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Optimal Post-Treatment Surveillance for Sarcoma, Colorectal and Appendiceal Neoplasms

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Optimal Post-Treatment Surveillance for Sarcoma, Colorectal and Appendiceal Neoplasms

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An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2020

ABSTRACT

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By

Adriana C. Gamboa

The aim of a surveillance program is to detect cancer recurrence at an early stage so that a curative intervention can be implemented. The purpose of this study was to utilize two U.S.-based, multi-institutional databases to: 1) evaluate the optimal surveillance modality after curative resection of primary soft-tissue sarcoma(STS) 2) evaluate the optimal surveillance frequency after cytoreductive surgery(CRS) and hyperthermic intraperitoneal chemotherapy(HIPEC) for stage IV appendiceal or colorectal cancer 3) compare the costs to the US-Healthcare system between surveillance modalities and frequencies.

For aim 1, patients in the US-Sarcoma Collaborative(2000-2016) who underwent resection of primary, high-grade STS were included. When considering age, tumor size, location, margin status, and receipt of radiation, lung metastasis was independently associated with worse overall survival(OS) (HR:4.26; $p<0.01$) while imaging modality was not (HR:1.01; $p=0.97$). Patients surveyed with CXR did not have a worse 5-year OS compared to CT(71%vs60%, $p<0.01$). When analyzing patients in whom no lung metastasis was detected, both cohorts had a similar 5-year OS(73%vs74%, $p=0.42$), suggesting CXR was not missing clinically relevant lung nodules.

For aim 2, the US-HIPEC Collaborative(2000-2017) was reviewed for patients who underwent CRS+/-HIPEC for appendiceal or colorectal cancer. Radiologic surveillance frequency was divided into low-frequency surveillance(LFS) at every 6-12 months or high-frequency surveillance(HFS) at every 2-4 months. Despite less surveillance, patients surveyed at low-frequency had no decrease in median OS(non-invasive appendiceal: 106vs65 months, $p<0.01$; invasive appendiceal: 120vs73 months, $p=0.02$; colorectal cancer: 35vs30 months, $p=0.8$). On multivariable analysis, accounting for burden of disease, LFS was still not associated with decreased OS for any histologic type(non-invasive appendiceal: HR:0.28, $p=0.1$; invasive appendiceal: HR:0.73, $p=0.42$; colorectal cancer: HR:1.14, $p=0.59$).

When adhering to a guideline-specified protocol for 4,406 projected cases, surveillance with CXR results in savings of $5-8M/year. Similarly, when estimating annual incident cases of CRS/HIPEC at 375 for non-invasive appendiceal, 375 invasive appendiceal and 4410 colorectal, LFS compared to HFS saves $13-19M/year.

Utilizing CXR for surveillance of high-grade STS or LFS after CRS+/-HIPEC for appendiceal/colorectal cancer is not associated with decreased OS. Considering substantial savings to the US-healthcare system, surveillance protocols for patient cohorts could be modified accordingly to optimize resource utilization.

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INTRODUCTION

A rise in the number of cancer survivors has led to questions regarding effective surveillance strategies after curative-intent surgery. There are at least 14 million cancer survivors in the United States, with estimates projected to increase as the general population ages and treatment strategies continue to improve rates of disease-specific survival (1). Although several professional societies have proposed surveillance guidelines, clinical practice varies and the general trend is toward more intensive strategies with the perceived aim that detecting early disease will lead to improved survival. However, the evidence supporting intensive surveillance is relatively lacking, with most studies demonstrating no survival benefit with more intense surveillance strategies.

The main argument of routine surveillance and early detection of recurrent disease prior to symptom onset is the availability of salvage therapies which may be curative if implemented early for certain malignancies. With this advantage, however, arise concerns regarding cost-effectiveness, risks related to additional radiation exposure, and the possibility of additional tests or invasive procedures being conducted after potentially false-positive results. The Choosing Wisely campaign, an initiative of the American Board of Internal Medicine, not only endorses evidence-based practices but also promotes patient-provider discussions about healthcare options in an effort to decrease costs, improve outcomes, and prevent unnecessary testing.

The overarching aim of this multi-institutional, retrospective study is to address the most effective surveillance strategies after definitive treatment with curative intent in three malignancies including soft tissue sarcoma, and stage IV appendiceal neoplasms and colorectal adenocarcinoma, for which evidence-based surveillance strategies are lacking.

The Role of Surveillance in Soft Tissue Sarcoma

Soft tissue sarcomas are rare tumors which account for 1% of adult malignancies. In 2018, approximately 13,000 people were diagnosed with soft tissue sarcomas in the United States (2). During the past three decades, a multimodality approach has been used in the treatment of primary, high-grade soft tissue sarcomas leading to improvements in survival. Despite this, distant recurrences are common, with up to 60% of high-grade soft tissue sarcomas recurring in the lungs (3, 4). The rate of metastases depends

predominantly on tumor grade, and 70% of high-grade soft tissue sarcoma lung metastases will occur within the first two-years after resection (5-8).

Considering this rapid progression of high-grade soft tissue sarcomas, prompt detection of lung metastases may improve prognosis given therapeutic interventions currently available. Surgical metastasectomy remains the primary treatment modality for isolated LM, and although no randomized control trial has evaluated its benefit over medical therapy, several retrospective series have demonstrated 3-year survival rates of 40-50% after complete metastasectomy (3, 4, 8-19). Even when resection is not feasible, other lung-directed strategies, such as radiofrequency ablation or stereotactic body radiotherapy have demonstrated acceptable local control rates (20-22).

Due to the availability of salvage therapy and its association with improved survival, post-operative lung surveillance is crucial. However, consensus is lacking regarding the optimal imaging modality. Current National Comprehensive Cancer Network (NCCN) guidelines for high-grade soft tissue sarcomas recommend imaging with either chest radiography (CXR) or chest computed tomography (CT) (23). Although CXR is easily-accessible and minimizes radiation, the enhanced resolution of CT may improve the sensitivity of detection for lung nodules as small as 3-4 mm (24, 25). However, patients with <5 mm nodules have been shown to have equivalent survival to those with normal CT scans (26). Additionally, the higher false-positive rate for CT may result in costly, unnecessary assessments / procedures with potential increased morbidity and patient anxiety (27). Furthermore, the cost between CXR and CT differs by an order of magnitude. Intuitively, elimination of unnecessary CT scans for lung surveillance of high-grade soft tissue sarcoma would result in significant savings to the US-healthcare system.

The Role of Surveillance in Stage IV Appendiceal or Colorectal Cancer

Peritoneal carcinomatosis is a subgroup of stage IV cancer characterized by intraperitoneal tumor dissemination with appendiceal and colorectal cancer representing two of the most frequent originating histologies. Appendiceal neoplasms account for approximately 1,500 annual cases with peritoneal carcinomatosis present in half of all new diagnoses (28). Conversely, colorectal cancer accounts for almost 150,000 cases annually, but only 20% of new diagnoses present with synchronous peritoneal carcinomatosis (2, 29-33).The management of appendiceal and colorectal PC has evolved considerably with the advent of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Several

single center studies, and two randomized controlled trials have demonstrated a significant survival benefit with a median disease-specific survival of more than ten years in appendiceal neoplasms, and up to 22 months in colorectal cancer (34-42). Despite the recent results of the PRODIGE-7 trial which demonstrated that HIPEC did not provide any added survival benefit over just cytoreductive surgery for colorectal cancer, these procedures continue to be widely performed (43).

Even after curative-intent cytoreductive surgery and HIPEC, disease commonly recurs within 2-5 years of treatment with recurrence rates approaching 30% for appendiceal neoplasms, and 80% for colorectal cancer with a high proportion confined to the peritoneal cavity (44-48). Knowledge of this anatomic and temporal pattern of recurrence is crucial for the development of surveillance recommendations. Furthermore, as some studies have demonstrated the feasibility as well as survival benefit with secondary cytoreductive surgery and HIPEC for peritoneal recurrences, surveillance is justified to facilitate prompt initiation of salvage therapy (49-54).

Several randomized-clinical trials and a 2016 meta-analysis have sought to address the optimal surveillance interval for stage I-III colorectal cancer with most studies demonstrating no survival benefit with more frequent surveillance, despite earlier detection of recurrences (55-61). Importantly, limited evidence is available regarding surveillance after curative treatment of stage IV appendiceal neoplasms or colorectal cancer (45, 57, 62, 63). Current recommendations by the National Comprehensive Cancer Network (NCCN) offer wide variability in the frequency of surveillance strategies with cross-sectional imaging ranging from 3-6 months for the first two-years and then every 6-12 months for a total of five-years (23, 60, 63-67). While more frequent surveillance may seem prudent, it carries potential risks including false positive findings, increased radiation exposure, and incremental costs to the US healthcare system. Notably, no study has evaluated the optimal surveillance strategy after curative-intent treatment with cytoreductive surgery and HIPEC.

