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Title

Bioelectrical impedance vector analysis (BIVA) as a method to compare body composition differences according to cancer stage and type

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1 **Abstract**

2 **Background & Aims**

3 Bioelectrical impedance vector analysis (BIVA) is a non-invasive method of measuring
4 human body composition . This offers the potential to evaluate nutritional and hydration
5 states in cancer. Analysis of BIVA data using z-score (the number of standard deviations
6 away from the mean value of the reference group) has the potential to facilitate
7 comparisons between different cancer types.

8 The aim of this study was to use the BIVA Reactance (R) / Reactance (Xc) z-score method to
9 evaluate body composition differences in cancer, using data from previously published BIVA
10 studies.

11 **Methods**

12 Previous studies using BIVA in cancer were identified from the literature. Bioimpedance
13 measures were analysed using the BIVA RXc z-score graph. The mean vector impedance
14 measures from the studied populations were transformed into standard deviates (with
15 respect to the mean and standard deviation of the reference populations). Body
16 composition was classified according to vector placement (i.e. normal athletic, cachectic,
17 oedematous and dehydrated).

18 **Results**

19 Seven male and three cancer female populations were evaluated. Body composition was
20 classified as normal for the majority (n=5), followed by cachexia (n=4) and athletic (n=1)
21 respectively. Variation in body composition for the studied populations appeared to be
22 related to factors, such as gender, disease type and severity.

23 **Conclusions**

24 The BIVA RXc z-score method has potential to evaluate body composition differences
25 between cancer groups. This method can study body composition, according to cancer type,
26 stage, gender and ethnicity. Limitations of the method relate to issues appropriate
27 reference populations and variability between bioimpedance analysers. Better body
28 composition assessment has the potential to personalise therapeutic, nutrition and
29 hydration management. Further work is essential to facilitate in-depth evaluation in these
30 areas, in order to achieve meaningful use of the BIVA method in clinical practice.

31 **Key words**

32 Bioelectrical impedance vector analysis; Bioelectrical impedance analysis; nutritional
33 assessment; cancer; body composition; palliative care

34 **Introduction**

35 People with advanced cancer commonly experience body composition changes (i.e. fat,
36 bone, water and muscle). [1-4]. Evidence demonstrates that cancer patients with reduced
37 physical function report poorer quality-of-life[5] and shorter life expectancy compared to
38 other patients.[6]Bioelectrical impedance analysis (BIA) is a non-invasive method of
39 measuring human body composition (i.e. analysis of fat, bone, water and muscle).[7] BIA,
40 delivers a low frequency electrical current and works on the principle that fluid and cellular
41 structures will provide different levels of resistance to an electrical current as it passes
42 through a living system.[7] BIA provides the following measurements: Resistance (R - Ohms),
43 assessing cellular hydration; Reactance (Xc - Ohms), assessing tissue integrity and Phase
44 Angle (PA - degrees), representing the arc-tangent between R and Xc (PA is a useful
45 indicator of health and prognosis.[7]). BIA technology has been used to evaluate hydration
46 and nutrition in several populations.[7, 8]

47 **Bioelectrical impedance vector analysis (BIVA) to assess body** 48 **composition in advanced illness**

49 Statistical vector analysis of BIA data enables further analysis of human body composition to
50 be conducted.[9] Bioelectrical impedance vector analysis (BIVA) uses graphical vectors to
51 analyse BIA data.[8] Using this method, impedance (Z) is plotted as a vector from its
52 components R (X axis) and Xc (Y axis), after being standardized by height (H). The RXc graph
53 represents the sex and race-specific tolerance intervals of a comparative reference
54 population. Tolerance ellipses are plotted on the RXc graph to represent the 50%, 75% and
55 95% centiles (i.e. confidence intervals) for the population. (Figure 1 - *The RXc graph with*

