demonstrate a survival benefit of ACT for all patients with high-risk stage II CC, but no subgroup analysis was performed for the pT4N0 patients.[21,22] Several studies demonstrated that the risk factors of <10 regional lymph nodes examined, poorly/undifferentiated tumor, lymphatic or vascular invasion and obstruction or perforation at presentation were of less prognostic and predictive value compared to pT4 status.[13,23-26] Therefore, in the most recent Dutch guideline the definition of high-risk stage II CC is restricted to pT4 as the only factor identifying patients in whom ACT may be indicated.

Guideline adherence has been shown to be limited in the adjuvant setting of CC and significant practice variation exists, which may negatively influence outcomes.[27,28] Especially elderly patients often do not receive ACT, although its safety and benefit have been demonstrated in this population.[27,29] Observed increased toxicity presumably explains a low rate of ACT in the elderly, but reduction of treatment duration might overcome an important amount of severe and persistent side effects.[29,30]

We hypothesize that the revision of the Dutch guideline may lead to a higher rate of guideline-adherence and ultimately to an improvement of clinical outcome. Here, we evaluate the implementation of the IDEA results and revised guideline in clinical practice.

2 | PATIENTS AND METHODS

2.1 | Data collection

Data from the nationwide population-based Netherlands Cancer registry (NCR) were used, managed by the Netherlands Comprehensive Cancer Organization (IKNL). Information on patients and tumor characteristics and treatment are routinely extracted from medical records by trained administrators. Anatomical site of the primary tumor is registered according to the
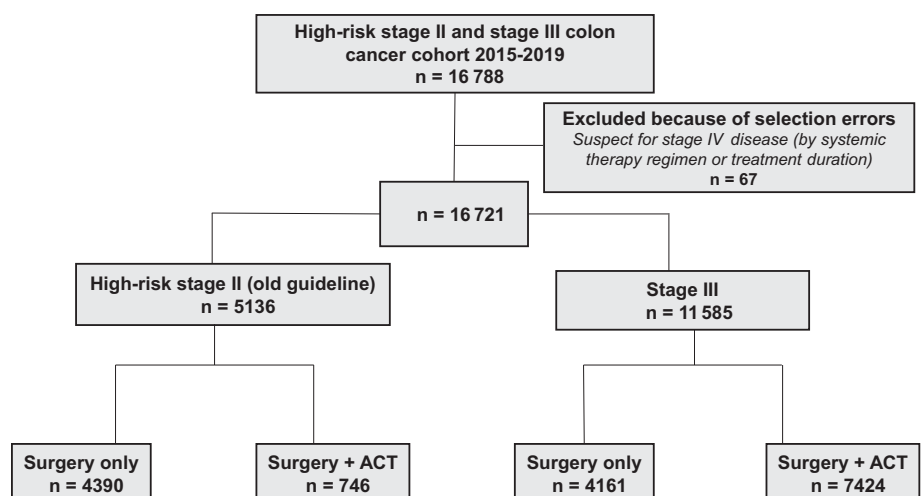
FIGURE 1 Flowchart of the study population

TABLE 1 Baseline demographic and clinical characteristics of the study population, stratified by incidence year