In order to address these questions, the Division of Surgical Oncology at Emory University has assembled the US Sarcoma Collaborative and the US HIPEC Collaborative, to address patient outcomes. These two multi-institutional registries include data on over 3,000 patients with a focus on perioperative morbidity, surveillance, disease recurrence, and survival for patients with soft tissue sarcoma, colorectal and appendiceal neoplasms.

METHODS

The US Sarcoma Collaborative (USSC) is a consortium formed to investigate outcomes in soft tissue sarcoma and constitutes eight academic centers (Emory University, Stanford University, Wake Forest University, Medical College of Wisconsin, University of Wisconsin, University of Chicago, The Ohio State University, Washington University). The USSC contains all patients who underwent resection of a primary or recurrent soft tissue sarcoma from 2000 to 2016. Similarly, the US HIPEC Collaborative is a consortium of twelve institutions including Emory University, The Ohio State University, City of Hope, Johns Hopkins University, Mayo Clinic, Medical College of Wisconsin, Moffitt Cancer Center, University of California San Diego, University of Cincinnati, University of Massachusetts, MD Anderson Cancer Center, and University of Wisconsin which contains all patients who underwent cytoreductive surgery and HIPEC from 2000-2017. Institutional Review Board approval was obtained at each institution prior to data collection.

Baseline demographic, preoperative, intraoperative, pathologic, and post-operative outcome data were collected retrospectively based on a review of the medical records for all patients. Pathologic review was performed at each institution by experienced GI pathologists. Pathologic staging and the extent of lymph node dissection were defined as per American Joint Committee on Cancer (AJCC) 7th edition guidelines (68). Data regarding neoadjuvant and adjuvant therapy, disease recurrence, and survival were additionally recorded. Survival information was verified with the Social Security Death Index, when appropriate.

All statistical analysis was conducted using SPSS 252.0 software (IBM Inc., Armonk, NY). Statistical significance for each endpoint was predefined as $p<0.05$. In order to better estimate oncologic-specific survival, all 30-day mortalities were excluded from survival analyses.

AIM 1

We aimed to evaluate the association of CXR versus CT lung surveillance with overall survival after curative-intent resection of high-grade primary soft tissue sarcoma. We hypothesized that surveillance with CT would not be associated with improved overall survival when compared with CXR.

Methods

Study Population

All patients with primary soft-tissue sarcoma from 2000 to 2016 were evaluated. In order to mitigate selection bias, only patients with high-grade tumors were included as pathological grade may affect selection of modality for lung surveillance. The analysis was further limited to patients with lung surveillance data available, and without metastatic disease at the time of resection or 30-day operative mortality. Clinicopathologic variables and post-operative outcomes were collected through chart review. As the study was conducted by eight academic institutions, NCCN guidelines for lung surveillance frequency were followed. Patients were considered to have CXR surveillance if they exclusively underwent imaging with CXR throughout the surveillance period. If a patient was transitioned from CXR surveillance to CT at any point in his / her lung surveillance period and prior to the detection of lung metastasis, they were included in the CT surveillance cohort. Due to limitations in the data, it was not discernible if a subject in the CXR cohort underwent confirmation of a suspicious lesion with a more sensitive modality.

Outcome Measures

The primary objective was to assess the association of CXR versus CT lung surveillance with overall survival after curative-intent resection of high-grade primary soft tissue sarcoma. Overall survival was defined as time from reoperation to death from any cause.

Statistical Analysis

All statistical analyses were performed using the SPSS 25.0 statistical package (IBM Inc., Armonk, NY). Statistical significance was pre-defined as 2-tailed $p<0.05$. Nominal variables were analyzed with Chi-square or Fisher's exact test. Continuous variables were analyzed using t-tests or the Wilcoxon signed-rank test. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used for comparison of survival between CXR and CT cohorts. Cox-regression analysis was used to determine the association of clinicopathologic factors with overall survival. A multivariable model was constructed using

sequential regression entry with variables statistically associated ($p<0.05$) with overall survival on univariate analysis.

Results

Demographic and Clinicopathologic Characteristics

Among 4,153 patients, 1,093 patients with high-grade soft tissue sarcoma underwent curative-intent resection and of these, 909 had lung surveillance data available. Tumor location included extremities in 71% (n=645), trunk wall in 12% (n=113), and retroperitoneum in 17% (n=151). Tumor size was <5 cm in 15% (n=137), 5–10 cm in 40% (n=366), >10 cm in 39% (n=351), with a median of 9 cm (IQR 5.5-14.5). Tumors were classified into six main histologic categories as follows: undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma 39% (n=355), leiomyosarcoma 12% (n=106), myxofibrosarcoma 8% (n=75), dedifferentiated liposarcoma 4% (n=40), synovial sarcoma 5% (n=48), pleomorphic liposarcoma 5% (n=44), and others 27% (n=241). Median follow-up was 33 months.

Among those patients who underwent curative resection (R0/R1), 48% (n=432) recurred and of these 34% were local/locoregional (n=149), 55% distant (n=239), and 10% synchronous locoregional / distant (n=42). Of all recurrences, 54% were in the lungs (n=232). Lung surveillance was performed with CXR in 20% (n=197) and CT in 80% (n=771).

Patients who underwent surveillance with CT had more retroperitoneal tumors, a higher proportion of dedifferentiated liposarcoma, and were more likely to have a LM ($p<0.05$). Importantly, both imaging modalities detected the majority of the lung metastases within the first two years (CXR: 91%, CT: 85%, $p=0.88$). Definitive therapy for these included ablation (CXR: 0%, CT: 0.4%), radiation (CXR: 9%, CT: 5%), surgery (CXR: 18%, CT: 40%) and chemotherapy (CXR: 18%, CT: 40%), and both groups had similar intervention rates to treat lung metastasis ($p=0.77$, Table 1.1).

Lung Metastases and Survival

On univariate Cox regression analysis, older age, retroperitoneal tumors, tumor size ≥ 5 cm, positive margin status, presence of lymphovascular invasion, and positive lymph node status were associated with worse overall survival. Lung metastasis was also strongly associated with worse overall

survival (HR 3.91; 95%CI 3.11-4.92, p<0.01), while lung surveillance with CXR was not associated with inferior overall survival when compared to CT (HR 0.62; 95%CI 0.45-0.85, p<0.01). On multivariable Cox regression analysis, when controlling for age, tumor location, tumor size, margin status, and receipt of radiation, lung metastasis remained an independent predictor of worse overall survival (HR 4.26; 95%CI 3.28-5.53, p<0.01), while lung surveillance modality had no effect on overall survival (HR 1.01; 95%CI 0.71-1.43, p=0.97, Table 1.2).

Survival Analysis by Lung Surveillance Modality

On log-rank analysis, patients in the CXR cohort had a non-inferior 5-year lung-specific recurrence free survival (CXR: 93% vs CT: 62%, p<0.01; Figure 1.1A) and 5-year overall survival (CXR: 71% vs CT: 60%, p<0.01; Figure 1.1B). However, when analyzing patients in whom no lung metastasis was detected, both imaging cohorts had identical 5-year overall survival (CXR: 74% vs CT: 73%, p=0.42; Figure 1.1C), suggesting that patients undergoing surveillance with CXR were not subjected to false negative imaging for clinically relevant lesions which otherwise would have resulted in decreased overall survival.

Discussion

Nearly 60% of patients with high-grade soft tissue sarcoma will develop lung metastases after curative-intent resection with the risk of recurrence being greatest within two years of surgery (69, 70). This study's findings are concordant with those in the literature with a lung metastasis rate of 52% (Table 1.1). Additionally, as previously known, our results demonstrate that lung metastasis is associated with a worse prognosis. Given this high rate of recurrence, the associated impact on survival, and the availability of salvage therapy, NCCN guidelines provide clear recommendations for lung surveillance. However, the optimal modality is unknown and either CXR or CT are accepted. Our results demonstrate that lung surveillance with CXR is associated with non-inferior overall survival compared to CT. Furthermore, depending on the frequency of imaging, a CXR-based protocol affords a potential cost savings of $5-8 million over a 5-year period to the US-healthcare system.