56 95%, 75% and 50% tolerance ellipses. *Reproduced and modified with permission*).[10] The
57 advantage of this method is that it allows information to be obtained simultaneously about
58 changes in tissue hydration or soft-tissue mass, independent of regression equations, or
59 body weight. Therefore, BIVA can be interpreted accurately even if patients are at extremes
60 of weight or volume distribution. BIVA has been used to study hydration status in a variety
61 of different diseases[11-19] and to undertake general body composition assessments in lung
62 cancer[18, 20] and cancers of the head and neck.[21] Our previous research used the BIVA
63 method to examine associations between hydration status, symptoms and survival in
64 advanced cancer patients.[22]

65 **BIVA RXc z-score analysis facilitates comparisons between** 66 **populations**

67 Statistical conversion of BIVA measurements to z-scores enables researchers to compare
68 body composition of different study populations.[23] Piccoli et al[23] used this method to
69 compare BIVA data for a variety of disease groups. To date, no studies have used the BIVA
70 RXc z-score method to synthesise cancer populations evaluated with BIVA. Consequently,
71 there is potential to use the BIVA Z score method to evaluate body composition by cancer
72 type and severity. Such information will potentially help support nutritional assessment and
73 management in cancer.

74 **Aim**

75 To determine the feasibility of the using the BIVA RXc z-score method to compare body
76 composition in cancer populations using published bioimpedance data.

77

78 **Materials and Methods**

79 A systematic review reporting BIVA in advanced cancer (published by Nwosu et al 2013[8])
80 was used to identify previous studies using BIVA to evaluate body composition in advanced
81 cancer. Further, an electronic search of the literature using MEDLINE, EMBASE and Pubmed
82 (combining keywords of "bioelectrical impedance vector analysis" and "Neoplasms[MesH]",
83 limited to English language and humans) was conducted to identify relevant studies.

84 **Inclusion criteria for studies**

85 Articles were eligible for review provided that they involved the use of BIA in adult humans
86 with cancer. The following data was required for the z-score analysis: (i) R/H (Ohm/m) and
87 Xc/H (Ohm/m) mean for the studied population, (ii) studied population size, (iii) sex-specific
88 bioimpedance data and (iv) details of the reference population used for the analysis.

89 Minimum standards for the reference population were as follows: the total sample size
90 $n \geq 100$, the R/H (Ohm/m) mean, R/H (Ohm/m) standard deviation (SD), Xc/H (Ohm/m) mean
91 and Xc/H (Ohm/m) SD. The Piccoli 1995 reference population (Caucasian Europeans, males
92 (n=354) and females (n=372) aged 18 - 85 years, body mass index (BMI) 16 -31 kg/m², Italy,
93 analyser = Akern-RJL systems [24]) was used for studies which did not meet the minimum
94 reference standard. We selected the Piccoli data as it was the most commonly selected
95 reference population for studies evaluating the BIVA method.

96 **Exclusion criteria for studies**

97 The following articles were excluded: Non English studies; those reporting paediatric
98 populations; absent data to facilitate the BIVA Z score analysis (see inclusion criteria).

100 **BIVA software and z-score analysis**

101 BIVA was conducted using software developed by Professor Antonio Piccoli, University of
102 Padova.[25] The mean vector impedance measures for study populations were transformed
103 into standard deviates with respect to the mean and standard deviation and compared
104 against their reference population.[24] The z-score is the number of standard deviations
105 away from the mean value of the reference group.[26] Z-scores can provide information
106 about an individual measured score, relative to others in the distribution.[27]
107 Transformation of the BIVA measurements to z-scores facilitates comparison between
108 different conditions and diseases (Figure 2). Using the RXc z-score graph, individuals within
109 the 50% tolerance ellipse are considered to have normal body composition, whereas those
110 in the 75% and 95% tolerance ellipses are abnormal.[25]
111 Vectors were plotted on the RXc z-score graph to facilitate data comparison. Vectors plotted
112 within the 50% tolerance ellipse were considered normal. Based on data from the Piccoli
113 study,[23] the BIVA RXc z-score graph was divided into four quadrants to classify body
114 composition of populations within the 75% and 95% (i.e. abnormal) tolerance ellipses. These
115 quadrants were (i) *Athletic* (high cell mass), top left, (ii) *Cachexia* (low cell mass), bottom
116 right; (iii) *Oedema*, bottom left and (iv) *Dehydrated*, top right (Figure 2). Body composition
117 was determined according to the plotted vector position. Further details on the equations
118 used to calculate the RXc Z score graph analysis are available in the appendix.