	2015 n = 3776	2016 n = 3549	2017 n = 3445	2018 n = 3375	2019[a] n = 2576
(A) All patients with high-risk stage II and stage III CC					
Gender					
Male	1986 (53%)	1888 (53%)	1757 (51%)	1743 (52%)	1253 (49%)
Age					
≥75 y	1255 (33%)	1228 (35%)	1222 (36%)	1334 (40%)	988 (38%)
WHO performance score					
0–1	1486 (39%)	1584 (45%)	1651 (48%)	1697 (50%)	1401 (54%)
≥2	134 (4%)	150 (4%)	147 (4%)	151 (5%)	119 (5%)
Unknown	2156 (57%)	1815 (51%)	1647 (48%)	1527 (45%)	1056 (41%)
Tumor location					
Right-sided	1826 (48%)	1764 (50%)	1734 (50%)	1696 (50%)	1350 (52%)
Left-sided	1902 (50%)	1751 (49%)	1680 (49%)	1643 (49%)	1201 (47%)
Unknown	48 (1%)	34 (1%)	31 (1%)	36 (1%)	25 (1%)
Type of hospital					
Academic	128 (7%)	136 (8%)	84 (5%)	94 (6%)	77 (6%)
Teaching	1023 (52%)	897 (50%)	830 (51%)	801 (51%)	651 (54%)
General	827 (42%)	748 (42%)	703 (44%)	678 (43%)	484 (40%)
pT stage					
pT1	114 (3%)	117 (3%)	87 (3%)	106 (3%)	64 (3%)
pT2	263 (7%)	290 (8%)	261 (8%)	269 (8%)	192 (8%)
pT3	2362 (63%)	2234 (63%)	2175 (63%)	2052 (61%)	1628 (63%)
pT4	1031 (27%)	904 (26%)	913 (27%)	941 (28%)	688 (27%)
pTx	6 (0%)	4 (0%)	9 (0%)	7 (0%)	4 (0%)
pN stage					
pN0	1149 (30%)	1059 (30%)	1100 (32%)	1022 (30%)	768 (30%)
pN1	1771 (47%)	1687 (48%)	1602 (47%)	1669 (50%)	1291 (50%)
pN2	848 (23%)	793 (22%)	741 (22%)	674 (20%)	508 (20%)
pNx	8 (0%)	10 (0%)	2 (0%)	9 (0%)	9 (0%)
TNM stage (eighth AJCC)					
Stage II high-risk	1157 (31%)	1069 (30%)	1102 (32%)	1031 (31%)	777 (30%)
Stage III	2619 (69%)	2480 (70%)	2343 (68%)	2344 (70%)	1799 (70%)
Low-risk (pT1-3N1)	1430 (55%)	1391 (56%)	1302 (56%)	1349 (58%)	1051 (58%)
High-risk (pT4/N2)	1189 (45%)	1089 (44%)	1041 (44%)	995 (42%)	748 (42%)
Mismatch repair status					
pMMR	949 (25%)	1600 (45%)	1763 (51%)	1700 (50%)	1325 (51%)
dMMR	231 (6%)	362 (10%)	372 (11%)	402 (12%)	349 (14%)
Unknown	2596 (69%)	1587 (45%)	1310 (38%)	1273 (38%)	902 (35%)
	2015 n = 1157	**2016 n = 1069**	**2017 n = 1102**	**2018 n = 1031**	**2019 n = 777**
(B) Additional characteristics of subgroup of patients with high-risk stage II CC					
pT4 stage					
Yes	421 (36%)	367 (34%)	385 (35%)	408 (40%)	295 (38%)
Perforation at presentation					
No	950 (82%)	852 (80%)	896 (81%)	825 (80%)	620 (80%)
Yes	130 (11%)	166 (16%)	133 (12%)	152 (15%)	110 (14%)
Unknown	77 (7%)	51 (5%)	73 (7%)	54 (5%)	47 (6%)

TABLE 1   (Continued)

	2015 n = 1157	2016 n = 1069	2017 n = 1102	2018 n = 1031	2019 n = 777
Obstruction at presentation					
No	812 (70%)	777 (73%)	795 (72%)	774 (75%)	542 (70%)
Yes	320 (28%)	265 (25%)	279 (25%)	246 (24%)	217 (28%)
Unknown	25 (2%)	27 (3%)	28 (3%)	11 (1%)	18 (2%)
Differentiation grade					
Grade I-II	780 (67%)	681 (64%)	769 (70%)	758 (74%)	572 (74%)
Grade III-IV	277 (24%)	291 (27%)	263 (24%)	234 (23%)	174 (22%)
Unknown	100 (9%)	97 (9%)	72 (7%)	39 (4%)	31 (4%)
<10 lymph nodes resected					
Yes	140 (12%)	108 (10%)	114 (10%)	96 (9%)	64 (8%)
Lymphatic invasion					
No	920 (80%)	873 (82%)	897 (81%)	844 (82%)	612 (79%)
Yes	149 (13%)	147 (14%)	170 (15%)	159 (15%)	132 (17%)
Unknown	88 (8%)	49 (5%)	35 (3%)	28 (3%)	33 (4%)
Vascular invasion					
No	423 (37%)	625 (59%)	759 (69%)	748 (73%)	546 (70%)
Yes	239 (21%)	264 (25%)	302 (28%)	267 (26%)	204 (26%)
Unknown	495 (43%)	180 (17%)	41 (4%)	16 (2%)	27 (3%)
High risk factors					
>2	96 (8%)	116 (11%)	108 (10%)	104 (10%)	88 (11%)

Note: High-risk stage II CC according to the Dutch guideline valid until 2017.

