The effect of surveillance intensity on long-term survival following
curative surgical treatment for solid cancers:
A systematic review and meta-analysis

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Abstract

Background

The number of cancer survivors continues to increase due to advancements in cancer treatment. Consequently, the number of patients requiring post-operative surveillance protocols have increased, highlighting the need to develop post-operative surveillance protocols that increase survival benefit while remaining both cost- and resource-effective.

Methods

We carried out a comprehensive and systematic literature search of medical databases for randomized controlled trials (RCTs) in which patients with solid tumors 18 years of age or older that had undergone surgical resection with curative intent and had no metastatic disease at presentation, were randomized to different surveillance regimens to assess the effect on overall survival (OS). According to *a priori* definitions, surveillance programs were classified as (1) biological test, (2) frequency, (3) imaging, or (4) practitioner type. We carried out a pooled effect size estimate on risk ratios (RR) to evaluate the effect of more intensive versus less intensive surveillance strategies in each of the surveillance program categories on overall survival (OS).

Results

Our search yielded a total of 32,216 articles for review. Following all screening stages, 18 distinct RCTs were included in the systematic review. Most studies evaluated colorectal cancer patients (11/18, [61%]). Twenty-one comparisons from the 18 trials were included in the meta-analysis, with no significant difference in OS for any of the more intensive surveillance program categories analysed. One comparison evaluated biological test interventions and therefore, a meta-analysis was not conducted. Six comparisons were classified as frequency interventions with a combined RR of 0.96 (95% CI: 0.79-1.16). Eleven comparisons were classified as imaging interventions with a combined RR of 0.99 (95% CI: 0.91-1.08). Two comparisons were classified as practitioner type interventions with a combined RR of 1.106 (95% CI: 0.64-1.91). No difference in OS was observed in any of the cancer type subgroup analyses.

Conclusion

The cost of cancer care is steadily rising due to the growing number of cancer survivors, leading to questions in the ability of healthcare systems to meet the needs of patients. This study demonstrated that there is currently no evidence to support any kind of more intensive surveillance in solid cancers after treatment when considering OS as the primary outcome. However, due to persistent clinical equipoise and advancements in surveillance options, further large RCTs are required to evaluate the most optimal surveillance protocol for individual cancer types.

Introduction

Surgical intervention is the primary treatment for an attempt at cure for many types of solid tumors including breast, colorectal, testicular and non-small cell lung cancers¹. Following surgery, the risk of local recurrence or metastases remains a concern for patients and clinicians. Therefore, the use of post-operative surveillance protocols, which include follow-up appointments, biochemical tests and surveillance imaging in likely areas of recurrence or metastases, have become the standard of care in the management of solid cancers². However, the development of post-operative surveillance protocols that increase survival benefit while being both cost- and resource-effective remains challenging².

Clinicians are presented with multiple surveillance possibilities in the post-operative period due to recent advancements in available imaging modalities and molecular diagnostic tests to detect malignant disease. However, adverse effects of surveillance programs that make use of more intensive imaging modalities and / or more frequent follow-up visits are noteworthy. Patients have expressed concern over harmful levels of energy and radiation exposure used in advanced imaging techniques, as well as the direct and indirect costs associated with more frequent follow-up visits²⁻⁶. Direct costs to the healthcare system for more intensive surveillance programs are also notable, ranging from \$20,000 to \$30,000 USD per patient for an intensive five-year post-operative cancer surveillance protocol that often have little to no clinic benefit compared to minimal surveillance protocols⁷⁻¹¹. Moreover, *The American Society of Clinical Oncology* recommends not to perform additional surveillance testing or imaging in asymptomatic patients if available evidence suggests these tests do not improve outcomes¹². The number of cancer survivors continues to increase, with an estimated 16.9 million individuals as of January 2019 in the United States alone. This figure is expected to grow to an estimated 22.1 million individuals as of 2030, resulting in an even greater

emphasis on the development of evidence-based post-operative treatment guidelines that balance cost efficacy and patient quality of life¹³.

The National Comprehensive Cancer Network (NCCN) develops and updates guidelines as well as provides recommendations on best-practice treatment and surveillance for various cancers based on the best available evidence, with large randomized controlled trials (RCTs) sought as the highest-quality evidence^{14,15}. In order to inform future guidelines, we carried out a systematic review and meta-analysis of studies in which cancer patients were randomized to different biological test surveillance, frequency surveillance, imaging surveillance or practitioner type surveillance regimens to determine if less intensive post-operative surveillance effects overall survival (OS) in this patient population as a whole, with a focus on different cancer types when possible.

Methods

This systematic review adheres to and is reported according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was submitted for registration on the International Prospective Register of Systematic Reviews (PROSPERO) (ID:150689).

Eligibility Criteria

The study population included solid cancer patients, 18 years of age or older that had previously undergone surgical resection of their tumors and had no metastatic disease at presentation. All oncology subspecialties were eligible. Included studies were RCTs, including cluster RCTs. All RCTs that evaluated the efficacy of a post-operative surveillance regimen were eligible for inclusion. Specifically, we included studies that investigated different follow-up frequencies (e.g., post-operative clinic follow-up visits every three months vs. every six months), different imaging or laboratory diagnostic techniques (e.g., post-operative Computed tomography (CT) scans vs. plain radiographs), or different practitioner visit types (e.g., post-operative nurse visits vs. specialist visits). Studies were eligible for inclusion if they assessed overall survival as one of their primary or secondary outcomes. Only published journal articles in the English language were considered, with no lower limit on the study publication year.

Information Sources

A comprehensive and systematic literature search of MEDLINE (OVID Interface, 1946 to present), EMBASE (OVID interface 1974 to present), and CENTRAL databases was conducted on 21 August 2019. Additionally, reference lists of included articles were scanned by reviewers for potentially eligible titles.