119 **Ethical Statement**

120 This study was a secondary analysis of previously published research. Therefore, ethical
121 approval was not required.

122 **Results**

123 The literature search returned 15 full text articles using BIVA in people with cancer (Figure
124 3). Two of these articles were rejected as they are not specific to patients with advanced
125 cancer. Two studies (Lundberg et al[28] and Gnagnarella et al[29]) were excluded as
126 insufficient data was available to enable the RXc z-score analysis to be conducted. Of the
127 remaining eleven studies, some presented the same BIVA data. These included two different
128 studies, which both reported data for the same breast cancer sample.[30, 31] Similarly, two
129 studies reported data for the same head and neck cancer sample.[21, 32] We grouped the
130 relevant studies together to avoid confusion. Consequently, nine of the eleven eligible
131 studies were included. These nine studies provided data for seven male and three female
132 populations (Table 1). The studies described different cancer types and stages, which
133 included advanced cancer of different origin;[22] lung cancer (including a sample of patients
134 in remission),[18, 20] breast cancer,[30] head and neck cancer[21, 33] and gynaecological
135 cancer.[34] Details of patient demographics, type of analyser and BIVA z-score analysis are
136 presented in Table 1.

137 **BIVA RXc z-score analysis**

138 The reference population of Piccoli et al[24] was used as the chosen reference population
139 for the authors of the Cardoso[34] and Nwosu studies. However, the seven populations
140 described by Toso et al[18, 20] and Malecka-Massalska[21, 31, 35] [30, 32] used control
141 groups with sample sizes of $n < 100$ as a reference. We used the Piccoli data[24] as a
142 reference population for these studies. Consequently, the Piccoli reference population was
143 used as the reference for all studies in this paper.

144 The z-score analysis is presented in Figure 4 and Table 2 (supplementary file). Five
145 populations were normal (50% tolerance ellipse). These were the male and female cohorts
146 with various cancers (Nwosu et al 2016[22]), males with lung cancer in remission(Toso et al
147 2003[18]), males patients with stage III lung cancer (Toso et al 2000 [20]) and females with
148 gynaecological cancer (Cardoso et al 2017[34]). Comparatively greater cell mass was noted
149 in females with the newly diagnosed breast cancer[30] (the vector was superior to the 95%
150 tolerance ellipse of the athletic quadrant) had. Four groups were cachectic (vectors within
151 the 75% and 95% tolerance ellipse). This included males with stage IV lung cancer (Toso et
152 al 2000[20] - 75% tolerance ellipse), males with local and disseminated lung cancer(Toso et
153 al 2003[18] - 75% tolerance ellipse), and two populations of males with head and neck
154 cancer (Malecka-Massalska et al 2013[33]– 75% tolerance ellipse, and Malecka-Massalska et
155 al 2012, 2014[21, 32] - 95% tolerance ellipse). .

156 **Discussion**

157 **Main findings**

158 Seven male and three cancer female populations were evaluated. Body composition was
159 classified as normal for the majority (n=5), followed by cachexia (n=4) and athletic (n=1)
160 respectively. Variation in body composition for the studied populations appeared to be
161 related to factors, such as gender, disease type and severity.