Abbreviations: dMMR, deficient mismatch repair; pMMR, proficient mismatch repair; WHO, World Health Organization.

[a]Not all cases in 2019 were registered yet, leading to lower absolute counts in this year.

FIGURE 2   Percentage of patients who treated with ACT (all regimens) per subgroup and per year in high-risk stage II and stage III CC from 2015 until 2019 in The Netherlands. High-risk stage II is divided in patients with pT4N0 disease and pT3N0 disease with ≥1 of the following risk factors: <10 lymph nodes resected, poorly/undifferentiated tumor, lymphatic or vascular invasion and obstruction or perforation at presentation
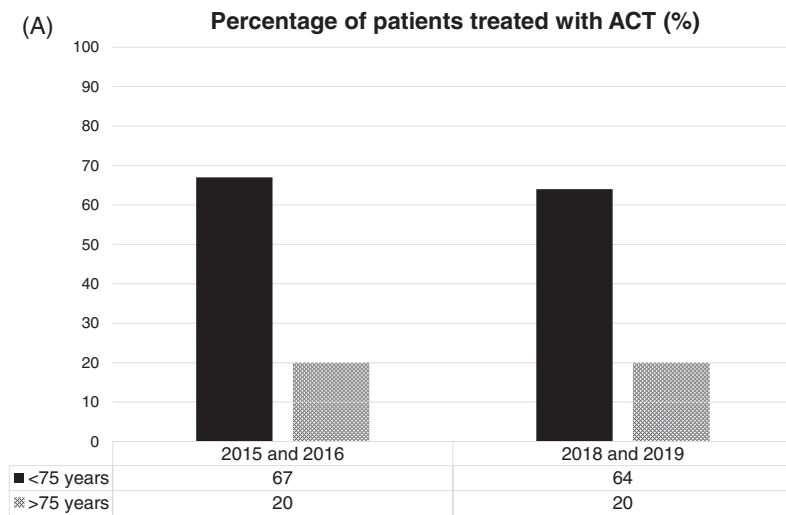

Percentage of patients per substage treated with ACT (%)

	2015	2016	2017	2018	2019
□ pT3N0	15	10	6	2	3
▪ pT4N0	26	29	20	29	29
▪ pT1-3N1	66	64	63	61	61
■ pT4N1-2 and/or pTxN2	69	66	65	62	63
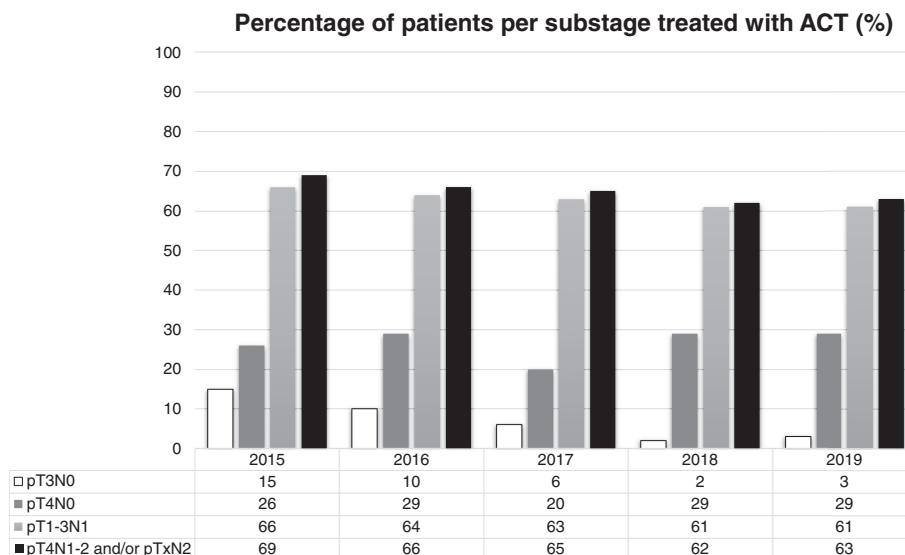
International Classification of Disease-Oncology (ICD-O).[31] The tumor-node-metastasis (TNM) classification is used for stage reporting of the primary tumor according to the valid edition at the time of CC diagnosis.

