**The use of bioelectrical impedance analysis to predict post-operative complications in adult patients having surgery for cancer: A systematic review**

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**Abstract**

**Background**

Patients undergoing surgery for cancer are at particular risk of post-operative complications. The pre-operative period is an opportunity to identify and mitigate risk factors and improve outcome. Bioelectrical impedance analysis (BIA) may offer an additional means of identifying patients at risk of post-operative morbidity.

**Aims**

The aim of this systematic review was to assess the use of measures and estimates of body composition determined by BIA as markers of peri-operative risk in adult patients undergoing elective surgery for cancer.

**Methods**

This review was performed in accordance with the PRISMA guidelines. The electronic databases of MEDLINE, EMBASE, CINAHL, CENTRAL and the Web of Science were searched from inception. Studies of adult participants having elective surgery for cancer were included if participants underwent BIA in the peri-operative period and were assessed for post-operative complications.

**Results**

2578 studies were identified, of which 12 were eligible for inclusion. In total the studies report data from 1508 subjects. Five studies examined phase angle or standardized phase angle, six examined derived measures and one examined both. Eight of the 12 demonstrated an association between phase angle and/or body composition and an increased risk of post-operative complications.

**Conclusions**

Bioelectrical impedance analysis in the peri-operative period may be useful in predicting the risk of complications following elective cancer surgery. Phase angle more consistently demonstrates an association than derived estimates. Further high quality studies are needed and should report the raw impedance values, standardized phase angle and the equations used to derive body composition.

**Keywords**

1. Bioelectrical impedance analysis
2. Phase angle
3. Body composition
4. Cancer surgery
5. Post-operative complications

**Abbreviations**

BIA – Bioelectrical impedance analysis

BMI – Body mass index

PA – Phase angle

SPA – Standardized Phase Angle

1. **Introduction**

By 2030, 45 million surgical procedures will be needed globally each year for patients living with cancer, many of whom will require major surgery[1]. Patients undergoing major surgery have significant increases in stress catabolism and malnutrition[2], with cancer patients facing additional risk due to inadequate nutritional intake, skeletal muscle depletion and systemic inflammation[3]. Reduced lean mass and metabolic derangements are common in this group[4], prognostic of poor outcome[5] and, importantly, amenable to treatment[6].

With an incidence of major complications in high income countries as much as 18%[7] one of the key purposes of pre-operative assessment is to identify those at increased risk of post-operative morbidity and mortality. Comprehensive, objective, risk assessment is a vital tool in guiding shared decision making, planning perioperative management and referral to post-operative critical care facilities where indicated[8]. It may also be used to direct personalised care through interventions such as multi-modal prehabilitation[9] and may reduce the healthcare costs associated with excess morbidity[10].

The perioperative period offers a window to intervene to improve outcome for patients undergoing surgery for cancer[11]. Functional investigations, such as cardio-pulmonary exercise testing, can help the peri-operative clinician to assess the likelihood of morbidity due to cardiovascular or pulmonary limitation[12]. However, there are few tools at their disposal with which to assess a patients’ metabolic and nutritional state and subsequently guide supportive interventions.

Objective measures of bioelectrical impedance or their derived estimates of body composition from BIA may offer a means of identifying peri-operative risk. Impedance is the measure of the resistance and reactance of the body. Resistance is the opposition caused by the body to the flow of an alternating current whilst reactance is a measure of the capacitive effect produced by the tissue interfaces and cell membranes. Impedance measures can be made at single or multiple current frequencies using different lead configurations and then by applying assumed values for the resistivity of body water and population means, predict total body water, and in turn fat free mass and fat mass. Fat free mass derived from BIA has been shown to be significantly lower in malnourished hospitalised patients, even in those who maintained their body weight[13] and fat free mass at admission has been shown to be associated with worse clinical outcomes such as increased length of stay[14] and 28-day mortality in intensive care[15].

Clinical use of BIA to derive body composition in subjects at extremes of BMI ranges or with abnormal hydration and fluid shifts is not recommended for routine assessment[16] and so attention has been increasingly directed towards the clinical utility of raw impedance measures where the application of assumptions that underlie the prediction may be uncertain. Phase angle is the arc tangent value of the ratio of the reactance versus resistance, reflecting both intracellular water and body cell mass, and does not require the measurement of height or weight. Phase angle can be reported as the raw value (degrees) but as this is influenced by gender, age and BMI it may be more appropriate to report the standardized phase angle[17],[18],[19]. The standardized phase angle is calculated as [(observed phase angle - mean phase angle)/standard deviation of the phase angle] and converts the phase angle into a Z-score. The mean and standard deviation are obtained from reference values most appropriately generated using the same device, electrode configuration and skin contact. A Z-score of 0 indicates a value at the mean of the reference population, whilst 68.3% of the population would be expected to fall within +/- 1 Z-score and 95% between +/- 1.96 Z-score. This allows comparison of values among patients differing in age, sex and BMI. Since standardized phase angle values indicate individual deviations from the population, more complex information is gained than with a dichotomous cut-off (e.g. below or above the 5th reference percentile). Phase angle, as both raw values and standardized phase angle, has been shown to be a predictor of mortality in colorectal[20], pancreatic[21], head and neck[22] and lung[23] cancer as well as those with chronic medical diseases[24] and patients admitted to critical care[25],[26].

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Thus, the aim of this review was to assess whether measures and estimates of body composition determined by BIA can identify adult patients at risk of complications following elective surgery for cancer.

1. **Methods**
   1. *Protocol and registration*

This review was performed in accordance with the PRISMA guidelines[27]. The review protocol was registered with the PROSPERO database: http://www.crd.york.ac.uk/PROSPERO/display\_record.php?ID=CRD42018103604

* 1. *Eligibility criteria*

This review was conducted in order to answer the question: What is the effectiveness of BIA as a tool in identifying adult patients at higher risk of complications following elective surgery for cancer? Using the PICO strategy, we defined “P” as Adult patients aged 18 and over having elective surgery for cancer, “I” as the use of BIA during the peri-operative period and “O” as one or more post-operative complications. (We did not include a comparator group, “C”.)

