NATIONAL BOWEL CANCER AUDIT

How to best capture adjuvant chemotherapy use in stage III colon cancer with linked HES-APC and SACT data

NBOCA: Methodological Development

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1. Executive Summary

The Systemic Anti-Cancer Therapy (SACT) dataset is a relatively new data source which captures information about chemotherapy use in England. To date, there is limited use of SACT data within the literature, however, some studies have highlighted potential limitations regarding data completeness and quality. Chemotherapy use is also captured within Hospital Episode Statistics Admitted Patient Care (HES-APC).

Given the data quality issues which have been raised so far, this short report aims to explore how best to capture adjuvant chemotherapy use with linked HES-APC and SACT datasets by evaluating i) whether information from SACT and HES-APC can be combined to reliably capture adjuvant chemotherapy use in stage III colon cancer patients and ii) whether information from SACT and HES-APC can be combined reliably to capture the number of cycles of adjuvant chemotherapy in stage III colon cancer patients.

NBOCA provides annual hospital-trust indicators of adjuvant chemotherapy provision in patients with stage III colon cancer. SACT is currently only available for English providers. Welsh chemotherapy data is taken from an NBOCA data item which obtains only broad information about the receipt of pre-operative treatment.

This methodological work uses data from NBOCA patients undergoing major resection for pathological stage III colon cancer between 01 June 2014 and 30 April 2017 with linked SACT and HES-APC data from June 2014 to April 2018 to allow sufficient time for completion of adjuvant chemotherapy accounting for delays.

This report demonstrates that the majority of patients are identified as receiving adjuvant chemotherapy in both SACT and HES-APC, but a considerable proportion are identified in either SACT or HES-APC alone. The reasons for this are likely to be multifactorial, however, a major limitation of capturing chemotherapy use within HES-APC is the absence of chemotherapy regimen details which likely leads to overestimation of adjuvant chemotherapy use. SACT appears to capture oral chemotherapy use more effectively than HES-APC.

This report also demonstrates that, for patients who are captured in both datasets, there is good agreement between datasets on the number of cycles of adjuvant chemotherapy provided. Again, there is likely to be some overestimation of cycles of adjuvant chemotherapy within HES-APC because of the absence of chemotherapy regimen details. There are nuances to the capture of chemotherapy cycles in each dataset in isolation and possible discrepancies in the proportion of regimens being captured by each.

These findings lead to the proposition of an approach to capture the provision and number of cycles of adjuvant chemotherapy, making use of the information in both SACT and HES-APC. This approach is likely to overcome many of the limitations within each dataset. It is anticipated that this will increase the sensitivity of capturing adjuvant chemotherapy use and number of cycles, accepting a degree of overestimation for those captured in only HES-APC.

NBOCA plan to further investigate the completion of adjuvant chemotherapy and how this relates to outcomes. As such, it is important to validate the capture of overall adjuvant chemotherapy use and the number of cycles of adjuvant chemotherapy recorded, both for future work by NBOCA and for other analysts generally planning to use SACT data. Additionally, this work could support the development of methodology for Patient Episode Database for Wales (Welsh equivalent of HES-APC) and allow us to obtain more detailed chemotherapy information for Welsh providers.

The resulting recommendations from this short report are:

1. SACT should be used in combination with HES-APC to capture whether or not patients received adjuvant chemotherapy for stage III colon cancer.
2. SACT should be used in combination with HES-APC to ascertain the number of cycles of chemotherapy that patients have received. Apart from a select group identified as receiving palliative treatments in SACT, the highest number of cycles in either dataset should be used.
3. Further work should be carried out to include assessing whether it is possible to ascertain chemotherapy regimens from HES-APC (as this may further improve agreement between the two datasets) and whether chemotherapy details can be obtained from Welsh data.

2. Introduction

The SACT dataset is held by the National Cancer Registry and Analysis Service (NCRAS) at Public Health England (PHE).[1] SACT is a unique dataset which aims to capture detailed information about chemotherapy administration, including oral agents and biological therapies.

Data collection began in April 2012 and submission for all English NHS providers of chemotherapy in any inpatient, day case, outpatient or community setting became mandatory from April 2014. Most data is collected via e-prescribing systems.

SACT contains approximately 43 data items, some of which are mandatory. Variability in data completeness and quality has been described across these data items.[2] Data completeness and quality have improved over time as increasing numbers of hospitals have implemented e-prescribing and more rigorous checking mechanisms have evolved. Despite this, an inherent limitation with all electronic healthcare databases remains the dependence on clinical staff uploading data in an accurate and timely fashion.