For our study we analyzed data from patients aged ≥18 years with histologically proven high-risk stage II and stage III CC diagnosed between 2015 and 2019. Data of 2019 were incomplete with not all cases being registered at the time of this analysis.

The selection of high-risk stage II patients was based on high-risk factors in the guideline valid until 2017; a pT4 primary tumor, <10 regional lymph nodes examined, poorly/undifferentiated tumor,

(A) **Percentage of patients treated with ACT (%)**

	2015 and 2016	2018 and 2019
■ <75 years	67	64
▓ >75 years	20	20

(B)

Before introduction new guideline (2015-2016)
Proportion prescribed ACT regimens (%)

After introduction new guideline (2018-2019)
Proportion prescribed ACT regimens (%)

(C)

2015-2016

2018-2019

(D)

2015-2016

2018-2019

FIGURE 3 Prescribed ACT regimens before and after revision of the guideline in 2017. (A) Proportion of ACT treatment in patients with an indication for ACT per time period and per age group. (B) Proportions of chemotherapy regimens in patients treated with ACT before and after revision of the guideline in 2017 in all patients (high-risk stage II and stage III, all ages). (C) Proportions of chemotherapy regimens in patients aged <75 years treated with ACT before and after revision of the guideline in 2017. (D) Proportions of chemotherapy regimens in elderly patients aged ≥75 years treated with ACT before and after revision of the guideline in 2017
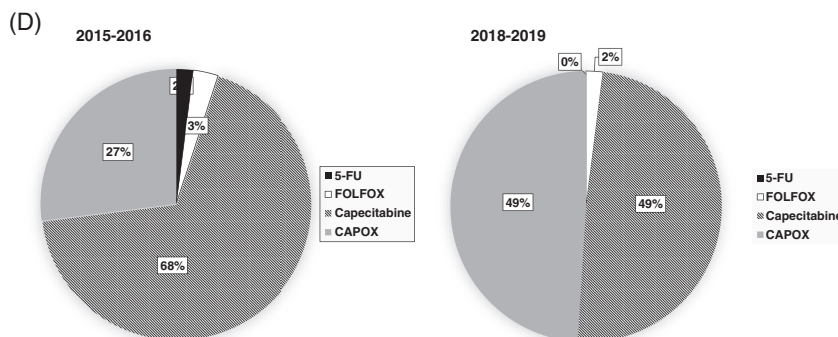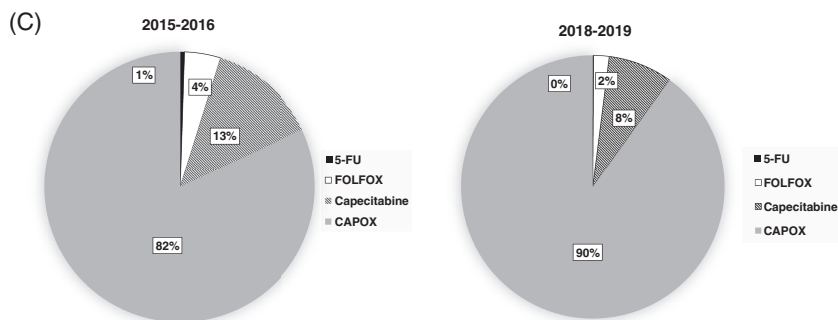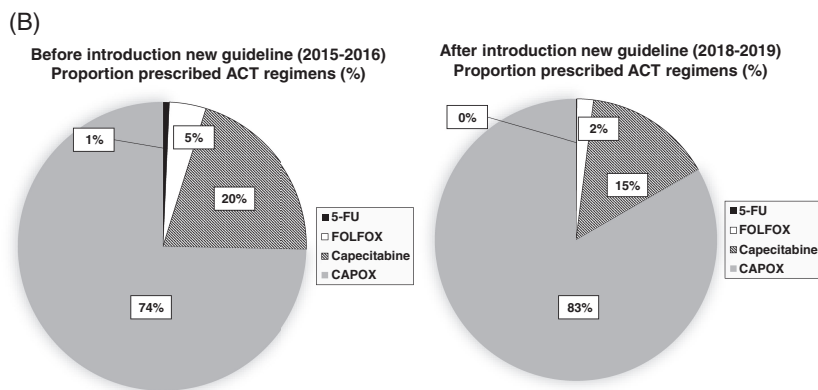
lymphatic or vascular invasion, obstruction or perforation at presentation. Stage III patients were divided into low risk (pT1-3N1) and high risk (T4 and/or N2) subgroups and in age groups (<75 years and ≥75 years of age) for subgroup- and age-specific analyses of ACT prescription. ACT regimens included fluoropyrimidine monotherapy, 5-fluorouracil plus leucovorin (5FU/LV), capecitabine monotherapy, CAPOX and FOLFOX.