*2.3 Exclusion criteria*

The following exclusion criteria were used: (A) duplicated publications or studies; (B) studies not evaluating an association between a BIA measure and post-operative complications; (C) case reports, case series, letters to the editor, responses to letters to the editor; (D) studies reporting non-cancer pathology; (E) studies reporting participants under 18 years of age; (F) studies reporting emergency surgery.

*2.4 Sources of information and search strategy*

The electronic databases of MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO), Cochrane Central Register of Controlled Trials (CENTRAL) and the Web of Science were searched from inception to 19th February 2019. We attempted to identify additional studies by examining the references of relevant publications and reviews. The search strategy was developed with the support of a university librarian. The detailed search strategy is available as Supplementary Information A.

*2.5 Study selection*

Included studies were imported into Mendeley and duplicates removed. Two authors (AB and LM) independently reviewed the titles and abstracts of included studies using Rayyan QCRI[28]. The full texts of all potentially relevant publications were assessed. If more information was required authors were contacted directly by e-mail. Conflicts were resolved by a third reviewer (SW).

*2.6 Data extraction*

The following data were extracted independently by the authors (AB and LM), using data forms created by the authors for this review: first author, year and country of publication, tumour site, study population characteristics, sample size, study setting and design, impedance variables, timing of BIA, definition of post-operative complication, main results, statistical methods and comparison with alternative methods of pre-operative risk prediction.

2.7 Quality assessment in individual studies

All included studies were observational studies. To analyse study quality we used a modified version of the Downs and Black checklist[29].

1. **Results**

The initial search returned 2578 studies of which 462 were duplicates. We screened the remaining 2116 titles and abstracts, of which 2026 were excluded. 90 articles were retrieved of which 75 were excluded following full-text review and an additional three during data extraction. Thus, 12 papers are included in this review (Figure 1).



**Fig. 1** Flow diagram of included studies

The general characteristics of the included studies are summarised in table 1. Taken together, the included studies report data from 1508 subjects. The median sample size was 108 (range 52 – 293). Studies were defined as “mixed” if they reported data from more than one surgical specialty. Study cohorts included colorectal[30],[31],[32], upper gastro-intestinal[33],[34],[35], gynaecological[36],[37],[38] and mixed[39],[40],[41] cancers. All studies were single centre observational cohort studies, ten were prospective and two were retrospective.

Bioelectrical impedance analysis was performed pre-operatively in all included studies. Reported parameters included the phase angle, standardized phase angle and derived measures of body composition. These included fat-free mass, fat-free mass index, lean body mass, lean body mass index, muscle mass index, skeletal muscle mass and skeletal muscle mass index. One study reported percentage body fat only.

Five studies[30],[36],[37],[39],[40] examined phase angle or standardized phase angle, six examined derived measures[32],[33],[34],[35],[38],[41] and one examined both[31]. Eight of the twelve (67%) demonstrated an association between phase angle and/or lean mass and an increased risk of complications. Four (33%) reported no association.

We present the data on phase angle and the derived measures of lean mass separately given the important differences in the way they are calculated. Phase angle is the arc tangent of the ratio of resistance to reactance and thus a direct measurement of bioelectrical impedance, whereas the derived measures are calculated using assumptions about the hydration status of the subject.

Five studies reported complications using the Clavien-Dindo classification[30],[33],[34],[35],[40] , three used other systems[36],[37],[39] and in four studies complications were defined by the authors[31],[32],[38],[41].

**Table 1**

General characteristics of the included studies

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author,  Year | Country | Cancer/s | Device | Lead configuration | Mode | Variables | Raw data | Reference population | Specific cut-off | Complication definition |
| Tamura, 2019[33] | Japan | Gastric (n=153) | Inbody 3.0, Biospace, Japan | Not reported | MF | MMI | Not reported | N/A | MMI < 1 σ study group | Clavien-Dindo |
| ­Mauricio, 2018[30] | Brazil | Colorectal (n=84) | Quantum X, RJL Systems, USA | Not reported | Not stated | SPA | Not reported | Brazilian | SPA ≤ or >  -1.65 | Clavien-Dindo |
| Pena, 2018[39] | Brazil | Mixed (n=121)  (58 Colorectal, 33 UGI, 15 HN, 15 HPB) | Quantum X, RJL Systems, USA | Not reported | SF | PA  SPA | Not reported | Brazilian[42] | SPA ≤ or > −1.65 | BACS |
| Uccella, 2018[36] | Italy | Ovarian (n=52) | 101 Anniversary Analyser, Zurich Instruments, Switzerland | Hand-Foot | SF | PA | Not reported | N/A | - | MSKCC |
| Cardoso, 2017[37] | Brazil | Endometrial and Cervical (n=208) | BIA 450, Biodynamics, USA | Not reported | SF | PA | Not reported | N/A | PA ≤ 25th centile study population | Reilly |
| Tsaousi, 2017[32] | Greece | Colorectal (n=90) | Bodyscout, Fresnius Kabi, Germany | Hand-Foot | SF  MF | FFMI  FMI | Not reported | Swiss[43],[44] | LoS ≤ 7 days | LoS |
| Harter, 2017[40] | Brazil | Mixed (n=60)  (20 GI, 17 HN, 11 GU, 6 Breast, 6 Other) | Body Bioelectrical Composition Analyser Quantum II, RJL Systems, USA | Not reported | SF | PA  SPA | Not reported | N/A | - | Clavien-Dindo |
| Sato, 2016[34] | Japan | Gastric (n=293) | MC-180 Body Composition Analyzer, Tanita, Japan | Not reported | Not stated | LBMI | Not reported | N/A | < 20th centile gender-specific LBMI | Clavien-Dindo |
| Ida, 2015[35] | Japan | Oesophageal (n=138) | Inbody 720, Biospace, Japan | Not reported | MF | SMM | Not reported | Not reported | SMM ≤ 90% standard SMM | Clavien-Dindo |
| Kerimoglu, 2015[38] | Turkey | Endometrial (n=94) | Inbody 720, Biospace, Korea | Not reported | MF | % BF | Not reported | N/A | BF < or ≥ 32% | Author defined |
| Berstad, 2013[31] | Norway | Colorectal (n=100) | Bodyscout, Fresnius Kabi, Germany | Hand-Foot | Not stated | PA  FM  FFM | Not reported | N/A | - | Author defined |
| Fritz, 1990[41] | Germany | Mixed (n=115)  (41 UGI, 38 GI, 23 HPB, 13 Other) | BIA-103, RJL Systems, USA | Hand-Foot | SF | LBM | Not reported | N/A | LBM < predicted normal LBM | Author defined |