162 **Strengths and uniqueness of this study**

163 This is first study to use the BIVA z-score method to compare body composition in cancer
164 populations, using data from previously published bioimpedance data. BIVA offers
165 advantages over traditional methods of body composition assessment, due to its non-
166 invasive nature and simplicity. BIVA has methodological advantage over traditional BIA

167 calculations due to its independence of regression equations (which lack accuracy in
168 cancer[7]). Furthermore, BIVA can facilitate longitudinal assessments to evaluate body
169 composition changes over time. These properties are useful to evaluate nutrition and
170 hydration in people affected by cancer, who are unable to tolerate more invasive methods
171 of assessment. This research demonstrates the potential to use published BIVA data for
172 larger analysis.

173 **Comparison with previous work**

174 The only previous study to use BIVA Rxc z-scores in cancer was the Piccoli et al 2002.[23]
175 Piccoli plotted data from the vector point for males with stage IV lung cancer (Toso et al
176 2000[20]) within the cachexia quadrant (75% tolerance ellipse). Our data builds on Piccoli's
177 study and describes how, in addition to Toso's stage IV lung cancer data, three other
178 populations were also classified as cachectic. This included a lung cancer sample with local
179 and disseminated disease,[18] and two head and neck cancer cohorts[21, 32, 33]). The
180 vectors for the advanced cancer population described by Nwosu et al[22] (although plotted
181 within the normal 50% ellipse) were in a similar position to the lung cancer studies by Toso
182 et al, [18, 20]. This suggests similarity between these groups (i.e. low muscle mass, with risk
183 of cachexia), even though body composition was classified as normal. Therefore,
184 interpretation of BIVA Rxc z-score data requires consideration of clinical factors in addition
185 to BIVA.

186 Previous work illustrates how patients with cancer are prone to develop cachexia as their
187 condition progresses.[1, 36] However, data about the stage of cancer was only available for
188 two populations. It is possible that stratification of data by cancer stage may have
189 demonstrated that individuals with more severe cancer were more likely to be cachectic.

190 Furthermore, assessments at different points in the disease trajectory may demonstrate
191 changing body composition over time.

192 Our data demonstrates that body composition appeared to be related to cancer type,
193 disease severity and gender.[37] For example, females with breast[30] and gynaecological
194 cancers[34] had increased cell mass compared to other populations (demonstrated by more
195 superior vector placement). Two factors may explain this difference. Firstly, individuals with
196 breast and gynaecological cancer were comparatively younger than other groups (the mean
197 age for the breast and gynaecological cancer groups were 53 and 60 years respectively,
198 whereas most other populations were aged >60 years). Secondly, these patients were
199 recruited at diagnosis, whereas participants in other studies were recruited later in their
200 illness.

201 **Limitations**

202 A limitation of this study is that nutritional screening tools were not used in all studies,
203 which makes nutritional based comparisons difficult. The Subjective Global Assessment
204 (SGA - a simple bedside method of assessing the risk of malnutrition [38]) was used in the
205 majority studies. Only one study (Cardoso et al[34]) reported body mass index (BMI) data
206 according to the requirements of the European Society for Clinical Nutrition and
207 Metabolism (ESPEN) malnutrition criteria.[39] Therefore, our ability to evaluate how BIVA
208 RXc z-scores relates to nutritional states is limited.

209 A small number of studies were evaluated in this analysis and the majority of participants
210 included in the studies were from white, European or North American populations, which
211 limits our ability to extrapolate the findings. The under-representation of non-white groups
212 in these studies may be due to various factors, such as language and cultural barriers.[40]

213 Further, as this analysis only included English language studies, it is possible that studies
214 using BIVA in different cultural contexts were excluded.