Several small studies and a randomized controlled trial have evaluated the optimal modality of lung surveillance in soft tissue sarcoma (70-73). In a prospective, single-institution study, Puri *et al.*

demonstrated that at a median follow-up of 42 months, surveillance with CXR after resection of extremity soft tissue sarcoma did not lead to worse survival when compared to CT (72). Additionally, a retrospective study by Whooley *et al*., evaluated the effectiveness of follow-up testing for detecting distant recurrences of extremity soft tissue sarcoma and showed that 83% of asymptomatic lung metastasis were detected by CXR (74). The current study differs from the existing literature in that it further establishes the utility of CXR for lung surveillance after resection of *high-grade* soft tissue sarcoma, a subset of sarcoma that has been deemed high-risk for lung metastases. On Kaplan-Meier analysis, patients in the CXR cohort had a non-inferior, and even superior, 5-year lung-specific recurrence-free survival (Figure 1.1A). It naturally follows to question whether this observation in recurrence-free survival is related to a decreased diagnostic sensitivity of the CXR modality, and hence a higher false-negative rate and inability to detect a metastasis. However, if patients surveyed with CXR had lung metastases that were not detected and therefore not treated, this cohort would likely have had a decreased overall survival when compared to the CT cohort. In contrast, the CXR cohort had a non-inferior 5-year overall survival (Figure 1.1B). In order to further investigate this observation, survival analysis was repeated after excluding patients in whom no lung metastasis was detected which demonstrated near identical 5-year overall survival between both imaging cohorts (CXR: 73 vs CT: 74%, p=0.42; Figure 1.1C). Given the known poor prognosis of untreated lung metastases, this finding suggests that CXR is not associated with a high false-negative rate of clinically significant nodules which would otherwise have led to a worse overall survival when compared to CT. These results were further supported with multivariable Cox regression which demonstrated that surveillance modality was not associated with decreased overall survival (HR: 1.01; 95%CI 0.71-1.4; p=0.97), when considering age, tumor size, tumor location, margin status, and receipt of adjuvant radiation. Thus, it appears that CXR provides an adequate detection threshold for clinically significant lung nodules.

The decreased survival observed in the CT cohort is a result of selection bias, namely unidentified factors that influenced the decision to survey with CT versus CXR. Given this study's retrospective design, these factors cannot be accurately identified. One potential explanation is that patients in the CT cohort were more likely to have primary retroperitoneal soft tissue sarcomas. It is well established that retroperitoneal sarcomas have a high propensity for early local recurrence, and that this local progression can be the main driver of disease-specific death (75). Given that these patients generally undergo local

abdominopelvic surveillance with CT, it is likely that lung surveillance would have been pursued with the same modality.

Notably, for both imaging cohorts, the majority of lung metastases were detected within the first 2-years (Table 1.1), a finding that is in accord with other series (76). Furthermore, there was no difference in the intervention frequency and type pursued, including ablation, radiation, surgery, or chemotherapy, for these lung metastases ($p>0.05$). Therefore, it does not seem that CT surveillance results in an earlier diagnosis of lung metastases and more prompt treatment, particularly since the overall survival was not superior to CXR surveillance.

Conclusion

In this large multicenter study, lung surveillance with CT was not associated with improved overall survival when compared to surveillance with CXR.

AIM 2

We aimed to evaluate the association between a high-frequency and low-frequency surveillance protocol after cytoreductive surgery and HIPEC for appendiceal and colorectal cancer. We hypothesized that surveillance at high-frequency would not be associated with improved overall survival when compared with surveillance at low-frequency.

Methods

Study Population

All patients, older than 18 years, with appendiceal neoplasms or colorectal cancer who underwent curative-intent cytoreductive surgery with or without HIPEC from 2000-2017 were assessed. Analysis was limited to patients who underwent a complete cytoreduction with no visible disease (CCR0), or with no remaining nodules >2.5 mm (CCR1). Patients who died within 30-days of cytoreductive surgery with or without HIPEC, and those without information on postoperative surveillance frequency were excluded.

Surveillance Frequency Groups

Surveillance was performed with cross-sectional imaging of the abdomen and pelvis and frequency was divided into two categories: high-frequency surveillance (HFS) every 2-4 months or low-frequency surveillance (LFS) every 6-12 months.

Outcome Measures

The primary objective was to assess the difference in overall survival between patients who underwent LFS compared to patients who underwent HFS. Overall survival was calculated from date of reoperation to date of death from any cause.

Statistical Analysis

Analysis was stratified by histology with appendiceal neoplasms further classified into non-invasive and invasive according to the 2016 Peritoneal Surface Oncology Group International diagnostic terminology (77). Non-invasive appendiceal neoplasms includes low-grade mucinous neoplasm, and high-grade appendiceal mucinous neoplasm, while invasive appendiceal neoplasms includes adenocarcinoma. All statistical analyses were performed using SPSS statistical package 25.0 (IBM Inc., Armonk, NY). Statistical significance was pre-defined as 2-tailed $p<0.05$. Chi-square or Fisher's exact test were used for categorical variables. Continuous variables were analyzed using t-tests or the Wilcoxon signed-rank test. Comparative analyses were conducted between HFS and LFS cohorts. Survival was estimated using the Kaplan–Meier (KM) method, and the log-rank test was used for comparison of survival between HFS and LFS cohorts. Univariate Cox regression was performed to determine associations between clinicopathologic variables and overall survival. Factors that were significantly associated with overall survival on univariate analysis or significantly different between surveillance cohorts on comparative analyses were included in a multivariable model.

Results

Demographic and Clinicopathologic Characteristics

Among 2,372 patients in the US HIPEC Collaborative, 975 patients were included of which 301 patients had non-invasive appendiceal neoplasms, 435 invasive appendiceal neoplasms, and 239 colorectal cancer.

In patients with non-invasive appendiceal neoplasms, median age was 47 (IQR 47-64) and 39% were male (n=117). CCR0 resection was achieved in 70% (n=211). Median follow-up was 28 months (IQR 12-50). HFS was used in 31% (n=93), and LFS in 69% (n=208). Patients who underwent HFS had a significantly higher median peritoneal cancer index (19 vs 10, p<0.01), but were well-matched for other clinicopathologic variables (Table 2.1).

In patients with invasive appendiceal neoplasms, median age was 55 (IQR 47-64) and 39% were male (n=170). CCR0 resection was achieved in 69% (n=301). Median follow-up was 29 months (IQR 16-51). HFS protocol was used in 37% (n=159), and LFS in 63%(n=276). Patients who underwent HFS had a higher median peritoneal cancer index (14 vs 10, p<0.01), more poorly/undifferentiated tumors (19% vs 7%, p<0.01), and were more frequently treated with adjuvant chemotherapy (22% vs 11%, p<0.01; Table 2.1).

In patients with colorectal cancer, median age was 55 (IQR 47-64), 50% were male (n=119). CCR0 resection was achieved in 79% (n=189). Median follow-up was 17 months (IQR 9-29). HFS was used in 73% (n=174), and LFS in 27% (n=65). Patients who underwent HFS had a higher median peritoneal cancer index (11vs8, p<0.01; Table 2.1).

Recurrence and Survival Analysis by Frequency of Surveillance

For patients with non-invasive appendiceal neoplasms, 27% of patients (n=81) recurred of which 43% underwent salvage-treatment with any modality, and 22% underwent repeat cytoreductive surgery/HIPEC. While HFS patients had more recurrences (40% vs 21%, p<0.01), LFS patients were treated with secondary cytoreductive surgery/HIPEC more frequently (11% vs 32%, p=0.02). There was no difference in median time to recurrence (13 vs 14 months, p=0.82, Table 1). On KM analysis, LFS patients had a non-inferior five-year overall survival compared to HFS (91% vs 62%, p<0.01, Figure 2.1). On univariate-analysis, CCR1 status, poorly/undifferentiated grade, presence of lymphovascular and perineural invasion, receipt of neoadjuvant or adjuvant chemotherapy, and recurrence were associated with

worse overall survival (Table 2.2). LFS was associated with non-inferior overall survival (HR: 0.22, p<0.01). When considering peritoneal cancer index, CCR, and tumor grade on multivariable-analysis, LFS remained associated with non-inferior overall survival (HR: 0.28, p=0.10).

For patients with invasive appendiceal neoplasms, 46% of patients (n=200) recurred of which 47% underwent salvage-treatment with any modality, and 8% underwent secondary cytoreductive surgery/HIPEC. Again, HFS patients had more recurrences (58% vs 39%, p<0.01), and a shorter median time to recurrence (12 vs 18 months, p<0.01, Table 2.1). LFS had a non-inferior five-year overall survival (72% vs 54%, p=0.02, Figure 2.1). On univariate-analysis, higher tumor grade, lymphovascular and perineural invasion, receipt of neoadjuvant or adjuvant chemotherapy, and recurrence were associated with worse overall survival (all p<0.01, Table 2.2). LFS was associated with non-inferior OS (HR: 0.64, p=0.02). When considering peritoneal cancer index, CCR, and tumor grade, LFS remained associated with non-inferior overall survival (HR: 0.73, p=0.42).