Legend: n = Number of subjects; UGI = Upper Gastro-intestinal; HN = Head and neck; HPB = Hepato-biliary; GI = Gastro-intestinal; GU = Genito-urinary; SF = Single frequency; MF = Multi-frequency; PA = Phase Angle; SPA = Standardized Phase Angle; MMI = Muscle Mass Index; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; LBMI = Lean Body Mass Index; SMM = Skeletal Muscle Mass; FM = Fat Mass; FFM = Fat Free Mass; BF = Body Fat; LBM = Lean Body Mass; σ = standard deviation; LoS = Length of Stay; BACS = Bulletin of the American College of Surgeons; MSKCC = Memorial Sloan Kettering Cancer Centre Surgical Secondary Events Grading

*3.1 Study quality*

All included publications were non-randomised observational studies. The median quality score was 13/28 (range 8 - 16) using a modified version of the Downs and Black quality assessment checklist.

*3.2 Phase angle and post-operative complications*

Of the six papers reporting either phase angle or standardized phase angle four[36],[37],[39],[40] (67%) reported an association with post-operative complications, two[30],[31] did not (33%). (Table 2)

Mauricio et al[30] assessed standardized phase angle in 84 patients undergoing surgery for colorectal cancer. This prospective study investigated the ability of standardized phase angle to predict post-operative complications, defined by the Clavien-Dindo classification. Participants were divided into those with an SPA ≤ or > -1.65 (the bottom 5th centile of a Brazilian reference population). Fifteen participants (17.8%) had an SPA ≤ -1.65. Seven participants in the low SPA group had a post-operative complication compared to 21 of the 69 participants with an SPA > -1.65 (RR 1.53, 95% CI: 0.79-2.92; p = 0.199). BMI/% weight loss, Patient Generated Subjective Global Assessment, CT assessed skeletal mass index (SMI) and SMI plus low strength were found to be independent predictors of complications in this study.

Pena et al[39] assessed standardized phase angle in 121 patients undergoing surgery for a heterogenous group of cancers (colorectal, gastric, hepato-biliary, head and neck). This prospective study investigated the ability of standardized phase angle to predict post-operative complications, defined by the Bulletin of the American College of Surgeons. Thirty-four participants (28.1%) had an SPA ≤ −1.65. These participants were more likely to have an infectious complication compared to those with a SPA > - 1.65 (OR 4.19, 95% CI: 1.52-11.53; p = 0.006). There was no relationship between non-infectious complications or length-of-stay. Hand-grip strength, midarm circumference and SGA were also examined in the same study but none were found to be predictive of complications.

Uccella et al[36] assessed phase angle in 52 patients undergoing primary cytoreductive surgery for ovarian cancer. This retrospective analysis explored the association between phase angle and the risk of post-operative complications, defined by the Memorial Sloan Kettering Cancer Centre secondary events grading scale[45]. Twenty-four participants (46.2%) had a post-operative complication ≥ grade 3. The authors found phase angle to be lower in the participants experiencing a post-operative complication compared to those who did not (5° vs. 5.4°, p = 0.03). Receiver operating characteristic curve analysis identified a phase angle of 4.95° as the optimal threshold value for predicting complications (sensitivity 89.3%, specificity 50%, AUC = 0.7). The authors noted that the majority of complications were due to infection or breakdown of anastomosis.

Cardoso et al[37] used phase angle to assess nutritional status in 208 women undergoing surgery for either endometrial or cervical cancer. This prospective study evaluated associations between phase angle and post-operative complications, defined by the Reilly classification[46]. In total 36 had a post-operative complication (17.3%). Patients in the bottom 25th centile had a higher rate of post-operative complications compared to those above the 25th centile (25.9% vs. 14.3%, p = 0.044). Notably, nearly all of the patients (94%) in the bottom 25th centile had endometrial cancer.

Harter et al[40] assessed pre-operative phase angle in 60 patients undergoing surgery for a heterogenous group of malignancies, including gastro-intestinal, head and neck and genito-urinary cancers. This prospective study explored the standardized phase angle as a predictor of post-operative complications, defined by the Clavien-Dindo classification[47]. Nine participants (15.0%) had a post-operative complication grade ≥ 3. Standardized phase angle was lower in patients who had a post-operative complication grade ≥ 3 compared to those who did not (-0.71 vs. 0.41, p = 0.007). Hand-grip strength and sarcopenia were explored in the same study but were not found to predict complications.

Berstad et al[31] assessed phase angle in 100 patients undergoing surgery for colorectal cancer, of whom 17 had missing bioimpedance data. This prospective study evaluated the relationship between phase angle and post-operative complications, defined by the authors. Twenty-four participants (28.9%) experienced a post-operative complication. There was no difference in phase angle between patients who did or did not have post-operative complications (5.5° vs. 5.4°, p=0.83). The authors also assessed fat mass and fat free mass, the results of which are discussed in the following section.