215 The lack of BIVA research in females limits the ability to extrapolate results to women.
216 Females differ physiologically to males (generally more body fat, less body water, shorter
217 height and reduced muscle mass compared to men[41, 42]). Of the three studies including
218 women, two studied female specific cancers (breast[30, 31], cervical[34]) and one studied
219 with a mix of cancer types.[22] Therefore, no studies in the literature provide meaningful
220 female-specific BIVA data for any cancers, other than those affecting the breast and cervix.
221 Our findings are limited by a lack of information about the reasons why reference
222 populations were chosen Reference populations may not be representative of the studied
223 population. This is problematic with the Cardoso et al[34] study, which used an
224 inappropriate reference population (European white adults) for their analysis of a Brazilian
225 Pardo (mixed race) sample.[34] It is likely this population was chosen due to the lack of
226 other suitable reference populations. Furthermore, seven populations used small control
227 groups (n<100) as their reference, which are inappropriate due to their small size. Although
228 we used the Piccoli population as the reference for these studies, other reference
229 population may have been more appropriate. This demonstrates the challenges of using the
230 BIVA Z score method appropriately when there is variability about how reference
231 populations are selected.

232 Different bioimpedance analysers were used throughout the studies included in this
233 analyser. This may result in slight differences in reactance and resistance values which may
234 alter the BIVA z-score interpretation. Finally, an inherent limitation of the BIVA method is
235 that it is a qualitative assessment method which does not provide absolute values of body
236 composition metrics.[8] Therefore, the method is unable to provide quantitative data on

237 body composition variables (e.g. fat free mass, and fluid volume). This is why stratification
238 of BIVA data according to clinical variables is important (e.g. disease stage, type and
239 ethnicity), in order to determine clinically meaningful outcomes.

240 **Implications to clinical practice and policy**

241 This analysis supports previous data that describes how body composition in cancer is
242 related to a number of factors (e.g. stage, type of disease).[36, 43, 44] This study
243 demonstrates the potential to use the BIVA RXc z-score method to undertake comparative,
244 multi-group, body composition analysis, which could be useful to compare differences in
245 cancer according to disease stage and type. This has the potential to personalise
246 therapeutic, nutrition and hydration based interventions according to an individual's
247 physiology. Although the BIVA RXc z-score method has potential use in clinical practice, we
248 are unable to recommend its routine use in clinical practice (in cancer), due to the limited
249 number of studies using the method and a lack of data to inform clinical interpretation.

250 **Future research possibilities**

251 Further research studies using bioimpedance are needed to evaluate differences in cancer,
252 according to disease type, stage, ethnicity and gender. In order to improve the clinical
253 usefulness of BIVA, future bioimpedance studies should report all the relevant data (and
254 standard deviations) required to conduct BIVA[45] (i.e. age (years), Height (m), BMI (Height
255 (H)²/m), weight(kg), R (Ohm), R/H (Ohm/m), Xc (Ohm), Xc/H (Ohm/m), PA (degrees)).
256 Researchers should justify the reasons for the choice of reference populations, stating why
257 the chosen population is best suited for their analysis. Inclusion of this information will
258 enable researchers to conduct BIVA analyses without needing to contact investigators for
259 further information. Researchers should aim to develop larger, appropriately powered,

260 reference populations, to facilitate stratification (by age, gender, ethnicity and other clinical
261 factors). As a priority, futures studies should generate data for non-white and female
262 individuals.

263 **Conclusions**

264 The BIVA RXc z-score method can be used to evaluate body composition in people with
265 cancer. This method can be used to conduct analysis of body composition according to
266 different variables such as cancer type, stage, gender and ethnicity. Improved assessment
267 will lead to better understanding of the physiological and biological processes of advanced
268 cancer. Consequently, BIVA may help healthcare professionals to personalise therapy in
269 patients with cancer according to their physiology.

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272 the RXc graphs and vector BIA analysis.