2.2 | Statistical analysis

Patient and tumor characteristics were analyzed using descriptive statistics. Differences between characteristics were tested using chi-square tests. The difference in mean duration of ACT between incidence years was tested using one-way analysis of variance. A P-value of <.05 was considered statistically significant, and all tests were 2-sided. Statistical analyses were performed using SPSS (version 27.0, IBM Corp, Armonk, New York).

3 | RESULTS

3.1 | Study population

A total of 16 788 patients were diagnosed with high-risk stage II and stage III CC between 2015 and 2019. Of these patients, 5136 (31%)
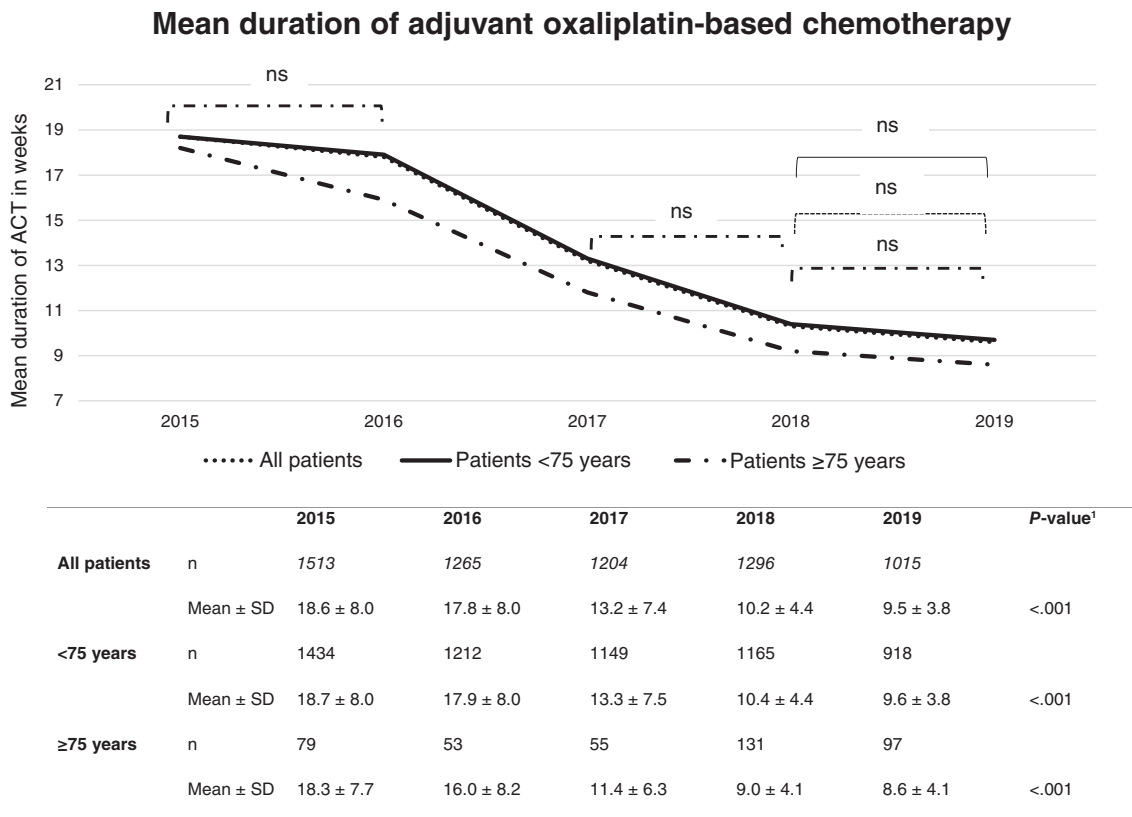
were diagnosed with high-risk stage II and 11 585 (69%) with stage III CC. Due to selection errors 67 patients were excluded.