To date, there has been limited use of SACT within the literature.[3-6] A recent study aimed to evaluate the extent to which chemotherapy cycles recorded in Hospital Episode Statistics Admitted Patient Care (HES-APC) are captured in SACT in a cohort of lung cancer patients.[7] It raised concerns about the validity of the SACT dataset, finding that 12.5% of individuals undergoing chemotherapy and 31% of chemotherapy cycles in HES APC did not have corresponding records identified in SACT. Data included chemotherapy administered between 01 January 2012 and 28 February 2017 with marked improvements noted over time (54% of cycles not captured in 2012 vs. 15.9% in 2016).

In addition, other potential difficulties with interpretation that have been raised include disproportionate numbers of patients within SACT with only one cycle of chemotherapy recorded and discrepancies in how oral chemotherapy data is entered into the dataset.[2]

The National Bowel Cancer Audit (NBOCA) recently published a study evaluating variation in the use of adjuvant chemotherapy in stage III colon cancer.[8] Within this more homogeneous cohort, it found that 10.9% of patients in HES-APC were not captured in SACT compared to 12.5% in the

previously mentioned lung cancer study.[7] However, it also demonstrated that 28.8% of patients in SACT were not captured in HES-APC. It was assumed that patients with a record of chemotherapy in either database had received adjuvant chemotherapy.

Further work planned by NBOCA includes more in-depth analysis on completion of chemotherapy and subsequent impact on survival. It is important to ensure that methodology for establishing adjuvant chemotherapy use is robust and validated. As described in the executive summary, this short report will explore whether information from SACT and HES-APC can be combined to reliably capture both use and number of cycles of adjuvant chemotherapy in stage III colon cancer patients.

3. Methods

3.1 Establishing eligible NBOCA patient cohort

Patients were identified who, according to NBOCA records, had undergone a major resection for stage III colon cancer between 01 June 2014 and 30 April 2017 in an English NHS Trust. Appendiceal cancers were excluded. These NBOCA records were linked to both SACT and HES-APC datasets. SACT and HES-APC data is currently only available in England.

3.2 Establishing adjuvant chemotherapy within SACT

Previous literature has suggested that not all English NHS Trusts were submitting SACT data until July 2014.[2] Cohort selection accounted for this and ensured that all patients had a minimum of 12 months SACT follow-up data from the NBOCA date of surgery to allow adequate time for chemotherapy completion, taking into account potential delays. SACT data covering the period of 30 June 2014 until 30 April 2018 was used.

The SACT dataset consists of a longitudinal hierarchical structure. A programme may consist of one or more chemotherapy regimens. A regimen can include single or multiple drugs. Each regimen can consist of an indefinite number of cycles. For each cycle, the individual drugs

administered within that cycle are listed along with further details such as administration route and drug dose. As a consequence of this structure, SACT contains multiple rows per patient with one row of data per drug administered.

Chemotherapy data is inherently complex as patients may stop and start treatment over many years. Linkage to SACT included all chemotherapy for each patient regardless of intent (e.g. curative or palliative). Previous work advises that the 'intent' data variable in SACT may not be reliable and should be confirmed via clinical interpretation.[9] As such, an algorithm was established to identify which chemotherapy was likely to have been given in the adjuvant setting using the drugs and dates of administration recorded in SACT, compared to the NBOCA date of surgery (Figure 1). This was developed using expert consensus from medical and clinical oncologists.

In line with NICE guidelines[10 11], standard adjuvant chemotherapy was considered as:

- 5-fluorouracil (5-FU) alone
- 5-FU and oxaliplatin (FOLFOX)
- Capecitabine alone
- Capecitabine and oxaliplatin (CAPOX)

5,597 patients had at least one chemotherapy record in SACT within 4 months of surgery. 468 of these patients had either non-standard adjuvant regimens administered (i.e. not one of the four regimens listed above) or erroneous regimens recorded (oxaliplatin in isolation) and were therefore considered not to have had adjuvant chemotherapy according to SACT. 5,129 patients were therefore deemed as receiving adjuvant chemotherapy according to SACT.

3.3 Establishing adjuvant chemotherapy within HES-APC

As per previous methodology[8], patients were considered to have received chemotherapy according to HES-APC if they had an inpatient or daycase admission containing a relevant chemotherapy OPCS-4 (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision) or ICD-10 (International Classification of Diseases, 10th revision) code within 4 months of surgery.

The major limitation with HES-APC is that the only information available is the date and chemotherapy code; there are no regimen details. This means that the granularity of data available in SACT to aid clinical interpretation of which chemotherapy drugs may have been given as adjuvant therapy is not present. A similar algorithm was applied to establish likely adjuvant chemotherapy according to dates of administration of chemotherapy within HES-APC, compared to the date of surgery in NBOCA (Figure 1).