**Table 2**

Phase angle and post-operative complications

|  |  |  |  |
| --- | --- | --- | --- |
| Author, Year | Specific cut-off | Association reported | Results |
| Mauricio, 2018[30] | SPA ≤ or >  -1.65 | No | SPA ≤ -1.65 not associated with a higher rate of post-operative complications (RR 1.53, 95% CI: 0.79-2.92;  p = 0.199) |
| Pena, 2018[39] | SPA ≤ or >  -1.65 | Yes | SPA ≤ -1.65 associated with a higher rate of post-operative complications  (OR 4.19, 95% CI: 1.52-11.53; p = 0.006) |
| Uccella, 2018[36] | - | Yes | PA lower in patients who experienced a post-operative complication  (5° vs. 5.4°, p = 0.03) |
| Cardoso, 2017[37] | 25th centile of study population | Yes | PA ≤ 25th centile of study population associated with a higher rate of post-operative complications (25.9% vs. 14.3%,  p = 0.044) |
| Harter, 2017[40] | - | Yes | SPA lower in patients who experienced a severe post-operative complication (−0.71 vs. 0.41, p = 0.007) |
| Berstad, 2013[31] | - | No | No difference in PA between patients who did or did not have post-operative complications (5.5° vs 5.4°, p=0.83) |

Legend: PA = Phase Angle; SPA = Standardized Phase Angle; RR = Relative Risk, OR = Odds Ratio; CI = Confidence Interval;

a Clavien-Dindo grade 3-5

*3.3 Derived measures and post-operative complications*

Of the seven publications reporting a derived measure of lean mass or percentage body fat four[32],[33],[35],[41] (57%) demonstrated an association with post-operative complications, three[31],[34],[38] (43%) did not. (Table 3)

Tamura et al[33] assessed gender-specific muscle-mass index in 153 patients undergoing gastrectomy for gastric cancer. This prospective study explored sarcopenia as a predictor of post-operative complications, defined by the Clavien-Dindo classification. Sarcopenia was defined as a muscle mass index one standard deviation below the mean of the study cohort (males ≤ 15.55kg/m2, females ≤ 13.33kg/m2). Twenty-four patients (15.7%) were sarcopenic by this definition. Nine patients with sarcopenia experienced a post-operative complication compared to 21 of non-sarcopenic patients (37.5% vs. 16.3%, p = 0.024). When divided into infectious and non-infectious complications only the infectious complications maintained a significant association. At multivariate analysis sarcopenic patients were more likely to experience a post-operative infectious complication compared to non-sarcopenic patients (OR 4.358, 95% CI: 1.224 – 15.721; p = 0.024).

Tsaousi et al[32] measured fat free mass index and fat mass index in 90 patients (42 men and 48 women) undergoing surgery for colorectal cancer. This prospective study examined whether the fat mass index, fat free mass-index or presence of sarcopenic obesity were predictive of increased length of stay. Sixteen men (38.1%) and 23 women (47.9%) had a length of stay > 7 days. Men with a length of stay ≤ 7 days had a higher fat free mass index compared to those with a length of stay > 7 days (17.8 +/- 2.2kg/m2 vs. 14.7 +/- 2.1kg/m2, p = 0.000). Similarly, women with a length of stay ≤ 7 days had a higher fat free mass index compared to those with a length of stay > 7 days (16.2 +/- 1.6kg/m2 vs. 13.6 +/- 1.3kg/m2, p = 0.000). Furthermore, men with a length of stay ≤ 7 days had a lower fat mass index than those with length of stay > 7 days (7.2 +/- 2.6 kg/m2 vs. 9.2 +/- 2.5 kg/m2, p = 0.019). Similar results were found in women (9.7 +/- 1.8 kg/m2 vs. 11.3 +/- 1.9 kg/m2, p = 0.04).

Sato et al[34] assessed lean body mass index in 293 patients undergoing surgery for gastric adenocarcinoma. This retrospective study investigated the impact of muscle mass on post-operative complications, defined by the Clavien-Dindo classification. Patients with a gender-specific lean body mass index in the lowest 20th centile of the study population (n=58) were considered as having low lean body-mass index. Eight of the participants with low lean body mass index (13.8%) experienced a post-operative complication compared to 31 participants in the normal lean body mass index group (13.2%). There was no association between patients with a low lean body mass index and a post-operative complication grade ≥ 2 (OR 1.048, p = 1.0). Low hand-grip strength was also assessed and was associated with post-operative complications.

Ida et al[35] measured skeletal muscle mass in 138 patients undergoing oesophagectomy for oesophageal cancer. This prospective study assessed whether sarcopenia was predictive of post-operative complications, defined by the Clavien-Dindo classification. Patients were defined as sarcopenic if they had a skeletal muscle mass below 90% of the standard skeletal muscle mass. Sixty-one patients (44.2%) were sarcopenic by this definition. Twenty-one patients defined as sarcopenic (34.4%) had a respiratory complication compared to 9 of the non-sarcopenic patients (11.7%). At multivariate analysis sarcopenic patients were more likely to experience a post-operative respiratory complication compared to non-sarcopenic patients (OR 5.55, 95% CI: 2.15 – 15.6; p = 0.0003).

Berstad et al[31] (see previous section for description) also assessed percentage fat free mass and percentage fat mass. They found no difference in percentage fat free mass between patients who did or did not have post-operative complications (68.6% vs. 66.3%, p = 0.71). They also found no difference in percentage fat mass (31.4% vs. 33.2%, p = 0.83) between the two groups.

Fritz et al[41] assessed lean body mass in 115 patients undergoing surgery for a variety of gastrointestinal cancers (colorectal, oesophageal, hepato-biliary). This prospective study analyzed the relationship between lean body mass and post-operative complications, defined by the authors. Patients were divided into those with a lean body mass greater or less than the predicted normal for age and gender. Fifty-five participants (47.8%) were in the low lean body mass group. Seventeen participants in the low lean body mass group compared to six of those in the high lean body mass group experienced a severe complication or death (17% vs. 6%, p = 0.02). Total body water and body fat were also measured but their results were not discussed in the paper.