The majority of high-risk stage II patients (n = 4390, 86%) were treated with surgery alone and did not receive ACT. In contrast, in stage III CC, 4161 patients (36%) were treated with surgery alone and therefore the majority of 7424 patients (64%) received ACT (Figure 1).

Patient and tumor characteristics of the total population are presented by incidence year in Table 1A, and the population with high-risk stage II CC according to the Dutch guideline valid until 2017 in Table 1B.

3.2 | Treatment with ACT according to stage

The total population was divided in four subgroups to determine the proportion of patients treated with ACT according to stage over the years, that is, pT4 high-risk stage II, non-pT4 high-risk stage II (all other risk factors), low-risk stage III (pT1-3N1) and high-risk stage III (pT4N+ and/or pTanypN2). The only substantial change is the proportion of patients with non-pT4 high-risk stage II treated with ACT (Figure 2) which decreased from 15% in 2015 to 3% in 2019. Of non-pT4 high-risk stage II patients who received ACT after guideline revision (n = 29) the majority (88%) had ≥2 high-risk factors. In other subgroups there is no significant change in the use of ACT over time.

Mean duration of adjuvant oxaliplatin-based chemotherapy

		2015	2016	2017	2018	2019	P-value[1]
All patients	n	1513	1265	1204	1296	1015	
	Mean ± SD	18.6 ± 8.0	17.8 ± 8.0	13.2 ± 7.4	10.2 ± 4.4	9.5 ± 3.8	<.001
<75 years	n	1434	1212	1149	1165	918	
	Mean ± SD	18.7 ± 8.0	17.9 ± 8.0	13.3 ± 7.5	10.4 ± 4.4	9.6 ± 3.8	<.001
≥75 years	n	79	53	55	131	97	
	Mean ± SD	18.3 ± 7.7	16.0 ± 8.2	11.4 ± 6.3	9.0 ± 4.1	8.6 ± 4.1	<.001

FIGURE 4 Mean duration of adjuvant oxaliplatin-based ACT in weeks for all patients treated with ACT throughout the years. [1]Between-group significance. Except for the nonsignificant (ns) mean differences, all other comparisons significantly differ from each other

The proportion of pT4 high-risk stage II patients that received ACT remains low, and is less than 30%. Throughout the years the proportion of ACT in stage III disease is around 60% to 70%. No differences are observed between patients with low- and high-risk stage III disease.

3.3 | Adjuvant treatment regimens

Of all ACT treatment episodes the administered regimens were analyzed in the time periods 2015 to 2016 and 2018 to 2019, before and after guideline revision. Patients diagnosed in 2017 (n = 3445) when the new guideline was implemented are not included (Figure 3).

Administration of CAPOX increased from 74% to 83%. Treatment with 5-FU/LV or FOLFOX was only given in 5% of patients and decreased to 2%. Capecitabine monotherapy decreased from 20% to 15% of ACT prescriptions.

In 2015 to 2016, the majority of the patients ≥75 years of age received capecitabine monotherapy (68%) with a decrease to 49% in 2018 to 2019. In contrast, CAPOX was administered in only 27% in 2015 to 2016 and increased to 49%.

3.4 | Duration of adjuvant treatment

The reduction in treatment duration of oxaliplatin-based ACT after revision of the guideline in 2017 is illustrated in Figure 4. In 2015 to 2016, the mean time on treatment was 17.8 to 18.6 weeks of the recommended 24 weeks. After 2017, when the guideline recommended a duration of 12 weeks of ACT, the mean time on treatment decreased to 9.5 to 10.2 weeks.