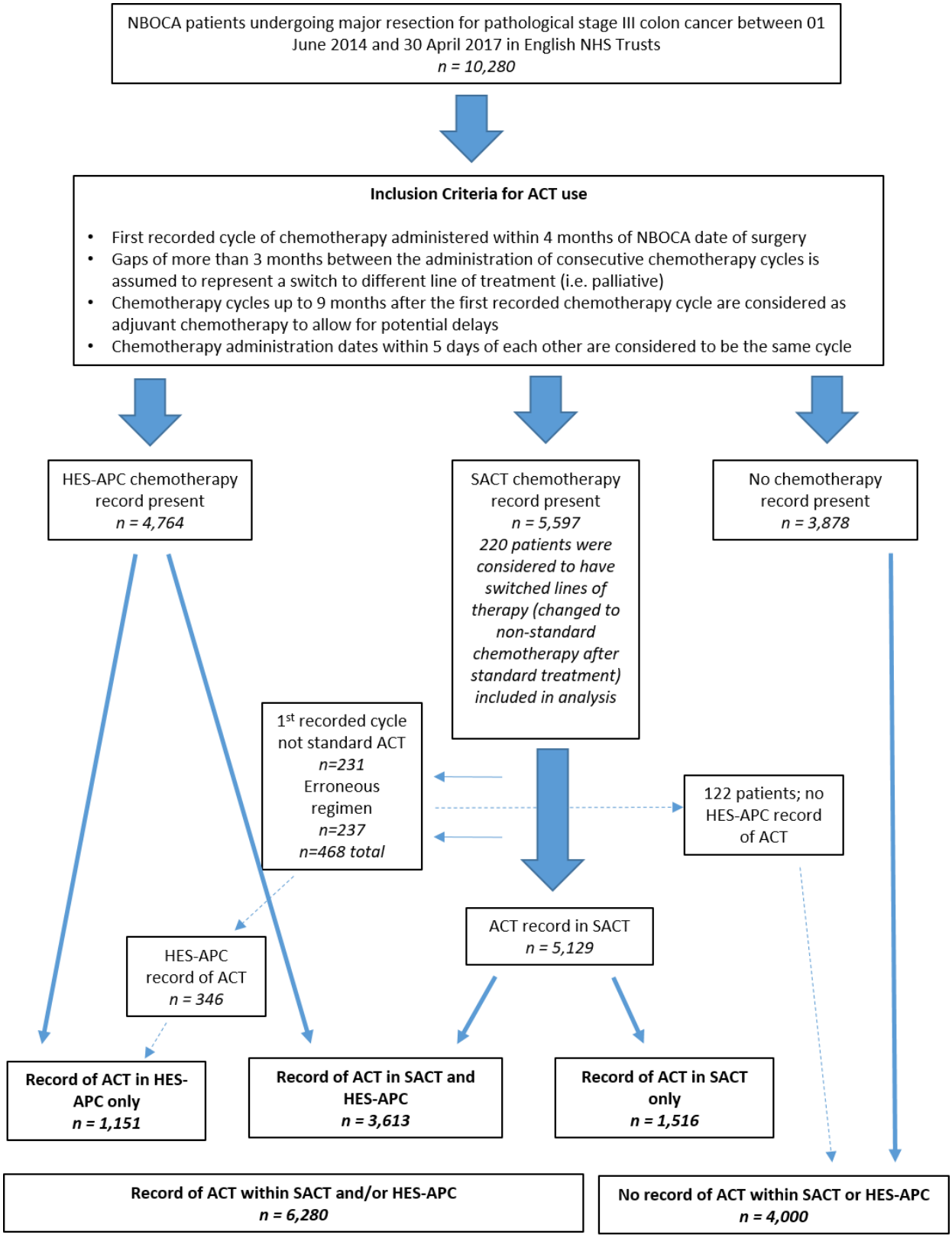
It could not be determined whether or not the first chemotherapy record after surgery was a colorectal regimen, but the assumption was that this was unlikely to be for a different cancer and therefore not a major issue. It was also not possible to identify i) patients starting immediately on non-standard regimens, or ii) patients switching to non-standard regimens partway through adjuvant treatment, both of which might represent palliative treatment. 4,764 patients were deemed to have received adjuvant chemotherapy according to HES-APC.

3.4 Final patient cohorts

Four groups of patients were established to include i) those with chemotherapy records in both SACT and HES-APC, ii) those with chemotherapy records in SACT only, iii) those with chemotherapy records in HES-APC only, and iv) those without a record of chemotherapy in either dataset. This information was presented in a two-by-two table to evaluate the extent to which chemotherapy is captured by each dataset.

Of the 10,280 patients identified as undergoing major resection for pathological stage III colon cancer, 6,280 patients were deemed to have received adjuvant chemotherapy according to SACT and/or HES-APC. 3,613 patients had records in both datasets according to the applied algorithms. 1,516 patients had records in SACT only and 1,151 patients in HES-APC only. 4,000 patients did not have a record of adjuvant chemotherapy identified in either SACT or HES-APC.