Kerimoglu et al[38] assessed percentage body fat in 94 women undergoing surgery for endometrial cancer. This prospective study evaluated the effect of percentage body fat on post-operative complications, defined by the authors. Patients were classified as either having normal or elevated percentage body fat (< or ≥ 32%). Eighty-three participants (88.3%) had elevated percentage body fat. There were 16 complications (19.3%) in the elevated body fat group compared to two (18.2%) in the normal body fat group (p-value not reported). Patients were also classified as obese or non-obese (BMI < or ≥ 30), finding no difference in the post-operative complication rate.

**Table 3**

Derived measures and post-operative complications

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author, Year | BIA variable/s | Specific  cut-off | Association reported | Results |
| Tamura, 2019[33] | MMI | MMI < 1 σ study population | Yes | Lower MMI associated with increased incidence of post-operative infectious complications (OR 4.358, 95% CI: 1.224 – 15.721; p = 0.024) |
| Tsaousi, 2017[32] | FFMI  FMI | Length of stay ≤ 7 days | Yes | Higher FFMI associated with LoS ≤ 7 days in both ♂ and ♀ (both p = 0.000)  Higher FMI associated with LoS > 7 days in both ♂ (p = 0.019) and ♀ (p = 0.004) |
| Sato, 2016[34] | LBMI | < 20th centile gender-specific LBMI | No | Lower LBMI not associated with a higher rate of post-operative complicationsa (OR 1.048, p = 1.0) |
| Ida, 2015[35] | SMM | SMM ≤ 90% standard SMM | Yes | Lower SMM associated with increased respiratory complications (OR 5.55, 95% CI: 2.15 – 15.6; p = 0.0003) |
| Kerimoglu, 2015[38] | % BF | BF <or ≥ 32% | No | Patients with BF ≥ 32% did not have a higher rate of post-operative complications (19.3% vs. 18.2%, p-value not reported) |
| Berstad, 2013[31] | FFM  FM | - | No | No difference in FFM between patients who did or did not have post-operative complications (68.6% vs. 66.3%, p = 0.71) |
| Fritz, 1990[41] | LBM | LBM < predicted normal LBM | Yes | Lower LBM associated with a higher rate of post-operative complications (17% vs. 6%, p = 0.02) |

Legend: MMI = Muscle Mass Index; σ = standard deviation; ♂= male; ♀= female; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; LBMI = Lean Body Mass Index; SMM = Skeletal Muscle Mass; FM = Fat Mass; FFM = Fat Free Mass; BF = Body Fat; LBM = Lean Body Mass; TBW = Total Body Water

a Clavien-Dindo grade 2-5

**Discussion**

Despite growing interest in the use of body composition analysis using BIA it has not been widely studied in the context of post-operative morbidity for patients undergoing surgery for cancer. This systematic review sought to assess the utility of measures and estimates of body composition determined by BIA as a means of predicting the risk of post-operative complications for adult patients having elective cancer surgery.

All included studies were single centre observational cohort studies of medium quality. The small sample size of some of the included studies makes it unlikely that these were adequately powered to detect differences in outcome. With the exception of one publication[31] they reported either phase angle or a measure of body composition derived from the raw data. Overall, eight of the twelve included papers found BIA measures to be predictive of post-operative complications. Bioelectrical impedance analysis was more frequently found to be predictive in the papers reporting phase angle rather than the derived measures. There is biological plausibility in this finding given that phase angle is directly calculated from resistance and reactance at a given frequency and is not affected by the assumptions made about an individuals’ state of hydration used in the formulae to derive lean mass[48].

We found that the apparent prognostic utility of impedance measures and estimates of body composition determined by BIA differed depending on which type of cancer was studied. Phase angle was predictive of complications in studies of gynaecological cancers[36], [38] (total n = 302) and mixed populations[39], [40] (total n = 181) but not apparent in either of the papers looking at a colorectal population[30],[31] (total n = 184). The variability in cancers included in this review limits the conclusions that can be drawn. However, it is conceivable that these differences reflect the impact of a particular malignancy on the nutritional and metabolic state of a patient. For example, a person with colorectal cancer is less likely to experience dysphagia than someone with an upper gastro-intestinal malignancy[49] and less likely to experience odynophagia and mucositis than someone undergoing treatment for head and neck cancer[50].

One of the difficulties in drawing strong conclusions from the studies reporting phase angle is that the raw data from which it is calculated is rarely reported. Phase angle is the arc tangent of the ratio of resistance to reactance and will, therefore, increase or decrease depending on changes in either or both of these two variables[48]. It is not possible to know whether changes in phase angle result from a change in resistance, reactance or both as these measures were not reported in any of the studies in this review. Only one paper reported impedance variables, but this was in the context of bioimpedance vector analysis rather than calculating the phase angle[37]. Impedance is also known to change with age and gender[51] which will impact interpretation of the phase angle as well as the validity of any derived variables, but few papers either acknowledged or adjusted for this in their reporting. Interpretation is further complicated by the variability in the use of cut-offs to determine what is deemed a “low” or “normal” phase angle or derived measure of lean mass. Some studies clearly state they use device-generated cut-offs[35], others use a reference population[30], [39] and some a cut-off within the study population[33], [34], [37]. Finally, none of the studies reporting estimates of lean mass provided the proprietary equations used to derive the values reported. Hence, these measures should be considered potentially insecure and reinforces the argument to report the raw data.

A wide range of reported complication rates (6% - 46.7%) in the included studies was evident which may reflect differences in study populations and the different reporting tools used. We also found a wide range of complication rates between studies using the same tool. This could reflect poor administration of the tool, genuine differences in complication rates between studies or selection bias. It should also be noted that the included studies are from different ethnic groups, continents and healthcare settings. As a consequence of this variability it is difficult to generalise findings to populations that may have significantly different complication rates due to underlying differences in peri-operative care, surgical expertise and cancer pathways.