For patients with colorectal cancer, 63% (n=151) recurred of which 48% underwent salvage-treatment with any modality, and 5% underwent secondary cytoreductive surgery/HIPEC. There was no difference in the proportion of recurrences between HFS and LFS protocols (66% vs 51%, p=0.08), or median time to recurrence (7 vs 12 months, p=0.08). HFS and LFS patients had an equivalent five-year overall survival (27% vs 28%, p=0.8, Figure 2.1). On univariate analysis, male sex, higher peritoneal cancer index score, CCR1 status, receipt of adjuvant radiotherapy, and recurrence were associated with worse overall survival (Table 2.2). LFS was associated with non-inferior overall survival (HR: 0.94, p=0.8). When considering sex, peritoneal cancer index, and CCR, LFS remained associated with non-inferior overall survival (HR: 1.14, p=0.59).

Discussion

No evidence-based guidelines exist for surveillance following cytoreductive surgery/HIPEC. To the authors' knowledge, this is the first analysis to examine the possible impact of surveillance frequency on the overall survival of patients with appendiceal neoplasms and colorectal cancer after curative-intent cytoreductive surgery/HIPEC. Our results demonstrate that although recurrence portends a poor prognosis

on overall survival for all three histologies (Table 2.2), a low-frequency surveillance protocol is associated with non-inferior overall survival compared to a high-frequency protocol.

In this study, each histology was analyzed according to two radiologic surveillance protocols: high-frequency surveillance every 2-4 months, or low-frequency every 6-12 months. Across all histologies, patients in the HFS group had higher peritoneal cancer index scores, a known prognostic factor for extent of peritoneal disease and worse overall survival. Accordingly, patients in the HFS group had significantly more recurrences (non-invasive appendiceal neoplasms: 40% vs 21%, invasive appendiceal neoplasms: 58% vs 39%, colorectal cancer: 66% vs 51%, all $p<0.01$). Importantly, for the patients with invasive appendiceal neoplasms, median time to recurrence was earlier in the HFS group (12 vs 18 months, $p<0.01$), and in colorectal cancer there was a trend towards earlier detection (7 vs 12 months, $p=0.08$) further suggesting a more aggressive tumor biology in the HFS cohort. Intuitively, these patients were surveyed more frequently, a finding that is consistent with some physician surveys which have indicated that disease severity may increase surveillance intensity (78). However, even when accounting for factors contributing to this selection bias for a HFS protocol, including peritoneal cancer index score and tumor differentiation, LFS was associated with a non-inferior overall survival for all histologies.

This finding has been previously reported in multiple randomized controlled trials for stage I-III colorectal cancer. Indeed, the COLOFOL trial evaluated the benefit of a HFS protocol and found no significant impact on overall survival for stage II/III disease as earlier detection did not translate into reduced mortality (56). Similarly, the FACS trial demonstrated that earlier diagnosis did not lead to improved overall survival (57). One reason why more frequent surveillance may not be associated with improved outcomes is that recurrences presenting as small nodules are likely to be missed by cross-sectional imaging. One study reported CT sensitivity as low as 60% in lesions 1-6 mm in size with sensitivity increasing to 80% for lesions >1cm in size (79). These findings also highlight the need for additional surveillance modalities that improve detection sensitivity, and better evaluate patient candidacy for repeat intervention. Additionally, it is likely that even if a small peritoneal nodule is detected after three months of follow-up, intervention is not pursued immediately, and the patient is imaged again at the next interval to evaluate disease progression, thus eliminating the potential benefit to earlier detection of disease.

Another reason that may explain the lack of benefit to more frequent surveillance, is that salvage therapy for recurrence of peritoneal metastases in high-risk patients may not be associated with improved outcomes. Several studies have established that iterative cytoreductive surgery/HIPEC is both feasible and safe in a highly select group with more favorable baseline prognostic characteristics. The results of this study suggest similar selection criteria, as iterative cytoreductive surgery/HIPEC was performed more frequently for patients with non-invasive appendiceal neoplasms and colorectal cancer who underwent LFS, and therefore had more favorable baseline clinicopathologic factors (non-invasive appendiceal neoplasms: HFS 11% vs LFS 32%, p=0.02, colorectal cancer: HFS 3% vs LFS 15%, p=0.01). As previously established, the early detection of recurrent disease is only useful if the patient's condition allows for repeated therapeutic intervention, and it is possible that patients who underwent HFS had more unfavorable characteristics which could result in fewer available options for salvage therapy.

There are several limitations to our study which arise from its retrospective design. There is certainly a selection bias between the patients in the HFS and LFS cohorts, although this was mitigated with the use of multivariable Cox regression analysis. Additionally, due to lack of available data, this study cannot comment on the true value of surveillance for this disease process. However, it would be unusual for a patient to not undergo surveillance after curative-intent CRS/HIPEC, as is evidenced by the low number of patients in our database who had no surveillance. Lastly, the limitations of the cost model result from several assumptions as the cohorts were derived by using published estimated incidence data. Additionally, cost data was estimated using Medicare payments as proxy given the interest in estimating cost to the US healthcare system. Although these costs may change over time and vary per institution, the economic impact of LFS is compelling. Lastly, some nuances of the physician-patient relationship cannot be captured in this study as patients may derive reassurance from knowing that they are disease-free. In fact, a study by Lewis et al. highlights that fear of recurrence is a major source of anxiety for patients (80). Conversely, patients may experience disappointment associated with recurrence detection for which salvage therapy may not be indicated. Accordingly, surveillance strategies must balance the advantage of a survival benefit with the limitations of imaging modalities, costs to the healthcare system, and patient satisfaction. The results of this study are not attempting to propose a protocol for generalized acceptance in stage IV disease, but rather suggesting that using a low-frequency surveillance protocol after

cytoreductive surgery/HIPEC may optimize these factors. These findings provide a foundation for clinical trials to validate surveillance protocols for peritoneal malignancies.

Conclusion

In conclusion, in this large multicenter study, low-frequency surveillance after cytoreductive surgery/HIPEC for appendiceal or colorectal cancer is not associated with worse overall survival, and may optimize resource utilization. Further prospective studies are needed to validate the appropriateness of a LFS strategy following cytoreductive surgery/HIPEC.

AIM 3

To develop a model to compare the cost to the US healthcare system of a five-year surveillance protocol after resection of primary soft tissue sarcoma using either CXR or CT or a two-year surveillance protocol after cytoreductive surgery/HIPEC for appendiceal neoplasms and colorectal cancer using either a low-frequency or high-frequency protocol.

Methods

Cost Model Comparing Lung Surveillance Modalities for Primary Soft Tissue Sarcoma

A cost model was developed to estimate total cost to the US-healthcare system over a 5-year period using either a CXR or CT-based surveillance protocol. The 2018 incidence data of non-metastatic, high-grade soft tissue sarcoma was determined based on published estimates. This hypothetical cohort was simulated to enter a CXR or CT-based protocol at low-frequency (every six months for four years, then annually) or high-frequency (every three months for the first two years, then every six months for two years, then annually). At each imaging time point there were three potential probabilities: no lung metastasis, true lung metastasis (true positive) or false lung metastasis (false positive). The probability of a true positive was calculated as the modality sensitivity multiplied by the true recurrence rate among those who did not die prior to the imaging time-point. The probability of a false positive is the modality false positive rate (1-specificity) multiplied by 1 minus true recurrence rate plus the death rate among those who did not die prior to the imaging time-point. The cost of each imaging modality or intervention was derived by using the 2018

Medicare Physician Fee Schedule and each service was identified using the Current Procedural Terminology (CPT) code (Table 3.1). If a recurrence was detected, the downstream cost of histologic confirmation via wedge resection was also included. Each model was simulated 1000 times, and the average cost to the US-healthcare system at 5-years is reported.