Figure 1 – Algorithms applied to SACT and HES-APC and resulting final patient cohorts for those identified as receiving adjuvant chemotherapy according to both SACT and HES-APC, SACT only and HES-APC only



3.5 Evaluating the recording of cycles of chemotherapy using SACT and HES-APC

To evaluate the numbers of cycles of chemotherapy completed, comparison was undertaken of the distribution and agreement of the recording of cycle numbers in SACT and HES-APC in the 3,613 patients with records in both. These distributions were also compared to those for the number of cycles in patients with records in SACT only and in those with records in HES-APC only.

4. Results

4.1 Can information from SACT and HES-APC be combined to reliably capture adjuvant chemotherapy for stage III colon cancer?

10,280 NBOCA patients were identified who had undergone major resection for pathological stage III colon cancer in an English NHS Trust. Of these, 6,280 (61.0%) were identified as having received adjuvant chemotherapy according to SACT and/or HES-APC within 4 months after surgery. Table 1 shows the proportion of these patients who were identified within each dataset.

Of the 6,280 patients who were identified as receiving adjuvant chemotherapy, 3,613 (57.5%) were identified in both datasets. 1,151 (18.3%) were identified in HES-APC alone and 1,516 (24.1%) were identified in SACT alone. Overall, there was 74.1% concordance between the two datasets (concordant cells/total number of patients). 70.4% of patients with adjuvant chemotherapy identified in SACT also had adjuvant chemotherapy identified in HES-APC and 75.8% of patients with adjuvant chemotherapy identified in HES-APC also had adjuvant chemotherapy identified in SACT.

Table 1 - Numbers of patients identified as commencing adjuvant chemotherapy within 4 months of major resection for pathological stage III colon cancer according to SACT and/or HES-APC datasets

	Adjuvant chemotherapy according to SACT		
Adjuvant chemotherapy according to HES-APC	**Yes**	**No**	**Total**
Yes	3,613	1,151	4,764
No	1,516	4,000	5,516
Total	5,129	5,151	10,280

Patients captured in HES-APC only

As HES-APC does not include specific regimen details there is a risk that patients commencing palliative colorectal chemotherapy, or chemotherapy for a synchronous non-colorectal primary may be included. The lack of granularity of the data limits clinical interpretation of what is likely to be adjuvant chemotherapy e.g. restriction to the four standard adjuvant chemotherapy regimens was not possible.

Other possible explanations for the identification of patients receiving adjuvant chemotherapy in HES-APC and not SACT could include linkage issues (NBOCA to SACT), coding errors within HES-APC, poor recording of SACT data by particular hospitals (possibly those without e-prescribing systems) and discrepancies in the date of administration of the first cycle of chemotherapy.

Patients identified in NBOCA will only be linked to SACT records where the primary ICD-10 diagnosis within SACT corresponds to colorectal cancer. This is in contrast to HES-APC where chemotherapy codes are not necessarily associated with a specific cancer code. This could mean that HES-APC captures additional chemotherapy for alternative synchronous cancers, although it is thought that this is of low significance given that this cohort of patients have recently undergone surgery for stage III colon cancer.

Patients captured in SACT only

The most likely explanation for the identification of patients receiving adjuvant chemotherapy in SACT alone is that SACT includes chemotherapy administered in the outpatient and community setting. HES-APC data includes only inpatient and daycase administration. Of note, capecitabine is an oral chemotherapy agent. If this drug is prescribed as a single agent (i.e. given without the intravenous oxaliplatin component), patients may be reviewed entirely in the outpatient setting and, therefore, not captured within HES-APC.

It was also noted that two of the largest tertiary oncology centres within England have low proportions of adjuvant chemotherapy recorded in HES-APC. If these hospitals are excluded from the

analysis, 80.0% of patients identified in SACT have corresponding HES-APC records (compared to 70.4% when they are included). Analysis of HES outpatients data will allow this issue to be explored further as it is likely these centres are coding chemotherapy in this dataset instead.

Chemotherapy coding in HES-APC is complex.[12] SACT largely uses e-prescribing systems to capture chemotherapy. It is therefore highly plausible that coding errors or omissions within HES-APC could occur. Other possible explanations for patients identified in SACT alone could be linkage issues (NBOCA to HES-APC) and discrepancies in the date of administration of the first chemotherapy cycle.

4.2 Can information from SACT and HES-APC be combined to reliably capture the number of cycles of adjuvant chemotherapy administered for stage III colon cancer?

Patients with adjuvant chemotherapy records identified in both SACT and HES-APC

3,613 patients were identified as receiving adjuvant chemotherapy in both SACT and HES-APC. HES-APC tended to capture more cycles of chemotherapy when compared to SACT with 31% of patients having more cycles recorded in HES-APC versus 22.4% in SACT.