Search

In conjunction with a health research methodologist (KM), the search strategy was developed uniquely for each medical database by combining exploded medical indexing terms (MeSH® terms for MEDLINE and CENTRAL, Emtree® terms for EMBASE) and keywords using Boolean operators ‘OR’ and ‘AND’. The search was limited to journal articles published in the English language and included terms to filter for RCTs as developed by the Scottish Intercollegiate Guidelines Network¹⁶. The full search strategy can be found in **Supplementary Materials - Appendix I**.

Study Selection

Duplicate removal was performed in two rounds. The first round of duplicate removal was conducted manually on RefWorks by one author (BL) after extracting a listing of articles from each medical database and uploading them on to the RefWorks System. After the completion of the first round of duplicate removal, remaining articles were uploaded onto the DistillerSR online software (www.evidencepartners.com) to create a study database. A second round of duplicate removal was conducted using DistillerSR’s duplicate identification feature, and two authors (BL and VG) independently audited the integrity of this feature by verifying that identified articles were in fact duplicates prior to deletion. Author pairs (BL and PS / BL and HB / BL and PT / LN and AB / ML and PT / VG and PS / VG and IM / PS and PW) independently screened titles and abstracts identified in the literature search to determine if the articles should be considered for inclusion. The following inclusion questions were used: (1) Does this article describe a RCT?, (2) Do the participants of this trial have a solid tumor?, (3) Was the cancer treated with surgery with curative intent prior to inclusion in the RCT?, (4) Does the RCT assess different post-operative follow-up regimens?, (5) Is there any other reason for exclusion of the study?. The full texts of

included abstracts were then reviewed in duplicate (VG and IM / PS and PW) for inclusion using the aforementioned inclusion questions, in addition to the following questions: (6) Were the participants of this trial non-metastatic at the time of inclusion in the RCT, and (7) Is overall survival evaluated as a primary or secondary outcome?. These two inclusion questions were added at the full-text screening stage as this information was found to only be available in the full text of papers when pilot testing eligibility questions. All discrepancies were resolved by consensus with the senior author (MG).

Data Collection Process and Data Items

Data was extracted in duplicate (VG and IM) using study-specific data collection forms uploaded to DistillerSR. Additional information on RCTs was obtained from protocols or dissertations as required. Authors were contacted on multiple occasions for any missing data.

Data extraction forms were pilot tested on two randomly selected full texts to ensure that reviewers extracted data consistently and to ensure the forms were unambiguous and free from errors. Study Characteristics, Risk of Bias, and Statistical Reporting data were collected on independent data extraction forms (**Supplementary Materials - Appendix II**). Statistical information including event rates and related effect measures for OS were extracted from each article. Event rates were calculated from OS percentages when raw results were not reported in the article and could not be obtained from the authors. The most recently published article was used for OS results when updated OS results were published for the same trial.

Studies were classified into categories in duplicate (VG and IM) based on the type of interventions assessed. If a trial was factorial in design, each comparison within the trial was categorized independently into an intervention category. Due to the large variation in surveillance programs, categories were predefined as per below:

1. Biological tests – any study that evaluates more intensive versus less intensive or sensitive (including a reduced number or none at all) laboratory tests.
2. Frequency – any study that evaluates more frequent versus less frequent (including a reduced number or none at all) clinic visits.

3. Imaging – any study that evaluates more intensive versus less intensive (including a reduced number or none at all) imaging modalities.
4. Practitioner type – any study that evaluates specialist (medical oncology or surgeon)-led versus primary care physician or nurse practitioner-led.

Interventions within each RCT were then categorized as either the more intensive- or less intensive-group (control group). Due to the wide range of intervention types, we defined more intensive surveillance as the most comprehensive treatment of the treatment groups in any given trial (i.e., the treatment that is: more frequent, contains more invasive surveillance component(s) or is specialist-led). Any disagreements were reconciled with the senior author (MG).

Risk of Bias in Individual Studies and Across Studies

Author pairs (VG and IM) individually assessed included studies on the quality of trial and risk of bias using the Risk of Bias form. This form follows the Cochrane Collaboration's Risk of Bias tool, which reports on the risk of bias as opposed to focusing on the quality of reporting¹⁷. Any disagreements were reconciled with the senior author (MG). A funnel plot was constructed and visually assessed for asymmetry for publication bias. The overall quality of evidence for each intervention category on OS is presented in the summary of findings using judgement from the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) factors: (1) limitations in study design or execution, (2) inconsistency of results, (3) indirectness of evidence, (4) imprecision and, (5) publication bias. All factors were considered in providing a final grade to the quality of evidence of any of, high, moderate, low or very low quality as described in the GRADE handbook¹⁸. A justification for each GRADE rating is provided by the review authors.

Summary Measures and Synthesis of Results

Descriptive statistics, percentages and means or medians were used to summarize categorical and continuous variables, respectively.

OS was the primary endpoint for this systematic review and meta-analysis. Effect measures (relative risks, odds ratios or hazard ratios) along with confidence intervals and hypothesis testing are presented for study characteristics whenever possible. When trials presented more than one hypothesis test, we selected the most adjusted test to report.

Pooled Analysis

We included all studies with poolable data in the meta-analysis. We chose to report meta-analysis findings as RRs with 95% CIs because RRs are most commonly reported in trials evaluating overall survival and they are easily interpreted by clinicians¹⁹. We evaluated each comparison in a factorial trial independently in their previously categorized intervention type category. We used random effects models in every analysis due to the hypothesized heterogeneity between studies (e.g. differences in cancer types, patient characteristics and details of intervention protocols). We assessed heterogeneity with the I^2 statistic. I^2 describes the percentage of variation across studies that is due to heterogeneity. Pooled analyses are presented as forest plots with RR and 95% confidence intervals.