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274 **Conflict of Interest Statement**

275 The authors declare that there is no conflict of interest.

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278 **Author Contribution Statement**

279 The author's responsibilities were as follows.

280 Research design: ACN

281 Data collection: ACN
282 Statistical analysis: ACN, TFC
283 Paper writing: ACN, CM, SM
284 Supervision: CM, SM, AV, JE
285 Critique and review of the final manuscript: ACN, CM, SM, TFC, SS, AV, JE

286 **List of abbreviations used**

287 BIA (bioelectrical impedance analysis), BIVA (bioelectrical impedance vector analysis), CAH,
288 (clinical assisted hydration), ECOG (Eastern Cooperative Oncology Group performance
289 status), H (height - m), M (mean), R (resistance - Ohm), R/H (resistance normalized by the
290 height - m), Xc (reactance - Ohm); Xc/H (reactance normalized by height), RXc,
291 (resistance/reactance); TBW (total body water), FFM (fat free mass), FM (fat mass), PA
292 (phase angle - degrees), ESPEN (European Society for Clinical Nutrition and Metabolism),
293 BMI (Body Mass Index - height/weight^2 [kg/m²]).

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473

474

475 **Appendix**

476 **Formulas for the calculation of the bio-impedance confidence and** 477 **tolerance ellipses**

478 The following section has been adapted (with permission) from Piccoli A , Pastori: BIVA
479 software.[25]

480 **Geometrical parameters for drawing the RXc Graph and the RXc-** 481 **score Graph**

482 Confidence and tolerance intervals can be calculated for the bivariate normal
483 distribution.[46-50] A simple linear correlation analysis can be used for calculation following
484 appropriate modification of the equations.[9, 23]

485 Given n pairs of observations x and y, with standard deviation s_x and s_y , and correlation
486 coefficient r, for a fixed α probability level, the Snedecor's F_α value is taken with 2 and n-2
487 degrees of freedom.

488 **RXc Graph**

489 The RXc graph semi-axes (L_1 and L_2) and the slopes (b_1 and $b_2 = -1/b_1$), of the axes of the
490 $100(1-\alpha)\%$ confidence and tolerance ellipses (e.g. $\alpha= 0.05, 0.25,$ and 0.50 for the 95th, 75th,
491 and 50th percentile, respectively) can be calculated using the equations 2a and 3a,
492 respectively.

493 **RXc-score graph**

494 The parameters of tolerance ellipses of bivariate Z-scores (RXc Zscore graph) can be
495 calculated accordingly, using equations 1b and 2b.[23]

496 **Equation 1 a**

497 **L1, L2 =**

$$498 \sqrt{K} \cdot \sqrt{(n-1)(s_{x^2} + s_{y^2}) \pm \sqrt{[(n-1)(s_{x^2} + s_{y^2})]^2 - 4(n-1)^2(1-r^2)s_{x^2}s_{y^2}}}$$

499

500 **Equation 1 b**

$$501 L1, L2 = \sqrt{K} \cdot \sqrt{2(n-1) \pm 2r(n-1)}$$

502

503 Where

504 $K = F/n \cdot (n-2)$ for confidence ellipses

505 $K = F \cdot (n+1)/n \cdot (n-2)$ for tolerance ellipses

506 **Equation 2 a**

$$507 b_1, b_2 = \left(b, -\frac{1}{b}\right) = (s_{y^2} - s_{x^2})/2rs_x s_y \pm \sqrt{1 + [(s_{y^2} - s_{x^2})/2rs_x s_y]^2}$$