On evaluation of the difference in the total number of cycles completed per patient according to SACT and HES-APC in those patients with records available in both, 46.5% of patients had cycle numbers that matched exactly and 84.3% matched or had discrepancies of up to 3 cycles (Table 2).

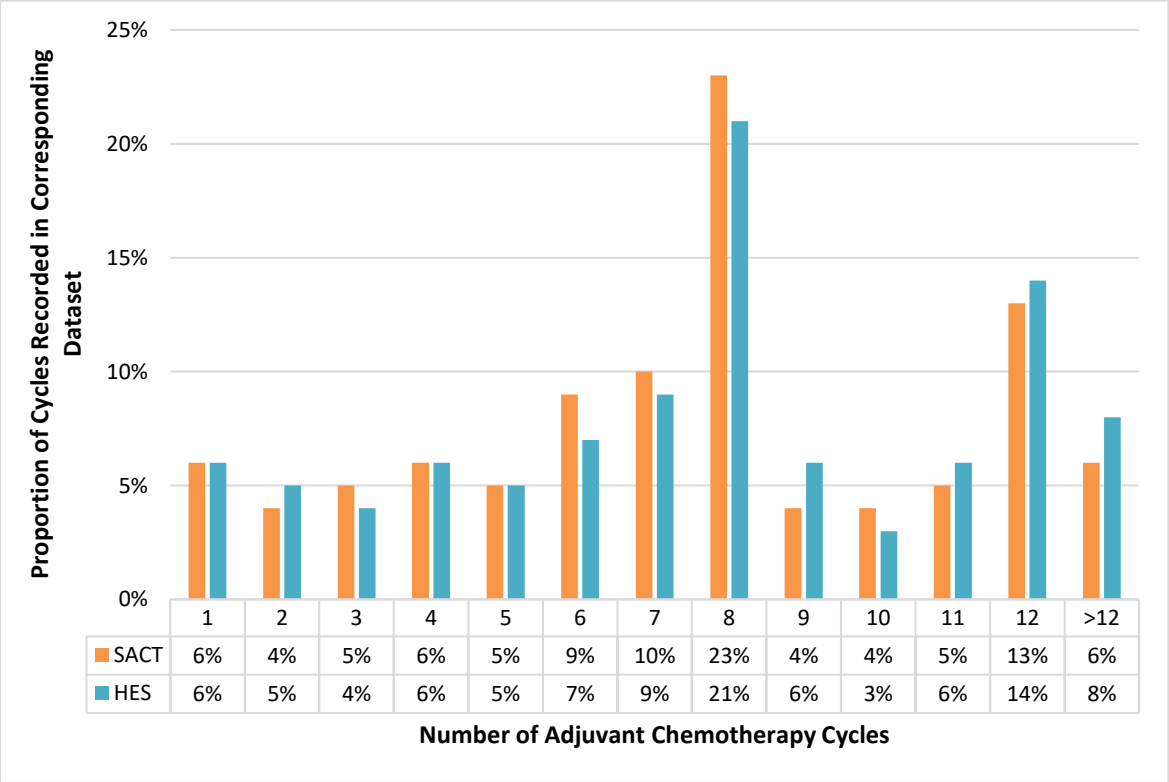
Table 2 – Difference in number of cycles per patient between datasets for patients with records in both SACT and HES-APC (n=3,613)

Number of cycles difference	Number of patients (%)	Cumulative proportion
0	1,679 (46.5)	46.5%
+/- 1	864 (23.9)	70.4%
+/- 2	306 (8.5)	78.9%
+/- 3	194 (5.4)	84.3%
> +/- 3	570 (15.7)	100.0%

The overall distribution of the number of cycles of chemotherapy for SACT and HES-APC for those in the combined cohort is very similar. A data quality concern which has been raised about SACT is that a disproportionately high number of just one cycle of chemotherapy gets recorded.[2] It is therefore reassuring that the proportion of one cycle of chemotherapy recorded is the same within HES-APC (Figure 2). In keeping with earlier findings, HES-APC tends to capture a higher frequency of patients having more than 8 cycles.

In addition, the two peaks on the bar charts are as expected, as during the timeframe of this study, standard adjuvant chemotherapy consisted of 8 cycles of either capecitabine or CAPOX and 12 cycles of FOLFOX or modified de Gramont single agent 5-FU. Single agent 5-FU may also be given as either 24 or 30 cycles, however, use of this regimen is infrequent.