We conducted subgroup analyses on OS to calculate a pooled effect estimate based on *a priori* categories of cancer types. If we could not conduct an analysis due to a lack of data, conclusions for each intervention category were summarized descriptively based on reported outcomes as: (1) less intense surveillance performed better than comparators for survival outcomes, (2) less intense surveillance performed worse than comparators for survival outcomes, or (3) no difference in survival outcomes. No additional analyses were conducted. P-values less than 0.05 were considered statistically significant. All analyses were performed with Review Manager version 5.3²¹.

Results

Study Selection

Our search of databases yielded 32,197 potentially eligible studies titles, with an additional 19 records identified through reference list screening. Following duplicate removal, 25,825 titles remained for screening. 25,772 studies were excluded following title and abstract screening due to not being RCTs, patients not having sarcoma or carcinoma, patients not treated with surgery, or the RCT not assessing different post-operative follow-up regimens. Fifty-three articles remained for full text screening. Thirty-two articles were excluded at this final stage, resulting in 21 articles reporting on 18 distinct trials being included in the systematic review²²⁻⁴². Two RCTs published extended follow-up time frame results^{28,34}, and one RCT published an additional cost-analysis based on the trial results, while also addressing overall survival results²⁴. Other reasons for

exclusion included the article being a conference abstract or preliminary results from a trial in which OS was not presented. Study selection is presented in **Figure 1**.

Study Characteristics

The 18 RCTs comprised a total of 9,020 participants from 11 different countries. Most trials' coordinating centres or initiating sites were based in Europe, 15/18 (83%)^{22-25,28-32,35-37,38-40} with the remaining sites in China (1/18, [6%])⁴¹, India (1/18, [6%])³⁴, and Australia (2/18, [11%])^{38,42}. Fourteen of the 18 RCTs (78%) were published prior to 2010^{22-25,28,30-31,35,37-39,41-42}. The most common type of cancer studied was colorectal cancer, (11/18 [61%])^{23,28,30-32,35,36,38-41}, and one RCT included patients with only colon cancer and not rectal cancer due to slightly different follow-up programs between the two cancers⁴². The remaining types of cancers studied included breast cancer (4/17 [22%])^{22,24-25,37}, lung cancer (1/18 [6%])²⁹, and bone and soft-tissue sarcomas (1/18 [6%])³⁴. Fifteen of the 18 RCTs were parallel group trials, (83%), with the other three of factorial design^{25,31,34}. Study characteristics of included studies are show in **Table 1**.

Due to multiple comparisons in factorial trials and one trial using different follow-up protocols for high-risk and low-risk patients³⁸, a total of 23 comparisons of intervention strategies were assessed in the 18 included trials. There was a high-level of variation in the intervention strategies used in each trial, with no two trials comparing identical intervention strategies. One comparison (4%) was classified as a biological test intervention, eight comparisons (35%) were classified as frequency interventions, 12 comparisons (52%) were classified as imaging interventions, and the remaining two comparisons (9%) were classified as practitioner type interventions. Often, comparisons in the imaging category evaluated the presence of an imaging test versus not using that imaging modality at all in the follow-up program.

Risk of Bias in Included Studies

Blinding of patients and research personnel was not possible due to the nature of the interventions, therefore all studies have a high risk of performance bias. Many trials did not report, or it was unclear, if the assessment of outcomes was blinded and if results were selectively reported in trials. This was due to most trials not publishing a protocol, possibly a consequence of the older publication dates of included trials. Overall risk and quality assessment of the trials are presented

in **Table 2**. A funnel plot was constructed for all included trials collectively due to the minimal RCTs available in each intervention category. The funnel plot (**Figure 2**) showed slight asymmetry, revealing possible publication bias. Frequency and imaging intervention results provided a moderate quality of evidence after considering all GRADE factors, whereas biological test and practitioner type interventions provided a low quality of evidence, primarily due to the number of trials and events in each of these intervention categories (**Table 4**).

Results of Individual Studies

Extracted event data, effect measures with associated CIs, and p-values are presented in **Table 3** for all comparisons described in each RCT. Only 8/23 (35%) of comparisons reported effect measures, and event rate data could be extracted from all but one RCT (two comparisons)²⁹. All RCTs reported p-values, however, four comparisons simply indicated results were not significant but did not provide point estimates^{25,29,37}. Computed effect estimates (RR) for are presented in **Figure 3** for frequency interventions, **Figure 4** for imaging interventions and in **Figure 5** for practitioner type interventions. The biological intervention RR is described in the results section below, as a meta-analysis could not be conducted for this category due to insufficient data.

Synthesis of Results

Seventeen trials (21 comparisons) were included in the meta-analysis as one trial did not present event rate data. The summary of results are presented in **Table 4** along with the GRADE quality of evidence.

Biological Test Interventions

As only one trial was categorized as a biological test intervention, a meta-analysis could not be conducted. This trial which evaluated colorectal cancer patients demonstrated no difference in more intensive versus less intensive biological test surveillance protocols on OS (RR: 0.96, 95% CI: 0.75-1.23).

Frequency Interventions

A total of six trials were included in the pooled effect size estimates for frequency interventions resulting in a total of 2997 patients analyzed. Heterogeneity was moderate for all combined trials, but this was not statistically significant ($I^2 = 53\%$, $p\text{-value} = 0.06$). The combined risk ratio was 0.96 (95% CI: 0.79-1.16), indicating no significant difference in OS between more intensive and less intensive post-operative frequency protocols (**Figure 4**). In the subgroup analysis of cancer types, the test for subgroup differences was not statistically significant ($p=0.12$).