Guideline-concordant treatment strategy (%)
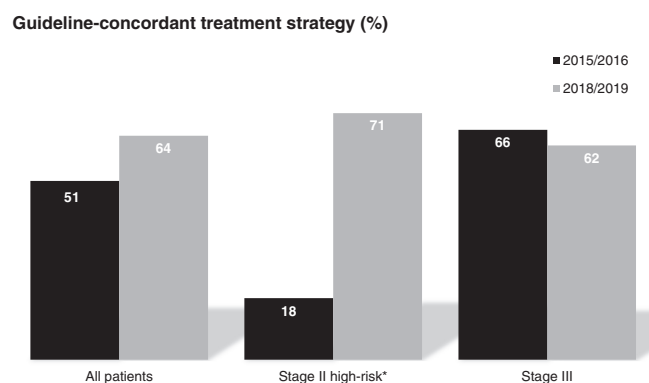
FIGURE 5 Proportion of patients treated according to the prevailing guideline, before and after revision of the guideline in 2017. The proportion indicates patients that were both appropriately treated or appropriately withheld from ACT. *In 2015 to 2016 the definition of high-risk stage II CC comprised several risk factors (pT4 tumor, <10 lymph nodes resected, poorly/undifferentiated tumor, lymphatic or vascular invasion and obstruction or perforation at presentation), in 2018 to 2019 this was restricted to pT4 tumors

In both patients aged <75 years and ≥75 years of age who received oxaliplatin-based ACT, there was a reduction in treatment duration after the guideline revision. The mean ACT duration in the elderly population was 1 to 2 weeks shorter compared to patients <75 years of age in all years.

3.5 | Guideline adherence

A comparison of the proportion of patients who did or did not receive ACT, according to the prevailing guideline, was made between 2015 to 2016 and 2018 to 2019 (Figure 5). In stage III CC the proportion of patients treated guideline-concordant marginally decreased, whereas in high-risk stage II, this proportion substantially increased. The selection of high-risk stage II patients in our analysis, throughout the years, included patients with a risk factor according to the guideline that was valid until 2017. The restriction of the definition of high-risk stage II CC to pT4 tumors led to a decrease in number of patients who inappropriately received ACT.

4 | DISCUSSION

In our study, we analyzed the impact of the IDEA study results and revised guideline in clinical practice in the Netherlands.[13]

We observed that new guideline recommendations for the duration of ACT, as well as the restricted indication for ACT in high-risk stage II disease, were rapidly implemented with a significant reduction of ACT duration in all subgroups of stage II and III CC patients to a mean duration of almost 3 months. This decline in ACT duration was already visible in 2017 before the revision of the guideline, when results of the IDEA trial were first presented at the ASCO Annual Meeting. This indicates a rapid integration of the new scientific insights in clinical practice. Interestingly, the proportion of oxaliplatin-based ACT increased from 27% to 49% in patients older than 75 years after 2017. This implies that with shortening of ACT duration, more elderly patients were regarded as suitable candidates and/or willing to undergo oxaliplatin-based ACT. The effect of this shift toward more oxaliplatin-based treatment in the elderly on survival outcomes will be evaluated over the next few years.

The proportion of stage II patients with other risk-factors than pT4 who were treated with ACT decreased to a small minority of 3%. Administration of ACT in this minority of patients without an indication for ACT after guideline revision, may be explained by the presence of ≥2 previous high-risk factors in the majority of these patients. Also the existence of discordant international guidelines regarding the definition of high risk stage II may play a role. Lastly, ignorance of the new guideline cannot be excluded. The restricted indication for ACT in stage II CC improved overall guideline adherence, mainly because refraining from ACT became guideline-concordant in the non-pT4 stage II patients.

Of the pT4 stage II patients only 30% received ACT, which remained stable over time. On the other hand, more than 60% of low-

risk stage III patients received ACT. This difference is remarkable as recurrence and mortality rates in pT4 stage II patients are higher compared to low-risk stage III patients.[32] There are several possible explanations for this observation. First, in the absence of prospective randomized trials showing the benefit of ACT in pT4 stage II CC, physicians may still be hesitant in offering ACT to these patients. Secondly, analysis of practice variation of stage II CC treatment in The Netherlands demonstrated large variation in administration rates on a hospital level, from 0% to 39%.[27] This could implicate that the choice of treatment largely depends on the individual hospital level strategy. This undesired practice variation can influence the quality of care for individual patients. Lastly, in our data there is an uneven age distribution in high-risk stage II vs stage III patients. Of all high-risk stage II patients, 44% is aged over 75 years compared to 33% of stage III patients. Since elderly patients are more often defined as unfit for oxaliplatin-based ACT, the majority receives fluoropyrimidine monotherapy in stage III CC. For stage II CC only oxaliplatin-based ACT is recommended, which may contribute to the fact that a substantial part of the elderly high-risk stage II patients did not receive ACT.