Figure 2 – Bar chart demonstrating the distribution of total adjuvant chemotherapy cycles recorded in SACT compared to HES-APC for those patients with chemotherapy records in both SACT and HES-APC (n=3,613)



	1	2	3	4	5	6	7	8	9	10	11	12	>12
SACT	6%	4%	5%	6%	5%	9%	10%	23%	4%	4%	5%	13%	6%
HES	6%	5%	4%	6%	5%	7%	9%	21%	6%	3%	6%	14%	8%

Agreement between each cycle number in SACT and then HES-APC for patients with records in both datasets was evaluated (Figure 3a and 3b) up to a maximum of 15 cycles (95th percentile of the number of cycles). Overall, these showed good agreement for both datasets from around 4 cycles to 12 cycles. Agreement was better for mean HES-APC cycles compared to actual SACT rather than the other way round, suggesting that the number of cycles recorded in SACT may be more reliable than the number recorded in HES-APC. Essentially, if cycles are recorded at the extremes (i.e. low or high numbers) then there is more likely to be a significant discrepancy between the two datasets.

Figure 3a – Scatter plot demonstrating agreement between the actual number of cycles of chemotherapy according to SACT and the mean number of cycles according to HES-APC

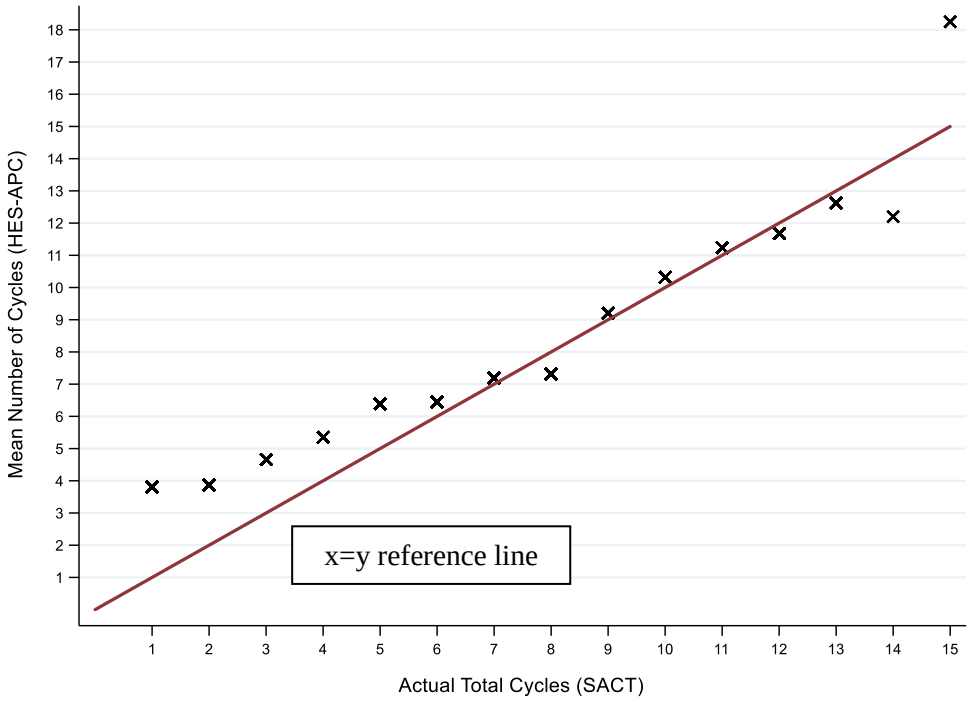
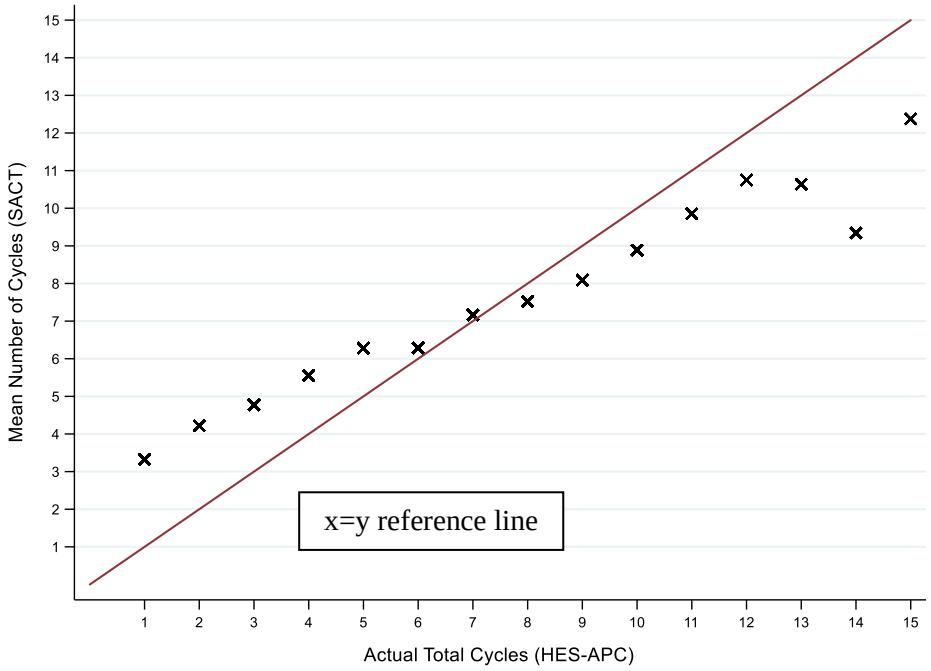