Imaging Interventions

A total of 12 trials were included in the pooled effect size estimates for imaging interventions resulting in a total of 7194 patients analyzed. Heterogeneity was low ($I^2 = 0\%$). The combined risk ratio was 0.99 (95% CI: 0.91-1.08), indicating no significant difference in OS between more intensive and less intensive post-operative imaging protocols (**Figure 5**). In the subgroup analysis of cancer types, the test for subgroup differences was not statistically significant ($p=0.67$).

Practitioner Type Interventions

A total of two trials were included in the pooled effect size estimates for practitioner type interventions resulting in a total of 467 patients analyzed. Heterogeneity was low ($I^2 = 0\%$). The combined risk ratio was 1.10 (95% CI: 0.64-1.91), indicating no significant difference in OS when using more specialized versus less specialized health care personnel for post-operative surveillance (**Figure 6**). There was insufficient data to perform subgroup analysis by cancer type.

Discussion

Summary of Results Quality of the Evidence

The purpose of this study was to investigate the effect of less intense post-operative biological test surveillance, frequency surveillance, imaging surveillance or practitioner type surveillance on OS in cancer patients that have undergone a solid tumor resection with curative intent. This is the only meta-analysis to our knowledge that evaluates all cancer types in each surveillance category and identifies the category of each surveillance protocol. No difference in OS was observed for all pooled effect estimates in any of frequency interventions, imaging interventions or practitioner type interventions. Furthermore, there was no difference in OS survival for any of the analyses when analyzing cancer type subgroups separately. However, it is worth noting that only colorectal

cancer for frequency and imaging interventions and breast cancer for imaging interventions had sufficient data to conduct a subgroup analyses due to insufficient number of RCTs for all other cancer types.

Implications and Discussion

By the end of 2020, the cost of cancer care in the United States is expected to be \$157.8 billion (USD), becoming one of the most expensive medical conditions⁴³. Advancements in oncology treatment have resulted in a growing number of cancer survivors that continue to utilize healthcare resources for longer periods of time⁴⁴. This calls into question the ability of our healthcare systems to meet the needs of patients, as both the number of primary care physicians and medical specialists, and available funds in the healthcare system are limited⁴⁴. It is therefore essential to devote research efforts to develop effective strategies in cancer care to reduce the strain on the healthcare system.

Routine follow-up after tumor resection surgery varies significantly among both country specific guidelines and physicians. Physician surveys and systematic reviews evaluating post-operative surveillance strategies report a lack of consensus in surveillance practice and an inability to provide recommendations on the most appropriate protocol due to high variability and minimal high-quality data⁴⁵⁻⁴⁷. Among included articles in this systematic review and meta-analysis, no two trials evaluated identical interventions in post-operative surveillance, emphasizing that clinical equipoise may exist with respect to how patients are followed after definitive treatment. Although surveillance recommendations should be cancer type specific, even when post-operative surveillance strategies were evaluated by cancer subgroups, variations were prevalent in the frequency of clinic visits, types of imaging or biological tests employed, and types of healthcare workers involved in the post-operative surveillance program. As these variations can be explained and are expected in surgical RCTs, the evidence was not downgraded due to inconsistency. However, it is important to note that cancer subgroup estimates should be considered by guideline developers, due to variations in treatment and disease prognosis across cancer types. A meta-analysis assumes that the magnitude of effect is similar across the range of patients, interventions, and ways of measuring outcomes⁴⁸. Patients, intervention specifics, and ways of measuring outcomes were not considered in the effect estimate, which could lead to inaccurate conclusions.

Overall survival measures ranged from a two-year follow-up analysis to a five-year follow-up analysis, possibly attributing to differing survival outcomes. We recommend that the results of this meta-analysis are viewed in light of these dissimilarities. Additional large RCTs with similar surveillance programs would need to be conducted for each cancer type in order to evaluate OS and provide recommendations for clinicians.

Although this meta-analysis evaluated only the effect of more intensive versus less intensive biological test surveillance, frequency surveillance, imaging surveillance or practitioner type surveillance strategies on OS, secondary outcomes including costs to the healthcare system and patient's quality of life should also be considered when recommending an optimal post-operative surveillance protocol. A systematic review of breast cancer surveillance programs reported that the adoption of less intensive surveillance programs that do not compromise overall survival can result in savings upward of \$8,000 USD per patient per quality adjusted life year⁴⁹. Furthermore, patient anxiety due to harmful levels of radiation from more intensive imaging modalities, and burdens due to more frequent follow-up visits could be reduced by a less intensive surveillance program. It is however important to note that patient psychological factors were not assessed in this meta-analysis, and future RCTs that evaluate post-operative surveillance programs on OS should also consider patient quality of life and a healthcare cost-analysis as important secondary outcomes.

Previous systematic reviews and meta-analyses of colorectal cancer demonstrated that intensive follow-up after curative resection for colorectal cancer improved survival at five years, conflicting with the results presented here^{46,50-53}. Limitations of the aforementioned studies include limited quantities of articles and the high risk of bias in the included trials. Furthermore, these meta-analyses, and its' included trials, predate advancements in the management of cancer, including wider tumor resection and the use of combined therapies, which have been documented to improve survival⁵⁴. Consequently, we believe our meta-analysis provides the most up-to-date evidence on post-operative colorectal cancer surveillance programs. It is however essential that all types of cancer continue to investigate post-operative surveillance programs by way of large RCTs, in order to inform high-quality, evidence-based recommendations on post-operative follow-up programs.