There is a clinical need for improving outcomes in pT4N0 patients. Careful consideration of recurrence risk and the guideline recommendations for ACT should be encouraged and unwanted practice variation avoided.

This is the first study that evaluated administration and duration of ACT on a national level after presentation of the pivotal IDEA study results. An international survey in 2019 that analyzed perspectives of 174 medical oncologists regarding results of IDEA and impact on clinical practice, demonstrated that 70% considered 3 months of ACT and discussed this option with patients, but how these perspectives translated into clinical practice was unknown.[33] In addition, concerns have raised about undertreatment of patients with a high recurrence risk that would possibly benefit from 6 months of ACT. The proportion of these high-risk patients is estimated to be 2% to 4% of stage III CC patients. Therefore, efforts should be made in exploratory analyses of the IDEA cohorts to find reliable predictive factors to identify these patients that are likely to benefit from a prolonged adjuvant treatment.[34]

The strength of our study is the high-quality and completeness of data in the NCR. Our study therefore reflects a reliable real-world situation. The advantage above RCTs is the unselected population for whom the guidelines are applicable.

A limitation of our study is the absence of data on outcomes like recurrence rate and overall survival. These data will become available in the next few years and will contribute to the evaluation of real-world treatment outcomes of current ACT guideline recommendations in different subgroups of CC. Another limitation is that reasons for deciding to withhold ACT in patients in whom this is indicated are unknown. This information would be of additional value to evaluate reasons for guideline nonadherence.

We conclude that the aim for every individual patient is to provide accurate information about prognosis and efficacy of treatment, which will lead to the most appropriate treatment strategy. However, current guidelines are lacking a tailored approach in the adjuvant setting of CC. In stage II disease there is a continuing debate about efficacy of ACT, and in stage III the established effect of ACT remains accompanied by a substantial overtreatment of patients who will not derive benefit of ACT. In a recent publication based on the extensive IDEA study population, a model was built to predict outcomes and benefit of ACT on an individual level based on 16 distinct T-N substages in stage III CC. This approach is an important first step in the way toward informed shared decision making and tailored treatment in the adjuvant setting.[7]

In addition, there are promising clinical and molecular developments that may contribute to this desired tailored treatment. For example, a new clinical strategy is the use of neoadjuvant chemotherapy, that could reduce postoperative complications and might improve clinical outcomes in patients with cT3-4 tumors.[35] In addition, new biomarkers such as circulating tumor DNA, the Immunoscore and the Consensus Molecular Subtypes may improve prognostication and may improve the selection of patients who will benefit from ACT.[36-38] This is currently being investigated in trials of which results will come available in the near future. We therefore advocate rapid integration of new scientific insights in frequently updated guidelines. Simultaneously, there should be regular evaluation of real-world clinical practice to optimize adaptation to continuously evolving knowledge.

5 | CONCLUSIONS

This large population-based representative study demonstrated that the revised Dutch guideline was quickly implemented in clinical practice with evident shortening of the duration of oxaliplatin-based ACT shortly after the results of the IDEA collaboration became available in 2017. Changes in ACT duration were even noticed before the renewed guideline was published, pointing to readiness to implement de-escalation of ACT in The Netherlands.

Stage III patients and patients below the age of 75 years received ACT more often than stage II and elderly patients. However, with shortening of the ACT duration, the proportion of oxaliplatin-based ACT in elderly patients increased substantially.

In stage II CC the only remaining indication for ACT in the guideline is a pT4 primary tumor. Although there was no increase in pT4N0 patients receiving ACT, the proportion of pT3N0 patients receiving ACT decreased substantially, thereby raising the proportion of guideline-concordant treatment in stage II CC.

Future research will evaluate how these findings affect clinical outcomes of patients with early-stage CC.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. **Karlijn L. van Rooijen**: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Methodology, Validation, Visualization, Writing—original draft, Writing—review &editing. **Jeroen W. G. Derksen**: Formal analysis, Methodology, Visualization, Writing—review & editing. **Helena M. Verkooijen**:

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