Cost Model Comparing Surveillance Frequencies for Appendiceal Neoplasms and Colorectal Cancer

The model aimed to estimate savings to the US healthcare system by using an LFS protocol. The 2018 incidence data of stage IV, resectable appendiceal neoplasms and colorectal cancer were determined based on previously published estimates. This hypothetical cohort was simulated to enter either a HFS or LFS protocol over a two-year period with a CT or MRI-based modality. Patients with non-invasive appendiceal neoplasms underwent either a contrast CT or MRI abdomen/pelvis at HFS every four months or LFS every twelve months. Patients with invasive appendiceal neoplasms and colorectal cancer underwent a non-contrast CT chest, and either a contrast CT or MRI abdomen/pelvis at HFS every three months or LFS every six months. According to the probabilities provided by this study's survival-analysis, patients could transition to death or remain on surveillance. The cost of each modality was derived by using the 2018 Medicare Physician Fee Schedule and each service was identified using the Current Procedural Terminology (CPT) code (Table 3.2). Each model was simulated 1000 times, and the average cost at two-years was reported.

Results

Cost Analysis of Lung Surveillance Modalities for Primary Soft Tissue Sarcoma

Estimated 2018 incidence data for non-metastatic, high-grade soft tissue sarcoma are shown in Table 3.1. Over a 5-year surveillance period, a CXR-based protocol compared to CT results in a savings of $5,525,413-$7,853,732 to the US-healthcare system based on the 2018 Medicare Physician Fee Schedule, depending on whether a low or high-frequency strategy is used, respectively (Table 3.3).

Cost Analysis of Surveillance Frequency Appendiceal Neoplasms and Colorectal Cancer

Estimated 2018 incidence data for each histologic cohort are shown in Table 3.2. Over a two-year surveillance period, an LFS CT-based protocol results in a savings of $13,780,294 or $18,746,543 for an MRI-based protocol (Table 3.4).

Discussion

Although cost should not be the primary driver of our decision-making, the importance of being thoughtful about the cost of each intervention is ever-increasing. Cost-effectiveness is commonly cited in studies on surveillance strategies for soft tissue sarcoma. However, few have examined the actual costs to the US-healthcare system of follow-up surveillance according to NCCN guidelines which recommend chest imaging with either CXR or CT every 3-6 months for 2-3 years, then every 6 months for the next two years, and then annually (23). A review by Goel *et al*. in 2004 summarized literature on the topic from 1982 to 2003 and found wide disparity in costs of 54 methods of following patients with soft tissue sarcoma (81). The financial analysis in our study, which is based on current NCCN guidelines and takes into account sensitivity and specificity of each modality, demonstrates that a CXR-based protocol could lead up to $5-8 million in savings to the US-healthcare system per 5-year surveillance period, depending on whether a low or high-frequency surveillance strategy is employed.

The decision to proceed with more frequent surveillance has significant economic implications, and given the increasing incidence of CRS/HIPEC procedures performed, the cumulative cost of surveillance represents a sizable expenditure for the US healthcare system. Our proposed cost model takes into account a hypothetical cohort of patients with stage IV, resectable AN and CRC. The model considers this cohort entering a high-frequency or low-frequency surveillance protocol. Based on cost data extracted from CMS, the model demonstrates a total savings to the US healthcare system of nearly $14 million for a CT-based protocol or $19 million for an MRI-based protocol.

Conclusion

In conclusion, surveillance with CXR for soft-tissue sarcoma or at low-frequency after cytoreductive surgery/HIPEC is associated with a substantial savings of nearly $30 million to the US-Healthcare System.

STRENGHTS AND LIMITATIONS: AIM 1

This study is the first to evaluate the optimal modality of surveillance for soft tissue sarcoma. Its multi-institutional design eliminates single-institution bias and the inclusion of patients with high-grade soft tissue sarcoma only homogenizes the study population. Additionally, the use of multivariable models ensures that all relevant and prognostic clinicopathologic factors are considered. The limitations of this aim stem from its retrospective design and lack of granular data regarding frequency of surveillance. It should also be noted that this study includes only patients who were selected for surveillance with either CXR or CT. This decision is inherently subject to bias as patients chosen to undergo surveillance with CT may have been deemed to be higher risk for distant recurrence. Indeed, in 2003, Sakata *et al.* examined whether tumor grade and size accounted for variation in follow-up of STS. The authors found that office visits, labs and imaging were ordered more frequently with increasing tumor size and grade (78). In an effort to reduce this selection bias, this study was limited to high-grade soft tissue sarcoma. However, it is difficult to account for all clinicopathologic differences between each group that could introduce bias.

STRENGTHS AND LIMITATIONS: AIM 2

Similar to aim 1, this study is the first in the literature to examine the role of frequency of surveillance after cytoreductive surgery and HIPEC. A multi-institutional database of twelve, large, US-based academic centers eliminates single-institution and single-provider bias. A stratified analysis by tumor type creates homogenous patient cohorts with similar disease biology. Lastly, creating two categories of surveillance frequencies captures the wide range of practice patterns for surveillance while still allowing some flexibility in frequency that will incorporate both patient and provider preference. The limitations of this aim predominantly arise from its retrospective design. There is certainly a selection bias between the patients in the HFS and LFS cohorts, although this was mitigated with the use of multivariable Cox regression analysis. Additionally, due to lack of available data, this study cannot comment on the true value of surveillance for this disease process. However, it would be unusual for a patient to not undergo surveillance after curative-intent cytoreductive surgery/HIPEC, as is evidenced by the low number of patients in our database who had no surveillance.

STRENGTHS AND LIMITATIONS: AIM 3

The cost models are simple to optimize reader interpretability yet robust to appropriately estimate the magnitude of savings. They take into account accurate estimates of the population of interest and simulate each patient's course through the surveillance regimen. The limitations of the cost model result from several assumptions as the cohorts were derived by using published estimated incidence data. Additionally, cost data was estimated using Medicare payments as proxy given the interest in estimating cost to the US healthcare system. Although these costs may change over time and vary per institution, the economic impact of surveillance with CXR after resection of soft tissue sarcoma or at low-frequency after cytoreductive surgery/HIPEC for appendiceal neoplasms and colorectal cancer is compelling. Lastly, some nuances of the physician-patient relationship cannot be captured in this study as patients may derive reassurance from knowing that they are disease-free. In fact, a study by Lewis et al. highlights that fear of recurrence is a major source of anxiety for patients (80). Conversely, patients may experience disappointment associated with recurrence detection for which salvage therapy may not be indicated. Accordingly, surveillance strategies must balance the advantage of a survival benefit with the limitations of imaging modalities, costs to the healthcare system, and patient satisfaction.

CONCLUSION

The results of this study are not attempting to propose protocols for generalized acceptance, but simply suggesting that the modality of lung surveillance in high-grade soft tissue sarcoma may include CXR and that the frequency of surveillance may be reduced for patients after cytoreductive surgery/HIPEC with no associated decrease in survival and a reduced financial burden to the US-healthcare system. These findings provide a foundation for clinical trials to validate surveillance protocols for soft tissue sarcoma and peritoneal malignancies.

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TABLES

Table 1.

Demographic and Clinicopathologic Factors of Patients with High-Grade Soft Tissue Sarcoma

	All patients n=1093 (%)	**Surveyed patients** n=909 (%)	**CXR** n=192 (%)	**CT** n=717 (%)	**CXR v CT *p* value**
Demographic variables					
Median age (years, IQR)	61 (49-72)	60 (48-71)	62 (51-76)	59 (48-71)	**0.02**
Sex					
Male	582 (53)	480 (53)	95 (49)	385 (54)	0.34
Female	511 (47)	429 (47)	97 (51)	332 (46)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Race					
White	818 (75)	679 (75)	144 (75)	535 (75)	0.87
Black	123 (11)	102 (11)	22 (11)	80 (11)	
Other	112 (10)	100 (11)	19 (10)	81 (11)	
Missing	40 (4)	28 (3)	7 (4)	21 (3)	
Primary location					
Truncal	131 (12)	113 (12)	18 (9)	95 (13)	**<0.01**
Extremity	762 (70)	645 (71)	157 (82)	488 (68)	
Retroperitoneal (RPS)	200 (18)	151 (17)	17 (9)	134 (19)	
Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Clinicopathologic factors					
Tumor size					
< 5 cm	174 (16)	137 (15)	38 (20)	99 (14)	0.13
5-10 cm	422 (39)	366 (40)	74 (39)	292 (41)	
> 10 cm	434 (40)	351 (39)	70 (36)	281 (39)	
Missing	63 (5)	55 (6)	10 (5)	45 (6)	
Histopathologies					
UPS/Malignant fibrous histiocytoma	424 (39)	355 (39)	79 (41)	276 (39)	0.56
Leiomyosarcoma	133 (12)	106 (12)	18 (9)	88 (12)	0.33
Myxofibrosarcoma	86 (8)	75 (8)	23 (12)	52 (6)	0.05
Liposarcoma, dedifferentiated	56 (5)	40 (4)	3 (2)	37 (5)	**0.03**
Synovial	53 (5)	48 (5)	11 (6)	37 (5)	0.89
Liposarcoma, pleomorphic	46 (4)	44 (5)	10 (5)	34 (5)	0.94
Other	295 (27)	241 (27)	48 (25)	193 (27)	0.66
Lymph node metastases					
Negative	121 (11)	95 (10)	9 (5)	86 (12)	0.69
Positive	25 (2)	20 (3)	3 (2)	17 (2)	
Missing	947 (87)	794 (87)	180 (93)	614 (86)	
Lymphovascular invasion					
Negative	625 (57)	551 (61)	130 (68)	421 (59)	0.12
Positive	54 (5)	41 (5)	5 (3)	36 (5)	
Missing	414 (38)	317 (35)	57 (29)	260 (36)	
Final resection status					
R0	888 (81)	755 (83)	161 (84)	594 (65)	0.82
R1	205 (19)	154 (17)	31 (16)	123 (17)	