Limitations

Despite the large sample size of this systematic review and meta-analysis, this study has some limitations. All patients in the RCT were post-operative patients who were treated for a solid tumor, excluding many trials and cancer types that are primarily treated by chemotherapy and radiation. Moreover, although there was generally a low risk of bias across all included trials, when extracting statistical information and further details about peri-operative treatment or baseline data of patients, many of these variables were not reported, highlighting the limited information reported in each trial. This may be due to the publication year of many of the trials, in which reporting guidelines prior to 2001 when more robust CONSORT guidelines were established. Adjuvant and neoadjuvant therapies, as well as tumor stage are also associated with prognosis in patients and may introduce bias as these variables were not considered in this meta-analysis. Furthermore, although the number of included studies was high for all intervention types, when interventions were categorized, minimal data was available for both biological test interventions and practitioner type interventions. Similarly, as very few studies were included in each subgroup analyses, these analyses could be underpowered. However, the confidence intervals for the subgroups overlap substantially so it is unlikely that there is a subgroup difference.

Quality of the Evidence

As this study evaluated RCTs, and the risk of bias was generally low across studies, the quality of evidence was not downgraded due to limitations in study design. Although every study had a high risk of bias for blinding of study participants and personnel, blinding in this manner was not possible for the type of interventions assessed, and therefore would not contribute to a high risk of bias in these studies. Reported effect measures were very similar in all included studies as demonstrated by the low I^2 value in each analysis. Although inconsistency remains across patients, interventions, and outcome measures even when evaluating each cancer subgroup separately, this is expected in surgical RCTs and does not warrant a downgrade in the level of evidence. All included RCTs were relevant to our research question, and provided insight to OS rates when different surveillance interventions were employed. Although there were differences in the population, interventions and outcome measures, the results provide an overview of intensive versus less intensive intervention strategies in post-operative surveillance for cancer patients, which is the overarching focus of this systematic review, and therefore the quality of evidence was

not downgraded due to indirectness of evidence. Biological test interventions and practitioner type intervention categories only included one and two trials, respectively. Due to the minimal amount of evidence, the low number of events, and the larger confidence intervals for these two categories, the quality of evidence was downgraded for imprecision. Both frequency and imaging interventions included multiple comparisons, meeting the optimal information size criteria and have small confidence intervals, therefore, these results were not downgraded for imprecision. As noted by the funnel plot, there is slight publication bias in the included studies. Therefore, the quality of evidence in each category is downgraded due to publication bias. Overall, frequency and imaging results provide a moderate quality of evidence after consideration of all factors, whereas biological test and practitioner type interventions provide a low quality of evidence, principally due to the lack of trials available to assess these intervention types.

Conclusion

In this systematic review and meta-analysis, we found that a less intensive post-operative biological test surveillance, frequency surveillance, imaging surveillance or practitioner type surveillance program had no effect on OS following solid tumor resection surgery. However, clinical equipoise persists, and the optimal surveillance protocol for each cancer type should continue to be investigated in large RCTs powered to evaluate OS, while also considering patient-important outcomes and health system costs.

Funding

McMaster University is the sponsor of this review. No funding has been received for this study.

Figure 1: PRISMA flow diagram

Table 1: Study characteristics of included studies.

	Country of Initiating Centre	Cancer Type	Type of Trial	Groups	Intervention Strategies	Sample Size	Follow- up Time Frame	Single Centre or Multi- Centre
<i>Ghezzi et al., 1994</i> ²¹	Italy	Breast cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; blood test at every visit; mammography annually; chest X-ray every 6 months; bone scan and liver echography annually	1320	5 Years	Multi-Centre
				Control	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually.			
<i>Kjeldsen et al., 1997</i> ²²	Denmark	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 6 months the first 3 years, then at 48, 60, 120, 150 and 180 months post-operatively	597	5 years	Single-centre
				Control	Clinic visits at 60, 120 and 180 months post-operatively			
<i>Koinberg et al., 2004</i> ²³	Sweden	Breast cancer	Parallel Group	Intensive	Specialist Physician visits every 3 months the first 2 years, then every 6 months the following 2 years and thereafter annually; annual mammography	264	5 Years	Multi-Centre
				Control	Specialist nurse check-up visits if requested by patient; annual mammography			
<i>Kokko et al., 2005</i> ^{24,25}	Finland	Breast cancer	Factorial	Intensive	Routine Diagnostic tests of blood tests, liver enzymes; Ca 15-3 markers, and CXRs every 6 months; mammogram annually; Liver US and bone scan every 2 years	472	5 years	Single-centre
				Control	Clinically Indicated Diagnostic tests			
				Intensive	Clinic visits every 3 months for 3 years, thereafter every 6 months			
				Control	Clinic visits every 6 months			
<i>Makela et al., 1995</i> ^{26,27}	Finland	Colorectal cancer	Parallel Group	Intensive	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; video colonoscopy (or fibresigmoidoscopy) annually; liver US every 6 months; CT of the liver and primary resection site annually.	106	5 years	Single-centre
				Control	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; rigid sigmoidoscopy at every visit for patients with rectal or sigmoid cancers; barium enema for all patients annually.			
<i>Monteil et al., 2010</i> ²⁸	France	Lung Cancer	Parallel Group	Intensive	CDET and Brain CT every 6 months for 2 years	69	2 years	Single-centre
				Control	Chest, liver and adrenal gland CT, abdominal US, bone scintigraphy if there were bone symptoms every 6 months for 2 years			