Is it possible that phase angle offers a different vantage point from current measures? Whilst the severely malnourished patient is usually apparent following screening, dietetic assessment or bedside examination it may be that phase angle identifies a sub-set of patients who do not appear overtly malnourished but have underlying metabolic derangement and are at risk of poor outcome. Phase angle has been consistently shown to be an indicator of risk of mortality[24] in those patients with advanced cancer[52] and, relevant to this review, those with pathology amenable to surgical intervention[53],[54],[23]. Whether or not it is a good indicator of nutritional and metabolic health remains open to debate[55], though it is of interest that it is positively associated with improvements in health from interventions such as exercise therapy[56].

Like all clinical tools, BIA will be best used when applied to the right population, in the right mode, at the right time. To have benefit in the peri-operative setting it must either outperform the tools currently in use, be simpler or safer to use, or add some additional discrimination that current methods are unable to offer. It is also important that the clinician determine whether BIA is being used as a marker of nutritional and metabolic health or to assess risk on the basis of a derived measurement of body composition. Whilst alternative body composition assessment methods, such as DEXA and CT, are recommended for patients with cancer[57] both share the risks of ionising radiation and neither are portable making them suitable only for research settings or where CT is part of routine care. Bioelectrical impedance has neither of these drawbacks and may be offer a point-of-care tool suited to repeated use throughout a surgical cancer pathway to give perioperative clinicians additional information about risk from either metabolic derangement or changes in body composition.

There are a number of problems, many highlighted within this review, that limit the synthesis and interpretation of published studies. Incomplete description of BIA methodology and restricted reporting of BIA results constrains our ability to assess the utility of BIA in the setting of peri-operative risk prediction for patients undergoing surgery for cancer and limit the strength of conclusions that can be drawn. Different measurements reported in different ways against different outcomes mean it is not possible to present the findings in a standardized way. We recommend that future studies consider i) better consistency and completeness of reporting BIA measurements as both the measured impedance values as well as the derived estimates of body composition; ii) reporting the standardized phase angle to mitigate the influence of BMI, age and gender using a reference population that appropriately reflects the population being sampled; and iii) ensuring that proprietary algorithms used to derive estimates of body composition have been validated in the population being sampled. The apparent differences in risk thresholds or cut offs reported between studies may be attributable to both differences in study populations and/or technical aspects of measurement and so need further study as does whether interventions targeted at those below such thresholds are associated with better outcomes for patients with cancer undergoing surgery.

1. **Conclusions and future directions**

The findings of this review suggest that impedance measures and derived estimates of body composition determined by BIA may have a role in predicting the likelihood of a patient with cancer having complications after planned surgery. Lack of standardization in the reporting of BIA makes comparisons between studies difficult, however phase angle more consistently demonstrated an association with complications than derived estimates of body composition. We encourage future work to report both the raw impedance values, standardized phase angle and the equations used to derive lean mass, where relevant. These studies should be adequately powered to detect a difference in complications. Bioelectrical impedance analysis may be a useful adjunct in identifying those with complex needs requiring specialist personalised care packages[58] early in cancer treatment pathways, informing peri-operative risk, stratification and guiding key interventions such as multimodal prehabilitation but further high quality studies are needed.

**Author contributions**

**Lewis Matthews:** Conceptualization, Formal analysis, Investigation, Writing – Original draft

**Andrew Bates:** Formal analysis, Investigation, Writing – Review and editing

**Stephen Wootton:** Writing – Review and editing, Supervision

**Denny Levett:** Writing – Review and editing, Supervision

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**Potential conflicts of interest**

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**References**

[1] Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global cancer surgery: Delivering safe, affordable, and timely cancer surgery. Lancet Oncol 2015. https://doi.org/10.1016/S1470-2045(15)00223-5.

[2] Gillis C, Carli F. Promoting perioperative metabolic and nutritional care. Anesthesiology 2015. https://doi.org/10.1097/ALN.0000000000000795.

[3] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017. https://doi.org/10.1016/j.clnu.2016.07.015.

[4] Mak M, Bell K, Ng W, Lee M. Nutritional status, management and clinical outcomes in patients with esophageal and gastro-oesophageal cancers: A descriptive study. Nutr Diet 2017. https://doi.org/10.1111/1747-0080.12306.

[5] Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol 2015;33:90–9. https://doi.org/10.1200/jco.2014.56.1894.

[6] Pan H, Cai S, Ji J, Jiang Z, Liang H, Lin F, et al. The impact of nutritional status, nutritional risk, and nutritional treatment on clinical outcome of 2248 hospitalized cancer patients: a multi-center, prospective cohort study in Chinese teaching hospitals. Nutr Cancer 2013;65:62–70. https://doi.org/10.1080/01635581.2013.741752.

[7] Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361:1368–75. https://doi.org/10.1056/NEJMsa0903048.

[8] Moonesinghe SR, Mythen MG, Das P, Rowan KM, Grocott MPW. Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review. Anesthesiology 2013;119:959–81. https://doi.org/10.1097/ALN.0b013e3182a4e94d.

[9] Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? Anaesthesia 2019. https://doi.org/10.1111/anae.14505.

[10] Scally CP, Thumma JR, Birkmeyer JD, Dimick JB. Impact of Surgical Quality Improvement on Payments in Medicare Patients. Ann Surg 2015;262:249–52. https://doi.org/10.1097/SLA.0000000000001069.

[11] Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncol 2015;12:213–26. https://doi.org/10.1038/nrclinonc.2014.224.

[12] Levett DZH, Jack S, Swart M, Carlisle J, Wilson J, Snowden C, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth 2018. https://doi.org/10.1016/j.bja.2017.10.020.