Missing	0 (0)	0 (0)	0 (0)	0 (0)	
Adjuvant multimodal treatment					
Chemotherapy	346 (32)	513 (35)	65 (34)	254 (36)	0.78
Radiation	582 (53)	513 (57)	105 (55)	410 (57)	0.55
Mode of lung surveillance					
CXR	192 (18)	192 (21)	--	--	
CT	717 (66)	717 (79)	--	--	
First recurrence	455 (43)	432 (48)	33 (17)	399 (56)	**<0.01**
Local/locoregional	156 (34)	149 (34)	16 (48)	133 (33)	0.3
Distant	249 (55)	239 (55)	15 (45)	224 (56)	
Both (locoregional + distant)	48 (11)	42 (10)	2 (6)	40 (10)	
Lung metastases	234 (51)	232 (54)	11 (6)	221 (31)	**<0.01**
Median follow-up (months)	41	33	48	43	0.128
Timing of Detection of Lung Metastases and Intervention Type					
Timing					
<2 years	−	−	10 (91)	188 (85)	0.88
2-5 years	−	−	1 (9)	27 (12)	
>5 years	−	−	0 (0)	1 (0.4)	
Intervention					
Ablation	−	−	0 (0)	1 (0.4)	0.77
Radiation	−	−	1 (9)	12 (5)	
Surgery	−	−	5 (45)	94 (43)	
Chemotherapy	−	−	2 (18)	88 (40)	

¥ Percentages in parentheses are based on cohort size and do not account for missing data

€ Bold indicates statistical significance

Table 1.2

Clinicopathologic Factors Associated with Overall Survival in R0/R1 Resection

Variable	Univariable Cox Regression		Multivariable Cox Regression	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age	1.02 (1.01-1.03)	**<0.01**	1.02 (1.01-1.03)	**<0.01**
Sex				
Male	Reference			
Female	1.06 (0.85-1.34)	0.60		
Race				
White	Reference			
African American	1.05 (0.73-1.51)	0.78		
Other	0.90 (0.61-1.33)	0.60		
Primary location				
Truncal/Extremity	Reference		Reference	
RPS	0.64 (0.48-0.83)	**<0.01**	1.32 (0.97-1.80)	0.08
Tumor size				
< 5 cm	Reference		Reference	
5-10 cm	1.79 (1.156-2.77)	**<0.01**	1.38 (0.87-2.18)	0.11
> 10 cm	3.03 (1.98-4.62)	**<0.01**	2.13 (1.36-3.34)	**<0.01**
Histopathologies				
UPS/MFH	0.86 (0.68-1.10)	0.23		
Leiomyosarcoma	1.06 (0.75-1.49)	0.74		
Myxofibrosarcoma	0.81 (0.51-1.29)	0.37		
Liposarcoma, dedifferentiated	1.29 (0.79-2.11)	0.31		
Synovial	0.79 (0.46-1.35)	0.39		
Liposarcoma, pleomorphic	1.16 (0.73-1.85)	0.53		
Other	1.18 (0.92-1.51)	0.20		
Lymph node metastases				
Negative	Reference			
Positive	2.61 (1.37-4.98)	**<0.01**		
Lymphovascular invasion				
Absent	Reference			
Present	1.94 (1.25-3.03)	**<0.01**		
Final margin status				
Negative	Reference		Reference	
Positive	1.64 (1.25-2.15)	**<0.01**	1.79 (1.34-2.39)	**<0.01**
Multimodal treatment				
Radiation	0.79 (0.63-0.99)	**0.04**	0.75 (0.58-0.96)	0.11
Chemotherapy	0.91 (0.72-1.16)	0.44		
Recurrence				
No recurrence	Reference		Reference	
Recurrence	7.1 (5.22-9.66)	**<0.01**	--	--
Lung metastases	3.91 (3.11-4.92)	**<0.01**	4.26 (3.28-5.53)	**<0.01**
Lung Surveillance Modality				
CXR	Reference		Reference	
CT	1.61 (1.17-2.21)	**<0.01**	1.01 (0.71-1.43)	0.97

¥ Abbreviations: HR – hazard ratio, CI – confidence interval

€ Bold indicates statistical significance

Table 2.1

Demographic and clinicopathologic factors of the entire cohort and comparing HFS vs LFS cohorts

	All patients	**HFS**	**LFS**	**HFS vs LFS p-value**
Non-Invasive Appendiceal Neoplasm	n=301	n=93	n=208	
Age at diagnosis (median, IQR)	55 (47-64)	58 (50-66)	54 (46-63)	0.20
Sex				
Female	184 (61)	56 (60)	128 (62)	0.93
Male	117 (39)	37 (40)	80 (38)	
Race				
White	266 (88)	79 (85)	187 (90)	0.41
Black	15 (5)	5 (6)	10 (5)	
Other	18 (6)	8 (9)	10 (5)	
ASA class				
1	2 (1)	0 (0)	2 (0.01)	0.40
2	63 (21)	22 (24)	41 (20)	
3	219 (73)	63 (68)	156 (75)	
4	11 (4)	5 (5)	6 (3)	
BMI				
≤18	7 (2)	0 (0)	7 (3)	0.11
18-25	79 (26)	24 (26)	55 (26)	
25-30	110 (37)	36 (39)	74 (36)	
30-35	91 (30)	31 (33)	60 (29)	
35-40	13 (4)	2 (2)	11 (5)	
Operative intent				
Curative	297 (99)	92 (99)	205 (99)	1.0
Prophylactic	3 (1)	1 (1)	3 (1)	
PCI (median, IQR)	12 (5-19)	19 (11-26)	10 (4-15)	**<0.01**
CCR				
CCR 0	211 (70)	52 (56)	159 (76)	**<0.01**
CCR 1	90 (30)	41 (44)	49 (24)	
Tumor grade				
Well	116 (39)	46 (49)	70 (34)	0.77
Moderate	19 (6)	9 (10)	10 (5)	
Poor/un-differentiated	6 (2)	2 (2)	4 (2)	
Lymph vascular invasion	7 (2)	5 (5)	2 (1)	0.10
Perineural invasion	1 (0.3)	3 (3)	1 (0.5)	0.14
Mutations				
KRAS	15 (5)	11 (12)	4 (2)	0.41
BRAF	1 (0.3)	0 (0)	1 (0.5)	
Multimodal treatment				
Neoadjuvant chemotherapy	32 (11)	14 (15)	18 (9)	0.14
Adjuvant chemotherapy	22 (7)	10 (11)	12 (6)	0.09
Recurrence	81 (27)	37 (40)	44 (21)	**<0.01**
Peritoneal	33 (41)	13 (35)	20 (45)	0.39
Distant	2 (3)	1 (3)	1 (2)	
Peritoneal and distant	0 (0)	0 (0)	0 (0)	–
Treatment for recurrence				
Systemic therapy, radiotherapy or targeted therapy	35 (43)	12 (32)	23 (52)	0.12
Repeat CRS/HIPEC	18 (22)	4 (11)	14 (32)	**0.02**