<i>Ohlsson et al., 1995</i> ²⁹	Sweden	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the next 2 years, thereafter annually; CEA, proctosigmoidoscopy, fecal hemoglobin, and CXR at every visit; endoscopic control of anastomosis at 9, 21 and 42 months; complete colonoscopy at 3, 15, 30 and 60 months; CT of pelvis (for required patients) at 3, 6, 12, 18, and 24 months.	107	5 years	Multi-Centre
				Control	No active follow-up			
<i>Pietra et al., 1998</i> ³⁰	Italy	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the next 3 years and annually thereafter; US and CEA test at every visit; CXR and colonoscopy annually.	207	5 years	Single-centre
				Control	Clinic visits every 6 the first year, thereafter annually after; US and CEA test at every visit; CXR, Colonoscopy and CT annually.			
<i>Primrose et al., 2014</i> ³¹	United Kingdom	Colorectal cancer	Factorial	Intensive	CEA test every 3 months for 2 years, then every 6 months for 3 years; Chest, abdomen and pelvis CT scan every 6 months for 2 years, then annually for 3 years.	1202	5 years	Multi-Centre
					CEA test every 3 months for 2 years, then every 6 months for 3 years; Chest, abdomen and pelvis CT scan at 12-18 months if requested at study entry by clinician.			
					Chest, abdomen and pelvis CT scan every 6 months for 2 years, then annually for 3 years.			
				Control	No scheduled follow-up; Chest, abdomen and pelvis CT scan at 12-18 months if requested at study entry by clinician.			
<i>Puri et al., 2018</i> ^{32,33}	India	Bone and soft tissue sarcoma	Factorial	Intensive	Clinic visits every 3 months	495	5 years	Single-centre
				Control	Clinic visits every 6 months			
				Intensive	Chest CTs			
				Control	CXR			
<i>Rodriguez-Moranta et al., 2006</i> ³⁴	Spain	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; abdominal CT every 6 months the first 2 years then annually the following 3 years; CXR and colonoscopy annually	259	5 years	Multi-Centre
				Control	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; colonoscopy at year 1 and year 3			

<i>Rosati et al., 2015</i> ³⁵	Italy	Colorectal cancer	Parallel Group	Intensive	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually; proctoscopy at 4 and 8 months; abdomen pelvic CT at 4, 12, 24 and 48 months	1228	5 years	Multi-Centre
				Control	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA tests at every visit; colonoscopy at 1 year and 4 years; Liver ultrasound at 4 months and 16 months. Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA test at every visit; colonoscopy at 12 and 48 months; Chest x-ray at 12 months; Liver US at 8 and 16 months			
<i>Rosselli Del Turco et al., 1994</i> ³⁶	Italy	Breast cancer	Parallel Group	Intensive	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years. Mammography annually; CXR and bone scan every 6 months.	1243	5 years	Multi-Centre
				Control	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually.			
<i>Schoemaker et al., 1998</i> ³⁷	Australia	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit; CXR, CT of the liver and colonoscopy annually	325	5 years	
				Control	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit			
<i>Secco et al., 2002</i> ³⁸	Italy	Colorectal cancer	Parallel Group	Intensive	High Risk patients: Clinic visits every 3 months for the first 2 years, then every 4 months the third year, thereafter every 6 months; CEA test at every visit; Abdominal and pelvis US every 6 months the first 3 years, then annually; Rigid rectosigmoidoscopy for rectal cancer patients and CXRs annually. Low Risk patients: Clinic visits every 6 months the first 2 years, thereafter yearly; CEA test and abdominal pelvic US at every visit; CXRs annually; Rigid rectosigmoidoscopy for rectal cancer patients annually for 2 years, then every 2 years.	358	5 years	
				Control	Minimal follow-up programme performed by physicians for each risk group			

<i>Sobhani et al., 2018</i> ³⁹	France	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT and 18FDG-PET/CT every 6 months; Liver US and CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3.	239	3 years	Multi-Centre
				Control	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT every 6 months; Liver US and CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3.			
<i>Wang et al., 2009</i> ⁴⁰	China	Colorectal cancer	Parallel Group	Intensive	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, CXR, liver imaging and colonoscopy performed at every visit.	326	5 years	Single-centre
				Control	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, CXR, and liver imaging performed at every visit; colonoscopy performed at 6, 30 and 60 months.			
<i>Wattchow et al., 2006</i> ⁴¹	Australia	Colon cancer	Parallel Group	Intensive	Followed by Surgeon; Visits every 3 months for the first 2 years, then every 6 months for the next 3 years; faecal occult blood tests every year; colonoscopy every 3 years	203	2 years	Multi-Centre

CEA = Carcinoembryonic antigen, CT = Computed tomography, CXR = Chest Radiograph (X-Ray), CBC = complete blood count, CDET = coincidence detection emission tomography, FDG - flurodeoxyglucose, LFT = liver function tests , US = ultrasonography, wbCT = whole body computed tomography, GP = general practitioner , PET = positron emission tomography

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Reported outcomes (other bias)	Sample size (other bias)	Method of analysis (other bias)	Conflicts of interest (other bias)
Ghezzi et al., 1994	+	+	-	?	+	?	+	+	+	+
Kjeldsen et al., 1994	+	?	-	?	+	?	+	-	?	+
Koinberg et al., 2004	+	+	-	?	-	?	+	?	+	+
Kokko et al., 2005	?	?	-	?	+	?	+	?	?	+
Makela et al., 1995	?	?	-	?	-	?	+	?	?	?
Monteli et al., 2010	?	?	-	?	+	+	+	?	?	+
Ohlsson et al., 1995	?	?	-	?	?	?	+	?	?	+
Pietra et al., 1998	?	?	-	?	+	?	-	?	?	?
Primrose et al., 2014	+	+	-	+	-	-	+	+	+	+
Puri et al., 2018	+	+	-	+	+	+	+	+	-	+
Rodriguez-Moranta et al., 2006	+	+	-	?	+	?	+	+	?	+
Rosati et al., 2015	?	+	-	?	+	-	+	+	+	+
Rosselli Del Turco et al., 1994	?	+	-	?	-	?	+	?	+	+
Schoemaker et al., 1998	+	-	-	+	+	?	+	+	?	?
Secco et al., 2002	?	?	-	?	+	?	+	?	?	?
Sobhani et al., 2018	+	+	-	-	+	?	+	+	+	+
Wang et al., 2009	+	+	-	?	+	?	+	+	?	+
Wattchow et al., 2006	+	+	-	+	+	?	+	+	+	+

Table 2: Risk and quality assessment of included studies.