[13] Kyle UG, Morabia A, Slosman DO, Mensi N, Unger P, Pichard C. Contribution of body composition to nutritional assessment at hospital admission in 995 patients: a controlled population study. Br J Nutr 2001. https://doi.org/10.1079/bjn2001470.

[14] Pichard C, Kyle UG, Morabia A, Perrier A, Vermeulen B, Unger P. Nutritional assessment: Lean body mass depletion at hospital admission is associated with an increased length of stay. Am J Clin Nutr 2004. https://doi.org/10.1093/ajcn/79.4.613.

[15] Thibault R, Makhlouf AM, Mulliez A, Cristina Gonzalez M, Kekstas G, Kozjek NR, et al. Fat-free mass at admission predicts 28-day mortality in intensive care unit patients: the international prospective observational study Phase Angle Project. Intensive Care Med 2016. https://doi.org/10.1007/s00134-016-4468-3.

[16] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr 2004;23:1430–53. https://doi.org/10.1016/j.clnu.2004.09.012.

[17] Barbosa-Silva MCG, Barros AJD. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. Curr Opin Clin Nutr Metab Care 2005;8:311–7. https://doi.org/10.1097/01.mco.0000165011.69943.39

[18] Barbosa-Silva MCG. Subjective and objective nutritional assessment methods: What do they really assess? Curr Opin Clin Nutr Metab Care 2008;11:248–54. https://doi.org/http://dx.doi.org/10.1097/MCO.0b013e3282fba5d7.

[19] Bosy-Westphal A, Danielzik S, Dörhöfer RP, Later W, Wiese S, Müller MJ. Phase angle from bioelectrical impedance analysis: Population reference values by age, sex, and body mass index. J Parenter Enter Nutr 2006. https://doi.org/10.1177/0148607106030004309.

[20] Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG, Grutsch JF, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. Am J Clin Nutr 2004;80:1634–8. https://doi.org/10.1093/ajcn/80.6.1634.

[21] Gupta D, Lis CG, Dahlk SL, Vashi PG, Grutsch JF, Lammersfeld CA. Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer. Br J Nutr 2004;92:957–62. https://doi.org/10.1079/BJN20041292.

[22] Buntzel J, Kraus T, Buntzel H, Kuttner K, Frohlich D, Oehler W, et al. Nutritional parameters for patients with head and neck cancer. Anticancer Res 2012; 32: 2119–23.

[23] Sanchez-Lara K, Turcott JG, Juarez E, Guevara P, Nunez-Valencia C, Onate-Ocana LF, et al. Association of nutrition parameters including bioelectrical impedance and systemic inflammatory response with quality of life and prognosis in patients with advanced non-small-cell lung cancer: a prospective study. Nutr Cancer 2012;64:526–34. https://doi.org/https://dx.doi.org/10.1080/01635581.2012.668744.

[24] Garlini LM, Alves FD, Ceretta LB, Perry IS, Souza GC, Clausell NO. Phase angle and mortality: a systematic review. Eur J Clin Nutr 2019. https://doi.org/10.1038/s41430-018-0159-1.

[25] Buter H, Veenstra JA, Koopmans M, Boerma CE. Phase angle is related to outcome after ICU admission; an observational study. Clin Nutr ESPEN 2017. https://doi.org/http://dx.doi.org/10.1016/j.clnesp.2017.12.008.

[26] Stapel SN, Looijaard WGPM, Dekker IM, Girbes ARJ, Weijs PJM, Oudemans-van Straaten HM. Bioelectrical impedance analysis-derived phase angle at admission as a predictor of 90-day mortality in intensive care patients. Eur J Clin Nutr 2018. https://doi.org/10.1038/s41430-018-0167-1.

[27] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009. https://doi.org/10.1136/bmj.b2535

[28] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016. https://doi.org/10.1186/s13643-016-0384-4.

[29] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998. https://doi.org/10.1136/jech.52.6.377.

[30] Mauricio SF, Xiao J, Prado CM, Gonzalez MC, Correia MITD. Different nutritional assessment tools as predictors of postoperative complications in patients undergoing colorectal cancer resection. Clin Nutr 2018;37:1505–11. https://doi.org/10.1016/j.clnu.2017.08.026.

[31] Berstad P, Haugum B, Helgeland M, Bukholm I, Almendingen K. Preoperative body size and composition, habitual diet, and post-operative complications in elective colorectal cancer patients in Norway. J Hum Nutr Diet 2013;26:359–68. https://doi.org/10.1111/jhn.12002.

[32] Tsaousi G, Kokkota S, Papakostas P, Stavrou G, Doumaki E, Kotzampassi K. Body composition analysis for discrimination of prolonged hospital stay in colorectal cancer surgery patients. Eur J Cancer Care (Engl) 2017. https://doi.org/10.1111/ecc.12491.

[33] Tamura T, Sakurai K, Nambara M, Miki Y, Toyokawa T, Kubo N, et al. Adverse Effects of Preoperative Sarcopenia on Postoperative Complications of Patients With Gastric Cancer. Anticancer Res 2019;39:987–92. https://doi.org/10.21873/anticanres.13203.

[34] Sato T, Aoyama T, Hayashi T, Segami K, Kawabe T, Fujikawa H, et al. Impact of preoperative hand grip strength on morbidity following gastric cancer surgery. Gastric Cancer 2016;19:1008–15. https://doi.org/https://dx.doi.org/10.1007/s10120-015-0554-4.

[35] Ida S, Watanabe M, Yoshida N, Baba Y, Umezaki N, Harada K, et al. Sarcopenia is a Predictor of Postoperative Respiratory Complications in Patients with Esophageal Cancer. Ann Surg Oncol 2015;22:4432–7. https://doi.org/https://dx.doi.org/10.1245/s10434-015-4559-3.