508

509 **Equation 2b**

$$510 b_1, b_2 = \pm 1$$

511 **Figure and Table Legends**

512 **Table 1 Details of the studies included in the BIVA RXc z-score analysis**

Key	Author	Characteristics	N	Mean age (years)	Gender	BMI (kg/m ²)	Tolerance	Body composition	Analyser
●	Nwosu 2016[22]	Mixed cancer Males (n=42) mean age 70.6 (SD 11.0), median 71.0) BMI 26.4 (SD 5.2) predominantly Caucasian, advanced cancer with different disease types. United Kingdom.	42	70.60	Male	26.4	50%	Normal	Analyzer The EFG3 ElectroFluidGraph Vector Impedance Analyser (Akern)
▲	Nwosu 2016[22]	Mixed cancer Female (n=48) mean age 71.6 (SD 13.3), median 74, BMI 24.1 (4.7) predominantly Caucasian, with different disease types. United Kingdom.	48	76.10	Female	24.1	50%	Normal	Analyzer The EFG3 ElectroFluidGraph Vector Impedance Analyser (Akern)
■	Toso 2000[20]	lung cancer stage IIIB	33	67.00	Male	25.0	50%	Normal	Analyzer BIA-101, RJL/Akern Systems, Clinton Town- ship, MI, USA

		Males, n=33. Mean age 67 (SD 5.0), BMI 25 (SD 5.5) Caucasian, lung cancer stage IIIB. Italy.							
○	Toso 2000[20]	lung cancer stage IV Males, n=30, mean age 64 (SD 7.0), BMI 25 (SD 3.1) Caucasian, lung cancer stage IV, Italy.	30	64.00	Male	25.0	75%	Cachexia	Analyzer BIA-101, RJL/Akern Systems, Clinton Township, MI, USA
△	Malecka-Massalska 2012[30] 2013[31]	Breast cancer Females, n=34, mean age =53.88 (SD 10.84) breast cancer (n=34) Poland.	61	53.88	Female	-	95%	Athletic	Analyzer ImpediMed bioimpedance analysis SFB7 Biolmp v1.55, Queensland, Australia.
□	Malecka-Massalska 2012[21] 2014 [32]	Head and neck cancer Males, n=28, mean age 57.1 (SD 7.3), BMI 22.8 (5.0), Caucasian, head and neck cancer.	34	57.10	Male	-	95%	Cachexia	Analyzer ImpediMed bioimpedance analysis SFB7 Biolmp v1.55, Queensland, Australia.
◆	Toso 2003[18]	Lung cancer	56	66.00	Male	25.0	75%	Cachexia	Analyzer BIA-101, RJL/Akern Systems, Clinton Township, MI, USA

		Males, n=61, mean age =66 (SD 6), BMI= 25 (SD 4), Caucasian, lung cancer, locally advanced and disseminated.							
X	Toso 2003[18]	Lung cancer in remission Males, n=31, mean age= 63 (SD 10), BMI= 25 (SD 4) Caucasian, lung cancer in remission (n=31)	31	63.00	Male	25.0	50%	Normal	Analyzer BIA-101, RJL/Akern Systems, Clinton Township, MI, USA
◇	Melecka-Massalska 2013[33]	Head and neck cancer Males, Caucasian n=67, mean age = 56.8 (SD 7.9), BMI 22.9 (SD 4.4), Caucasian, head and neck cancer, Poland.	67	67.00	Male	22.9	75%	Cachexia	Analyzer ImpediMed bioimpedance analysis SFB7 Biolmp v1.55, Queensland, Australia.
*	Cardoso 2017[34]	Gynaecological cancer Female, n=208, mean age= 60 (range 51-67), BMI = underweight (12(6%), normal 52(25%), overweight 55 (26%), obese 89 (43%). White n=89(43%), mixed races 92(42%), Black 26(13%). Gynaecological cancer. Brazil	208	60.00	Female	-	50%	Normal	BIA 450 Bioimpedance Analyzer, Biodynamics, Shoreline, WA, USA

514 *RXc z score data analysed with BIVA software using equations included in the appendix.*