Figure 2: Funnel plot of all included studies.

Table 3: Reported statistical results for all include comparisons.

Investigated Intervention Strategies			No. of Patients		No. of Deaths (%)		Reported Effect Measure	Hypothesis Test P-Value
	Intensive	Control	Intensive	Control	Intensive	Control		
Biological Test Interventions								
Primrose et al., 2014	CEA tests	No CEA tests	602	600	104 (17)	108 (18)	NR	0.74 ^a
Frequency Interventions								
Kjeldsen et al., 1997	Clinic visits every 6 months the first 3 years, then clinic visits at 48, 60, 120, 150 and 180 months post-operatively	Clinic visits at 60, 120 and 180 months post-operatively	290	307	88(30)	100 (33)	NR	0.48 ^a
Kokko et al., 2005	Clinic visits every 3 months	Clinic visits every 6 months	239	233	52 (22)	36 (15)	NR	NS
Ohlsson et al., 1995	Clinic visits every 3 months the first 2 years, then every 6 months the next 2 years, thereafter annually; CEA, proctosigmoidscopy, fecal hemoglobin, and Chest CXR at every visit; endoscopic control of anastomosis at 9, 21 and 42 months; complete colonoscopy at 3, 15, 30 and 60 months; CT of pelvis (for required patients) at 3, 6, 12, 18, and 24 months.	No active follow-up	53	54	15 (28)	22 (41)	NR	0.264 ^a
Pietra et al., 1998	Clinic visits every 3 months the first 2 years, then every 6 months the next 3 years and annually thereafter; US and CEA test at every visit; CT, CXR and colonoscopy annually.	Visits every 6 months the first year, thereafter annually; US and CEA test at every visit; CXR, and Colonoscopy annually.	104	103	28 (27)	43 (42)	NR	<0.02 ^{a**}
Primrose et al., 2014	More intensive follow-up including CEA tests, CT scans and clinic visits. Combination of patients from all other 3 factors in the trial	No scheduled follow-up; Chest, abdomen and pelvis CT scan at 12-18 months if requested at study entry by clinician.	901	301	164 (18)	48 (16)	NR	0.45 ^c
Puri et al., 2018	Clinic Visits every 3 months	Clinic Visits Every 6 Months	201	211	90 (45)	97 (46)	HR: 1.01 (90% CI: 0.82-1.2)	0.95 ^a
Secco et al., 2002	High Risk patients: Clinic visits every 3 months for the first 2 years, then every 4 months the third year, thereafter every 6 months; CEA test at every visit; Abdominal and pelvis US every 6 months the first 3	Minimal follow-up of high risk patients	108	84	NR	NR	NR	<0.05 ^{a**}

	years, then annually; Rigid rectosigmoidoscopy for rectal cancer patients and Chest CXRs annually.							
<i>Secco et al., 2002</i>	Low Risk patients: Clinic visits every 6 months the first 2 years, thereafter yearly; CEA test and abdominal pelvic US at every visit; Chest CXRs annually; Rigid rectosigmoidoscopy for rectal cancer patients annually for 2 years, then every 2 years.	Minimal follow-up of low risk patients	84	61	NR	NR	NR	<0.01 ^{***}
Imaging Interventions								
<i>Ghezzi et al., 1994</i>	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; blood test at every visit; mammography annually; chest X-ray every 6 months; bone scan and liver echography annually	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually.	655	665	132 (20)	122 (18)	OR: 1.12 (95% CI: 0.87-1.43)	0.42 ^a
<i>Kokko et al., 2005</i>	Routine diagnostic tests which included: blood test, liver enzymes and Ca 15-3 marker tests; CXRs every 6 months, Liver US and bone scan every 2 years;	All diagnostic tests only when clinically indicated	243	229	29 (12)	34 (15)	NR	NS
<i>Makela et al., 1995</i>	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; video colonoscopy (or fibresigmoidoscopy) annually; liver US every 6 months; CT of the liver and primary resection site annually.	Clinic visit every 3 months the first 2 years, then every 6 months the next 3 years; CBC, CEA, tests of occult fecal bleeding and chest x-ray at every visit; rigid sigmoidoscopy at every visit for patients with rectal or sigmoid cancers; barium enema for all patients annually.	52	54	23(44)	27 (50)	NR	0.5 ^a
<i>Monteil et al., 2010</i>	CDET and Brain CT every 6 months for 2 years	Chest, liver and adrenal gland CT, abdominal US, bone scintigraphy if there were bone symptoms every 6 months for 2 years	36	33	14 (39)	10 (30)	NR	NS ^b
<i>Primrose et al., 2014</i>	Chest CT scans	No Chest CT scans	601	601	108 (18)	104 (17)	NR	0.76 ^a
<i>Puri et al., 2018</i>	CT Scans	CXR	196	216	92 (47)	95 (44)	HR: 0.94 (90% CI: 0.78-1.1)	0.63 ^a
<i>Rodriguez-Moranta et al., 2006</i>	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; abdominal CT every 6 months the first 2 years then annually the	Clinic visits every 3 months the first 2 years and every 6 months the following 3 years; CBC, CEA and liver function tests at every visit; colonoscopy at year 1 and year 3	127	132	21 (17)	27 (26)	HR: 0.87 (95% CI: 0.49-1.54)	0.62 ^d