Figure 3b – Scatter plot demonstrating agreement between the actual number of cycles of chemotherapy according to HES-APC and the mean number of cycles according to SACT

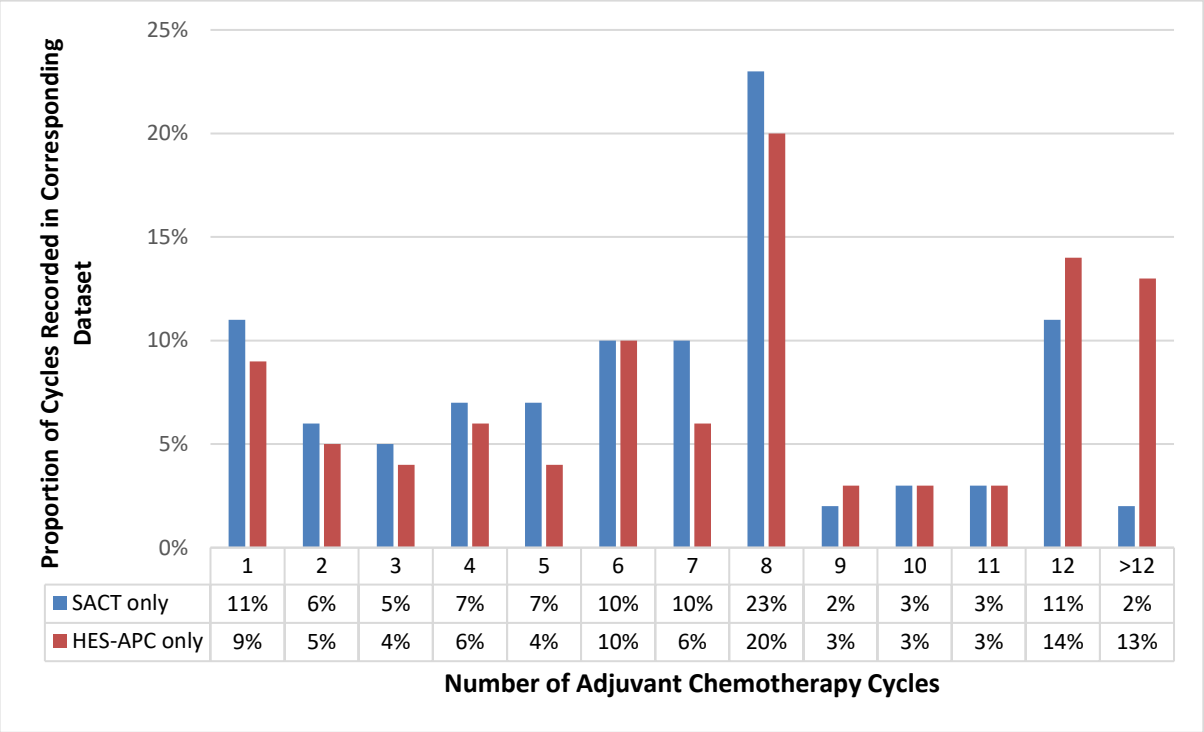


Patients with adjuvant chemotherapy records identified in only one of the datasets (SACT only or HES-APC only)

The distributions of number of cycles of chemotherapy for patients identified in HES-APC only compared to those identified in SACT only is largely similar apart from the recording of more than 12 cycles, whereby HES-APC has 13% of cycles compared to 2% in SACT (Figure 4).

346 patients originally present in the combined SACT/HES-APC group were excluded from SACT because they either commenced a non-standard regimen or had an erroneous regimen recorded (oxaliplatin administered in isolation), and subsequently made up a significant proportion of the final HES-APC only group. In addition, according to SACT data, 220 patients switched to non-standard regimens partway through treatment, indicating a probable switch to a palliative line of treatment. The over-estimation of cycle number in the HES-APC only group is therefore likely to be due to misclassifying some palliative chemotherapy as adjuvant chemotherapy.

Figure 4 – Bar chart demonstrating the distribution of total adjuvant chemotherapy cycles recorded for patients with records in SACT only (n=1,516) compared to those with records in HES-APC only (n=1,151)



	1	2	3	4	5	6	7	8	9	10	11	12	>12
SACT only	11%	6%	5%	7%	7%	10%	10%	23%	2%	3%	3%	11%	2%
HES-APC only	9%	5%	4%	6%	4%	10%	6%	20%	3%	3%	3%	14%	13%

When comparing the number of cycles for patients in the SACT/HES-APC cohort to the HES-APC only cohort, there remains a significant discrepancy in the more than 12 cycles group which supports non-adjuvant therapies being captured in the latter.