Median follow-up (months, IQR)	28 (12-50)	23 (9-47)	32 (14-51)	**0.03**
Median time to recurrence (months, IQR)	14 (7-22)	13 (6-19)	14 (8-30)	0.82
Invasive Appendiceal Neoplasm	n=435	n=159	n=276	
Age at diagnosis (median, IQR)	55 (47-64)	55 (46-65)	55 (47-63)	0.87
Sex				
Female	265 (61)	98 (62)	167 (61)	0.89
Male	170 (39)	61 (38)	109 (39)	
Race				
White	388 (90)	138 (87)	250 (91)	0.62
Black	23 (5)	10 (6)	13 (5)	
Other	21 (5)	9 (6)	12 (4)	
ASA class				
1	5 (1)	4 (3)	1 (0.3)	0.09
2	80 (18)	30 (19)	50 (18)	
3	334 (77)	115 (72)	219 (79)	
4	13 (3)	7 (4)	6 (2)	
BMI				
≤18	9 (2)	6 (4)	3 (1)	0.24
18-25	148 (25)	50 (31)	98 (36)	
25-30	131 (31)	52 (33)	79 (29)	
30-35	110 (26)	35 (22)	75 (27)	
35-40	29 (7)	11 (7)	18 (7)	
Operative intent				
Curative	432 (99)	158 (99)	274 (99)	1.0
Prophylactic	3 (1)	1 (0.6)	2 (0.7)	
PCI (median, IQR)	12 (5-19)	14 (8-22)	10 (4-17)	**<0.01**
CCR				
CCR 0	301 (69)	111 (70)	190 (69)	0.92
CCR 1	134 (31)	48 (30)	86 (31)	
Tumor grade				
Well	156 (36)	54 (34)	102 (37)	**<0.01**
Moderate	77 (18)	28 (18)	49 (18)	
Poor/un-differentiated	49 (11)	31 (19)	18 (7)	
Lymph vascular invasion	25 (6)	16 (10)	9 (3)	**0.03**
Perineural invasion	29 (7)	17 (11)	12 (4)	0.11
Mutations				
KRAS	42 (10)	27 (17)	15 (5)	**<0.01**
BRAF	–	–	–	–
Multimodal treatment				
Neoadjuvant chemotherapy	119 (27)	42 (26)	77 (28)	0.79
Adjuvant chemotherapy	64 (15)	35 (22)	29 (11)	**<0.01**
Recurrence	200 (46)	92 (58)	108 (39)	**<0.01**
Peritoneal	92 (46)	43 (47)	49 (45)	**0.05**
Distant	12 (6)	9 (10)	3 (3)	
Peritoneal and distant	6 (3)	5 (5)	1 (1)	
Treatment for recurrence				
Systemic therapy, radiotherapy or targeted therapy	94 (47)	56 (61)	38 (35)	**<0.01**
Repeat CRS/HIPEC	16 (8)	5 (5)	11 (10)	0.30
Median follow-up (months, IQR)	29 (16-51)	29 (14-47)	29 (17-56)	1.0
Median time to recurrence (months, IQR)	15 (9-24)	12 (7-20)	18 (11-35)	**<0.01**

Colorectal Cancer	n=239	n=174	n=65	
Age at diagnosis (median, IQR)	55 (47-64)	54 (47-63)	56 (47-65)	0.72
Sex				
Female	120 (50)	84 (48)	36 (55)	0.41
Male	119 (50)	90 (52)	29 (45)	
Race				
White	183 (77)	132 (76)	51 (78)	0.69
Black	22 (9)	15 (9)	7 (11)	
Other	32 (14)	25 (14)	7 (11)	
ASA class				
1	0 (0)	0 (0)	0 (0)	0.25
2	20 (8)	14 (8)	6 (9)	
3	188 (79)	133 (76)	55 (85)	
4	28 (12)	24 (14)	4 (6)	
BMI				
≤18	6 (3)	2 (1)	4 (6)	0.11
18-25	67 (28)	54 (31)	13 (20)	
25-30	85 (36)	63 (36)	22 (34)	
30-35	72 (30)	49 (28)	23 (35)	
35-40	6 (3)	5 (3)	1 (2)	
Operative intent				
Curative	238 (99)	174 (100)	64 (98)	0.27
Prophylactic	1 (0.4)	0 (0)	1 (2)	
PCI (median, IQR)	10 (6-16)	11 (7-17)	8 (5-14)	**0.01**
CCR				
CCR 0	189 (79)	140 (80)	49 (75)	0.50
CCR 1	50 (21)	34 (20)	16 (25)	
Tumor grade				
Well	21 (9)	17 (10)	4 (6)	0.74
Moderate	86 (36)	63 (36)	23 (35)	
Poor/un-differentiated	41 (17)	30 (17)	11 (17)	
Lymph vascular invasion	55 (23)	42 (24)	13 (20)	0.83
Perineural invasion	30 (13)	23 (13)	7 (11)	0.83
Mutations				
KRAS	61 (26)	50 (29)	11 (17)	0.90
BRAF	3 (1)	3 (2)	0 (0)	0.34
SMAD4	6 (3)	6 (3)	0 (0)	0.31
APC	15 (6)	13 (7)	2 (3)	0.76
PIK3CA	8 (3)	7 (4)	1 (2)	0.89
Multimodal treatment				
Neoadjuvant chemotherapy	130 (54)	88 (51)	42 (65)	0.07
Adjuvant chemotherapy	57 (24)	41 (24)	16 (25)	0.95
Recurrence	151 (63)	118 (68)	33 (51)	0.08
Peritoneal	42 (28)	34 (29)	8 (24)	0.72
Distant	19 (13)	15 (13)	4 (12)	
Peritoneal and distant	19 (13)	17 (10)	2 (3)	
Treatment for recurrence				
Systemic therapy, radiotherapy or targeted therapy	73 (48)	60 (51)	13 (39)	0.33
Repeat CRS/HIPEC	8 (5)	3 (3)	5 (15)	**0.01**
Median follow-up (months, IQR)	17 (9-29)	17 (9-30)	16 (9-28)	0.38
Median time to recurrence (months, IQR)	7 (5-14)	7 (4-13)	12 (6-16)	0.08

¥ Percentages in parentheses are based on cohort size € Bold indicates statistical significance

Table 2.2

Clinicopathologic Factors Associated with Overall Survival for Each Histology

	Univariable Cox Regression		**Multivariable Cox Regression**	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Non-Invasive Appendiceal Neoplasm				
Age at diagnosis	1.00 (0.97-1.04)	0.78		
Sex				
Female	Reference			
Male	0.78 (0.34-1.77)	0.56		
Race				
White	Reference			
Black	2.28 (0.53-9.80)	0.27		
Other	1.36 (0.18-10.26)	0.77		
PCI score	1.03 (0.99-1.08)	0.12	0.99 (0.93-1.04)	0.63
CCR				
CCR 0	Reference		Reference	
CCR 1	2.90 (1.32-6.38)	**<0.01**	2.18 (0.64-7.46)	0.22
Tumor grade				
Well-differentiated	Reference		Reference	
Moderately-differentiated	3.86 (1.26-11.83)	0.02	2.39 (0.72-7.93)	0.15
Poorly/un-differentiated	42.93 (6.65-277.09)	**<0.01**	42.34 (5.23-341.31)	**<0.01**
Lymph vascular invasion	16.65 (4.73-58.70)	**<0.01**		
Perineural invasion	28.51 (4.59-176.77)	**<0.01**		
Multimodal treatment				
Neoadjuvant chemotherapy	4.98 (2.06-12.09)	**<0.01**		
Adjuvant chemotherapy	10.37 (1.95-55.02)	**<0.01**		
Recurrence	7.25 (2.47-12.32)	**<0.01**		
Frequency of surveillance				
HFS	Reference		Reference	
LFS	0.22 (0.09-0.49)	**<0.01**	0.28 (0.06-1.26)	**0.10**
Invasive Appendiceal Neoplasm				
Age at diagnosis	0.99 (0.98-1.01)	0.77		
Sex				
Female	Reference			
Male	1.32 (0.89-1.85)	0.16		
Race				
White	Reference			
Black	1.31 (0.57-3.00)	0.52		
Other	1.73 (0.75-3.99)	0.19		
BMI				
≤18	Reference			
18-25	0.45 (0.16-1.29)	0.14		
25-30	0.64 (0.23-1.81)	0.40		
30-35	0.37 (0.13-1.08)	0.07		
35-40	0.45 (0.11-1.84)	0.27		
PCI score	1.02 (0.99-1.05)	0.08	1.04 (0.99-1.09)	0.07
CCR				
CCR 0	Reference		Reference	
CCR 1	1.25 (0.84-1.86)	0.27	1.26 (0.55-2.86)	0.58