[36] Uccella S, Mele MC, Quagliozzi L, Rinninella E, Nero C, Capuccio S, et al. Assessment of preoperative nutritional status using BIA-derived phase angle (PhA) in patients with advanced ovarian cancer: Correlation with the extent of cytoreduction and complications. Gynecol Oncol 2018;149:263–9. https://doi.org/http://dx.doi.org/10.1016/j.ygyno.2018.03.044.

[37] Cardoso ICR, Aredes MA, Chaves GV. Applicability of the direct parameters of bioelectrical impedance in assessing nutritional status and surgical complications of women with gynecological cancer. Eur J Clin Nutr 2017;71:1278–84. https://doi.org/http://dx.doi.org/10.1038/ejcn.2017.115.

[38] Kerimoglu OS, Pekin A, Yilmaz SA, Yavas G, Beyhekim F, Demirtas AA, et al. Effect of the percentage of body fat on surgical, clinical and pathological outcomes in women with endometrial cancer. J Obstet Gynaecol Res 2015. https://doi.org/10.1111/jog.12554.

[39] Pena NF, Mauricio SF, Rodrigues AMS, Carmo AS, Coury NC, Correia MITD, et al. Association Between Standardized Phase Angle, Nutrition Status, and Clinical Outcomes in Surgical Cancer Patients. Nutr Clin Pract 2018. https://doi.org/https://dx.doi.org/10.1002/ncp.10110.

[40] Härter J, Orlandi SP, Gonzalez MC. Nutritional and functional factors as prognostic of surgical cancer patients. Support Care Cancer 2017;25:2525–30. https://doi.org/10.1007/s00520-017-3661-4.

[41] Fritz T, Hollwarth I, Romaschow M, Schlag P. The predictive role of bioelectrical impedance analysis (BIA) in postoperative complications of cancer patients. Eur J Surg Oncol 1990; 16: 326–31.

[42] Barbosa-Silva MCG, Barros AJD, Wang J, Heymsfield SB, Pierson RN. Bioelectrical impedance analysis: Population reference values for phase angle by age and sex. Am J Clin Nutr 2005. https://doi.org/10.1093/ajcn.82.1.49.

[43] Genton L, Karsegard VL, Kyle UG, Hans DB, Michel JP, Pichard C. Comparison of four bioelectrical impedance analysis formulas in healthy elderly subjects. Gerontology 2001. https://doi.org/10.1159/000052821.

[44] Kyle UG, Genton L, Karsegard L, Slosman DO, Pichard C. Single prediction equation for bioelectrical impedance analysis in adults aged 20-94 years. Nutrition 2001. https://doi.org/10.1016/S0899-9007(00)00553-0.

[45] Strong VE, Selby LV., Sovel M, Disa JJ, Hoskins W, Dematteo R, et al. Development and Assessment of Memorial Sloan Kettering Cancer Center’s Surgical Secondary Events Grading System. Ann Surg Oncol 2015. https://doi.org/10.1245/s10434-014-4141-4.

[46] Reilly JJ, Hull SF, Albert N, Waller A, Bringardener S. Economic impact of malnutrition: A model system for hospitalized patients. J Parenter Enter Nutr 1988. https://doi.org/10.1177/0148607188012004371.

[47] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004. https://doi.org/10.1097/01.sla.0000133083.54934.ae.

[48] Baumgartner RN, Chumlea WC, Roche AF. Bioelectric impedance phase angle and body composition. Am J Clin Nutr 1988. https://doi.org/10.1093/ajcn/48.1.16.

[49] Daly JM, Fry WA, Little AG, Winchester DP, McKee RF, Stewart AK, et al. Esophageal cancer: Results of American College of Surgeons patient care evaluation study. J Am Coll Surg 2000. https://doi.org/10.1016/s1072-7515(00)00238-6

[50] Jager-Wittenaar H, Dijkstra PU, Vissink A, Van Der Laan BFAM, Van Oort RP, Roodenburg JLN. Critical weight loss in head and neck cancer - Prevalence and risk factors at diagnosis: An explorative study. Support Care Cancer 2007. https://doi.org/10.1007/s00520-006-0212-9.

[51] Lukaski HC. Evolution of bioimpedance: A circuitous journey from estimation of physiological function to assessment of body composition and a return to clinical research. Eur J Clin Nutr 2013;67:S2–9. https://doi.org/10.1038/ejcn.2012.149.

[52] Pereira MME, Queiroz MDSC, de Albuquerque NMC, Rodrigues J, Wiegert EVM, Calixto-Lima L, et al. The Prognostic Role of Phase Angle in Advanced Cancer Patients: A Systematic Review. Nutr Clin Pract 2018;33:813–24. https://doi.org/https://dx.doi.org/10.1002/ncp.10100.

[53] Barao K. Cavagnari MAV, Fucuta PS, Forones NM. Association between Nutrition Status and Survival in Elderly Patients with Colorectal Cancer. Nutr Clin Pract 2017;32:658–63. https://doi.org/http://dx.doi.org/10.1177/0884533617706894.

[54] Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL, Grutsch JF, et al. Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. BMC Cancer 2008;8:249. https://doi.org/https://dx.doi.org/10.1186/1471-2407-8-249.

[55] Rinaldi S, Gilliland J, O’Connor C, Chesworth B, Madill J. Is phase angle an appropriate indicator of malnutrition in different disease states? A systematic review. Clin Nutr ESPEN 2019. https://doi.org/10.1016/j.clnesp.2018.10.010.

[56] Mundstock E, Amaral MA, Baptista RR, Sarria EE, dos Santos RRG, Filho AD, et al. Association between phase angle from bioelectrical impedance analysis and level of physical activity: Systematic review and meta-analysis. Clin Nutr 2019. https://doi.org/10.1016/j.clnu.2018.08.031.

[57] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011. https://doi.org/10.1016/S1470-2045(10)70218-7.

[58] Comprehensive Personalised Care Model. NHS England, 2019. (Accessed August 6, 2019 at https://www.england.nhs.uk/wp-content/uploads/2019/02/comprehensive-model-of-personalised-care.pdf.)