A considerably higher proportion of capecitabine regimens are picked up within the SACT only group compared to the SACT/HES-APC group. As mentioned previously, SACT captures outpatient/community chemotherapy meaning that oral capecitabine administered in isolation is likely to be more readily captured in SACT compared to HES-APC. The pattern of cycles in the SACT only group may also reflect this higher proportion of capecitabine capture, skewing the distribution towards 1-8 cycles.

Both the SACT only cohort and the HES-APC only cohort have a higher proportion of patients with only 1 cycle recorded (11% and 9% respectively) compared to 6% in the SACT/HES-APC cohort (Figure 2 and 4). A possible explanation for this might be that if patients are only having one cycle of chemotherapy recorded then it is less likely to be captured by both datasets.

Issues pertaining to variation in the recording of oral chemotherapy within SACT have been raised. Data submitted are based upon prescription of the drug and because it is taken orally, it is taken outside of a formal healthcare setting. A single administration may include a prescription for multiple tablets, the quantity of which is not recorded within SACT. Hospitals may submit multiple rows of drug information for each administration on the prescription within the same cycle or, alternatively, may only record one administration for the entire cycle.[13]

This would only explain the higher proportion of one cycle recorded within the SACT only group if hospitals were recording one cycle for the entire regimen. An alternative explanation might be that patients managed on an outpatient basis are less likely to have their treatments recorded within SACT. This seems unlikely as they should still have regular clinician review, and would also not explain the similar rise in the HES-APC only group.

5. Summary

Through the use of a NBOCA/SACT/HES linked dataset, this work has demonstrated the ability to validate the capture of adjuvant chemotherapy use for patients with stage III colon cancer. It has shown that within this cohort approximately one fifth of NBOCA patients identified as receiving adjuvant chemotherapy were identified from HES-APC alone, and just under one quarter were identified from SACT alone.

Reasons for patients being captured in one dataset and not the other are likely multifactorial. An important consideration with the capture of patients in HES-APC alone appears to be a lack of granularity of the chemotherapy data available which negates the ability to identify specific regimens and leads to inclusion of non-standard chemotherapy regimens which may represent a palliative line of therapy.

With regards to patients being captured in SACT alone, it most importantly appears to capture oral chemotherapy more effectively than HES-APC. This is particularly important for patients with stage III colon cancer because one of the standard regimens is administered orally. In addition, two tertiary oncology centres do not routinely code chemotherapy within HES-APC.

This report suggests that the combined use of SACT and HES-APC is likely to account for some of these limitations and help to increase the sensitivity of capturing patients who have received adjuvant chemotherapy.

In terms of capturing numbers of chemotherapy cycles administered, it has been demonstrated that most patients who have been captured in both datasets have good agreement of cycle numbers, but agreement tends to be worse in those with small numbers of cycles recorded in either dataset and in those with more than 12 cycles recorded in HES-APC.

HES-APC only is more likely to overestimate the number of cycles due to lack of regimen details restricting clinical interpretation of the data. Both HES-APC and SACT in isolation capture a disproportionate number of patients with only one cycle for which the explanation is not clear.

The optimal solution to enabling best capture of chemotherapy cycles would be the ability to identify which chemotherapy agents have been given within HES-APC. This would enhance the accuracy of capture within HES-APC only and allow further investigation of discrepancies in the distribution of cycles in each dataset in isolation.

6. Conclusions

The following conclusions are made in line with the recommendations listed in the executive summary:

1. Adjuvant chemotherapy captured in either SACT or HES-APC should be used to indicate whether or not patients receive adjuvant chemotherapy for stage III colon cancer, accepting that a proportion of those patients identified in HES-APC may represent non-adjuvant treatment.

2. SACT should also be used in combination with HES-APC to ascertain the number of cycles of chemotherapy that patients have received. For patients with records in both datasets, we would suggest using the cycle number from SACT for anyone identified as commencing or switching to a non-standard regimen. For all other patients we would suggest using the

highest cycle number available in either SACT or HES-APC, accepting that there may be overestimation of cycles in a proportion of patients identified within HES-APC alone.

3. Further work should be carried out to include:

    a) Ascertaining if it is possible to establish chemotherapy regimens from HES-APC and therefore improve the accuracy of cycles measured from this data source. If possible, we would hope that this might improve the agreement of cycle number between the two datasets.

    b) Assessing whether use and cycles of adjuvant chemotherapy can be captured in the Patient Episode Database for Wales (PEDW). This would allow a step forwards in the capture of adjuvant chemotherapy information in Wales because SACT only covers England.

    c) A sensitivity analysis using data from SACT only in order to compare results for future work with the methodology suggested here using both datasets.

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