	following 3 years; chest CXR and colonoscopy annually							
<i>Rosati et al., 2015</i>	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA and CBC tests at every visit; colonoscopy and chest x-ray annually; Liver ultrasound every 4 months the first year, then annually; proctoscopy at 4 and 8 months; abdomen pelvic CT at 4, 12, 24 and 48 months	Colon: Clinic visits every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA tests at every visit; colonoscopy at 1 year and 4 years; Liver ultrasound at 4 months and 16 months. Rectum: Clinic visits and rectal exam every 4 months the first 2 years, then every 6 months the next 2 years, then annually the 5th year; CEA test at every visit; colonoscopy at 12 and 48 months; Chest x-ray at 12 months; Liver US at 8 and 16 months	615	613	113 (18)	105 (17)	HR: 1.14 (95% CI: 0.87-1.48)	0.34 ^d
<i>Rosselli Del Turco et al., 1994</i>	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years. Mammography annually; Chest CXR and bone scan every 6 months.	Clinic visits every 3 months the first 2 years, then every 6 months the following 3 years; mammography annually.	622	621	116 (19)	121 (19)	NR	NS ^b
<i>Schoemaker et al., 1998</i>	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit; CXR, CT of the liver and colonoscopy annually	Clinic visits every 3 months for 2 years, then every 6 months for 5 years; CBC, LFTs, CEA and fecal occult blood tests at every visit	167	158	43 (26)	55 (35)	OR: 0.69 (95% CI: 0.47-1.04)	0.07 ^d
<i>Sobhani et al., 2018</i>	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT and 18FDG-PET/CT every 6 months; Liver US and Chest CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3.	Clinic visits every 3 months; blood tests, liver function tests and tumor marker tests at every visit; wbCT every 6 months; Liver US and Chest CXR at all visits where wbCT did not occur; colonoscopy at year 1 and 3.	120	119	13 (11)	7(6)	RR: 1.83 (95% CI: 0.76-4.42)	0.17 ^d
<i>Wang et al., 2009</i>	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, Chest CXR, liver imaging and colonoscopy performed at every visit.	Clinic visits every 3 months the first year, then every 6 months the next 2 years, then annually; CEA test, Chest CXR, and liver imaging performed at every visit; colonoscopy performed at 6, 30 and 60 months.	161	158	42 (26)	50 (32)	HR: 1.41 (95% CI: 0.92-2.14)	0.25 ^a

Practitioner Type Interventions

<i>Koinberg et al., 2004</i>	Specialist Physician visits every 3 months the first 2 years, then every 6 months the following 2 years and thereafter annually; annual mammography	Specialist nurse check-up visits if requested by patient; annual mammography	131	133	14 (11)	14 (11)	NR	0.6 ^a
<i>Wattchow et al., 2006</i>	Followed by Surgeon; Visits every 3 months for the first 2 years, then every 6 months for the next 3 years; faecal occult blood tests every year; colonoscopy every 3 years	Followed by GP; Visits every 3 months for the first 2 years, then every 6 months for the next 3 years; faecal occult blood tests every year; colonoscopy every 3 years	106	97	11 (10)	8 (8)	NR	0.69 ^a

CEA = Carcinoembryonic antigen, CT = Computed tomography, CXR = Chest Radiograph (X-Ray), CBC = complete blood count, CDET = coincidence detection emission tomography, FDG - flurodeoxyglucose, LFT = liver function tests , US = ultrasonography, wbCT = whole body computed tomography, GP = general practitioner , PET = positron emission tomography, RR = Risk Ratio, OR = Odds Ratio, HR = Hazards ratio, CI = Confidence Interval, NR = Not reported, NS = Not significant (authors in respective articles stated the difference was not significant but did not present a value). ^a Calculated by log-rank test, ^b Calculated by Student's T-test, ^c Calculated by Chi squared statistic, ^d Calculated by Cox proportional hazards test, ** Significant, as reported by the trial authors.

Figure 3: Forest plot of frequency interventions. p-value < 0.05 is considered significant.

Figure 4: Forest plot of imaging interventions. p-value < 0.05 is considered significant.

Figure 5: Forest plot of practitioner type interventions. p-value < 0.05 is considered significant.

Table 4: Summary of Findings

Summary of findings:

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-intensity	Risk with high-intensity				
High-intensity biological tests compared to low-intensity biological tests						
Deaths (OS)	180 per 1,000	173 per 1,000 (135 to 221)	RR 0.96 (0.75 to 1.23)	1202 (1 RCT)	⊕⊕○○ LOW ^{a,b}	High-intensity biological tests likely results in little to no difference in overall survival.
High-frequency compared to low-frequency surveillance						
Deaths (OS)	286 per 1,000	275 per 1,000 (226 to 332)	RR 0.96 (0.79 to 1.16)	2997 (6 RCTs)	⊕⊕⊕○ MODERATE ^a	High frequency likely results in little to no difference in overall survival.
High-intensity imaging compared to low-intensity imaging						
Deaths (OS)	210 per 1,000	208 per 1,000 (191 to 227)	RR 0.99 (0.91 to 1.08)	7194 (11 RCTs)	⊕⊕⊕○ MODERATE ^a	High-intensity imaging likely results in little to no difference in overall survival.
High-intensity practitioner compared to low-intensity practitioner						
Deaths (OS)	96 per 1,000	105 per 1,000 (61 to 183)	RR 1.10 (0.64 to 1.91)	467 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	High-intensity practitioner likely results in little to no difference in overall survival.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- Funnel plots demonstrate probable publication bias
- Number of included trials and events were low leading to large confidence intervals and possible imprecision in data

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