Tumor grade				
Well-differentiated	Reference		Reference	
Moderately-differentiated	2.76 (1.58-4.83)	**<0.01**	5.11 (2.15-12.14)	**<0.01**
Poorly/un-differentiated	5.89 (3.17-10.95)	**<0.01**	11.68 (4.70-28.98)	**<0.01**
Lymph vascular invasion	3.8 (1.84-7.87)	**<0.01**		
Perineural invasion	3.38 (1.50-7.60)	**<0.01**		
Multimodal treatment				
Neoadjuvant chemotherapy	2.64 (1.77-3.91)	**<0.01**		
Adjuvant chemotherapy	1.98 (1.19-3.31)	**<0.01**		
Recurrence	5.36 (2.85-10.07)	**<0.01**		
Frequency of surveillance				
HFS	Reference		Reference	
LFS	0.64 (0.43-0.94)	**0.02**	0.73 (0.34-1.56)	**0.42**
Colorectal Cancer				
Age at diagnosis	1.00 (0.99-1.02)	0.61		
Sex				
Female	Reference		Reference	
Male	1.56 (1.05-2.32)	**0.03**	1.45 (0.96-2.19)	0.07
Race				
White	Reference			
Black	0.55 (0.24-1.27)	0.16		
Other	0.97 (0.54-1.74)	0.91		
BMI				
≤18	Reference			
18-25	2.44 (0.33-17.86)	0.38		
25-30	1.49 (0.20-10.88)	0.70		
30-35	1.25 (0.17-9.22)	0.83		
35-40	1.13 (0.10-12.50)	0.92		
PCI score	1.06 (1.04-1.09)	**<0.01**	1.06 (1.03-1.08)	**<0.01**
CCR				
CCR 0	Reference		Reference	
CCR 1	22.34 (1.53-3.59)	**<0.01**	1.32 (0.77-2.27)	0.32
Tumor grade				
Well-differentiated	Reference			
Moderately-differentiated	0.74 (0.36-1.51)	0.41		
Poorly/un-differentiated	1.28 (0.61-2.67)	0.52		
Lymph vascular invasion	1.57 (0.94-2.64)	0.09		
Perineural invasion	1.33 (0.73-2.44)	0.35		
Mutations				
KRAS mutation	1.17 (0.68-1.99)	0.58		
BRAF mutation	1.19 (0.16-8.86)	0.86		
Multimodal treatment				
Neoadjuvant chemotherapy	0.94 (0.63-1.39)	0.75		
Adjuvant chemotherapy	1.12 (0.68-1.86)	0.66		
Neoadjuvant radiotherapy	0.94 (0.29-2.99)	0.91		
Adjuvant radiotherapy	8.98 (2.61-30.90)	**<0.01**		
Recurrence	1.92 (1.16-3.17)	**0.01**		
Frequency of surveillance				
HFS	Reference		Reference	
LFS	0.94 (0.60-1.47)	0.8	1.14 (0.71-1.84)	**0.59**

€ Abbreviations: HR – hazard ratio, CI – confidence interval

Table 3.1

Cost Model Assumptions for Soft Tissue Sarcoma

Soft-Tissue Sarcoma Incidence		
	%	**Number**
Incidence of soft tissue sarcoma (2018)	--	13,040 (2)
Non-metastatic soft tissue sarcoma	80%	10,432 (82)
High-grade soft tissue sarcoma	64%	6,676 (75)
Retroperitoneal soft tissue sarcoma	40%	2,671 (75)
Trunk soft tissue sarcoma	10%	668 (75)
Extremity soft tissue sarcoma	16%	1,068 (75)
Final cohort		**4,406**
Cost Data		
Modality	**CPT**	**Cost**
CXR	71046	$30.96
CT chest without contrast	72178	$183.96
Video-Assisted Thoracoscopic Wedge Resection	32666	$904.31

Table 3.2

Cost Model Assumptions for Appendiceal Neoplasms and Colorectal Cancer

Non-Invasive Appendiceal Neoplasms Incidence

	%	Number
Number appendectomies/year	−	500,000 (83)
Appendiceal neoplasms	0.3%	1500 (28)
Low-grade incidence	50%	150 (84)
Stage IV	50%	375 (28)
Final cohort		**375**

Invasive Appendiceal Neoplasms Incidence

	%	Number
Number appendectomies/year	−	500,000 (83)
Appendiceal neoplasms	0.3%	1500 (28)
Low-grade incidence	50%	150 (84)
Stage IV	50%	375 (28)
Final cohort		**375**

Colorectal Cancer Incidence

	%	Number
Incidence of colorectal cancer	−	150,000 (2)
Incidence of adenocarcinoma/year	98%	147,000 (85)
Stage IV (synchronous PC)	10%	14,700 (30)
Stage IV (metachronous PC)	20%	29,400 (86)
Eligible for CRS/HIPEC	10%	4,410
Final cohort		**4,410**

Cost Data

Modality	CPT	Cost
CT chest without contrast	72178	$183.96
CT abdomen with contrast	74160	$235.08
CT pelvis with contrast	74170	$267.48
MRI abdomen with contrast	74182	$390.60
MRI pelvis with contrast	72196	$354.60

Table 3.4

Cost Model Results for a Five-Year Surveillance Period for High-Grade STS

Surveillance Protocol	Mean cost (std) – LFS protocol	Mean cost (std) – HFS protocol
CXR	$2,333,224 ($32,057.71)	$2,985,268 ($33,626.64)
CT	$7,858,637 ($62,783.94)	$10,839,000 ($77,141.49)
Savings	$5,525,413	$7,853,732

¥ LFS: Low Frequency Surveillance
€ HFS: High Frequency Surveillance

Table 4.4

Cost Model Results for a Two-Year Surveillance Period

Non-Invasive Appendiceal Neoplasms (n=375)

Surveillance Protocol	**Mean cost (std) – CT protocol**	**Mean cost (std) – MRI protocol**
HFS	$1,128,898.02 ($978.61)	$1,673,898.05 ($1,480.37)
LFS	$374,997.21 ($986.81)	$556,119.66 ($1,442.76)
Savings	$753,900.81	$1,117,778.39

Invasive Appendiceal Neoplasms (n=375)

Surveillance Protocol	**Mean cost (std) – CT protocol**	**Mean cost (std) – MRI protocol**
HFS	$2,055,575.44 ($2,642.02)	$2,782,120.61 ($3,485.31)
LFS	$1,025,012.12 ($3,082.02)	$1,387,454.23 ($4,021.93)
Savings	$1,030,563.32	$1,394,666.38

Colorectal Cancer (n=4410)

Surveillance Protocol	**Mean cost (std) – CT protocol**	**Mean cost (std) – MRI protocol**
HFS	$23,945,828.58 ($32,283.47)	$32,408,996.73 ($42,196.84)
LFS	$11,949,998.25 ($18,098.09)	$16,174,898.12 ($23,887.23)
Savings	$11,995,830.33	$16,234,098.61
Total savings	$13,780,294.46	$18,746,543.38

FIGURES

Figure 1.1

Kaplan-Meier curves of patients with pulmonary metastasis compared according to chest imaging modality: a) lung-specific recurrence free survival b) overall survival c) overall survival excluding patients with documented lung metastases

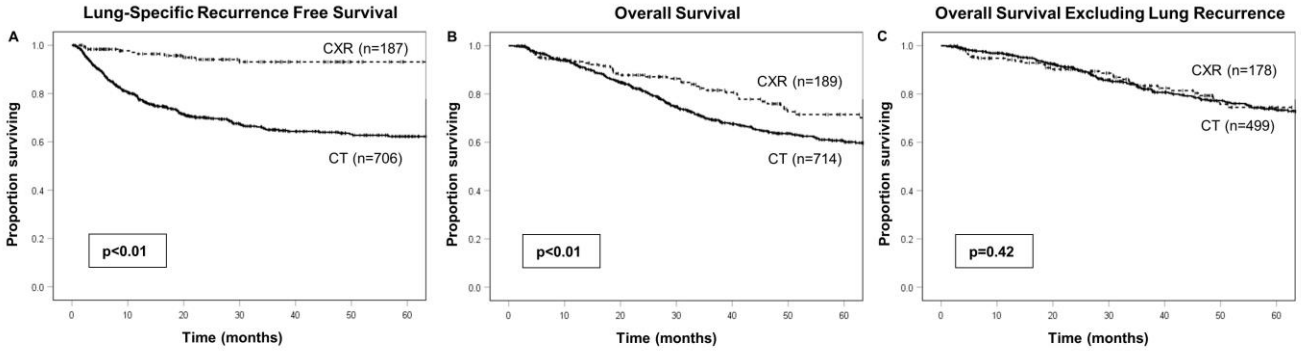

Figure 2.1

Kaplan-Meier curves for overall survival comparing surveillance frequencies a) non-invasive appendiceal neoplasm b) invasive appendiceal neoplasm c) colorectal cancer