515

516 **Table 2: Bioimpedance Z score data for the included studies**

Study details	R/H (Ohm/m)	Xc/H (Ohm/m)	Reference population data*					Z(R) score	Z(Xc) score
			N	R/H (Ohm/m) mean	R/H (Ohm/m) SD	Xc/H (Ohm/m) Mean	Xc/H (Ohm/m) SD		
			Males, mixed cancer - Nwosu 2016[22]	306.6	26.1	354	371.9		
Females, mixed cancer - Nwosu 2016[22]	372.2	29.1	372	298.6	49.0	34.4	7.7	0.01	-0.69
Males, White, Lung cancer stage IIIB, - Toso 2000[20]	302.0	25.0	354	371.9	43.2	30.8	7.2	0.08	-0.81
Males, White, Lung cancer stage IV, - Toso 2000[20]	314.0	24.0	354	371.9	43.2	30.8	7.2	0.36	-0.94
Females with breast cancer - Malecka-Massalska 2012[30] 2013[31]	377.54	53.58	372	298.6	49.0	34.4	7.7	0.12	2.49
Males with head and neck cancer- Melecka-Massalska 2013[33]	342.54	27.62	354	371.9	43.2	30.8	7.2	1.02	-0.44
Males with lung cancer locally advanced and disseminated - Toso 2003[18]	317	26.0	354	371.9	43.2	30.8	7.2	0.43	-0.67
Males with lung cancer in remission - Toso 2003[18]	287	25.0	354	371.9	43.2	30.8	7.2	-0.27	-0.81
Males with head and neck cancer - Melecka-Massalska 2013[33]	327.01	28.04	354	371.9	43.2	30.8	7.2	0.66	-0.38
Females (mixed race) gynaecological cancer - Cardoso 2017[34]	349.8	34.4	372	298.6	49.0	34.4	7.7	-0.45	0.00

517 **The Piccoli et al 1995[24] reference population data was used for all studies included in this analysis. BIVA software equations are included in*
 518 *the appendix.*

519

520

521 **Figure 1: The RXc graph with 95%, 75% and 50% tolerance ellipses. Reproduced and**
522 **modified with permission.[51]**

523

524 **Figure 2: The BIVA z-score graph: data drawn from the literature and plotted on the RXc z-**
525 **score graph after transformation of the impedance measurements from several disease**
526 **groups into bivariate z-scores (with respect to their reference population). Modified with**
527 **permission.[23]**

528 *Solid and open circles represent male and female, respectively. A forward or backward*
529 *displacement of vectors parallel to the major axis of ellipses was associated with*
530 *dehydration or fluid overloading, respectively, reaching extremes out of the poles. Single*
531 *score vectors are from athletes,[52] obese subjects of class I to III[53] or patients with*
532 *chronic renal failure in conservative treatment, nephrotic syndrome (oedema), lung*
533 *cancer,[20] acquired immunodeficiency syndrome in stages WR 3 to 5 or WR 6,[54] and*
534 *anorexia nervosa.[55] Repeated score vectors are from climbers before and after high*
535 *altitude dehydration,[56] Haemodialysis patients, either lean[57] or obese,[53] before and*
536 *after fluid removal with a dialysis session, and dehydrated patients with cholera before and*
537 *after fluid infusion.[12] Vectors above or below the major axis (meaning upper left or lower*
538 *right half of ellipses) were associated with more or less cell mass in soft tissues, respectively,*
539 *with extremes along the minor axis. Abbreviations: CRF = chronic renal failure; HD=*
540 *haemodialysis; HDo= obese haemodialysis patients; HIV= human immunodeficiency virus*
541 *stages 1-6; Ob/1-3= obese subjects of classes I to III; WR= Walter Reed stages 1-6.*
542 *Reproduced with permission.[23]*

543 **Figure 3: Overall selection process for clinical studies included in the BIVA Z score analysis**

544

545 **Figure 4: RXc z-score graph analysis of bioelectrical impedance vector analysis (BIVA) data**

546 **from studies of patients with cancer.**

547 *Data drawn from the literature and plotted on the RXc-score graph after transformation of*

548 *impedance measurements from several disease groups into bivariate Z scores (with respect*

549 *to the Piccoli 1995 reference population[24]). Further details of the equations used for the*

550 *analysis are available in the appendix.*

