Advanced Body Measurement Techniques Can Complement Current Methods of Cytotoxic Chemotherapy Dose Prescription

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applied sciences

MDPI

Opinion

Advanced Body Measurement Techniques Can Complement Current Methods of Cytotoxic Chemotherapy Dose Prescription

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Featured Application: This opinion piece discusses the limitations of the current cytotoxic dosing methods and how advanced body measurement techniques could be used by oncology practitioners to determine cytotoxic chemotherapy dosages for patients, regardless of their body size.

Abstract: Within chemotherapy, estimates of a patient's body surface area (BSA) are used to calculate drug dosages. However, the use of BSA for calculating chemotherapy dosage has been heavily criticised in previous literature, with potentially significant implications for the effectiveness and toxicity of treatment. BSA has been found to be a poor indicator of optimal drug exposure that does not account for the complex processes of cytotoxic drug distribution and elimination. In addition, differences in BSA estimates between existing formulae have been shown to be so large that they can affect patients' mortality, particularly in patients with atypical body types. This uncertainty associated with BSA prediction may decrease the confidence of practitioners when determining chemotherapy dosages, particularly with regards to the risk of excess toxicity from over-dosing, or a reduced anti-cancer effect due to under-dosing. The use of national dose-banding in the UK may in some cases account for possible inaccuracies, but the threshold of variance in this case is small (+/−6%). Advanced body measurement techniques, utilising digital tools such as three-dimensional (3D) surface imaging, capture accurate external dimensions and detailed shape characteristics of the human body. Measures of body shape describe morphological variations that cannot be identified by traditional anthropometric techniques and improve the prediction of total body fat and distribution. It is our view that the use of advanced body measurement techniques can provide practitioners with tools for prescribing chemotherapy dosages that are valid for individuals, regardless of their body type.

Keywords: body surface area; cancer; pharmacokinetics; morphology; digital anthropometry; human body shape

Citation: Thelwell, M.; Masters, N.; Appleyard, R.; Bullas, A.M. Advanced Body Measurement Techniques Can Complement Current Methods of Cytotoxic Chemotherapy Dose Prescription. *Appl. Sci.* **2024**, *14*, 834. https://doi.org/10.3390/app14020834

Academic Editor: Maria Filomena Botelho

Received: 21 December 2023
Revised: 12 January 2024
Accepted: 17 January 2024
Published: 18 January 2024

1. Introduction

Measurement of body surface area (BSA) plays a key role in several medical applications, including the treatment of burns [1] and the prescription of conventional cytotoxic chemotherapy drug dosages within systemic anti-cancer treatment (SACT). However, the use of BSA for calculating chemotherapy dosage has been heavily criticised, with potentially significant implications for the effectiveness of anti-cancer treatment [2–6].

Cytotoxic chemotherapy has been the mainstay of systemic treatment for malignancy for over 70 years. Several chemotherapy drugs have since been developed and found to be successful in combating a variety of cancers in paediatric and adult patients. However, conventional cytotoxic chemotherapy drugs are not tumour specific, and their administration

can result in significant acute and chronic toxic effects to normal healthy tissue. Effectively determining the dosage of chemotherapy drugs is vital to balance the effectiveness of treatment with acceptable levels of toxicity to normal tissues, enabling patients to tolerate treatment and have better long-term treatment outcomes. Improvements in cancer survival and longer duration of treatment for individual patients may also lead to increasing numbers of patients developing treatment-related toxicities. Despite recent advances in anti-cancer treatment and the development of targeted agents and immunotherapeutics [7], which offer advantages in delivering growth inhibitory or cytotoxic effects in a more cell-specific manner, it is likely that cytotoxic chemotherapy will continue to be used into the foreseeable future [3]. Therefore, further research to optimise methods for determining chemotherapy dosage is warranted.

BSA is currently the key anthropometric variable used to determine the cytotoxic drug dosage for patients receiving conventional chemotherapy as part of their cancer treatment. Investigations into BSA as a physiological quantity began in the late 19th century, with the discovery that small animals utilise more oxygen and produce more heat relative to larger animals, due to having a larger surface area per unit mass [8]. These findings were subsequently applied to humans and led to the practice of describing the basal metabolic rate in terms of BSA rather than body weight [8]. Further exploration led to the observation of relationships between BSA and several physiological processes including, water turnover, blood volume, quantities of circulating plasma proteins and renal function, giving rise to the belief that BSA was correlated with the size and function of drug-metabolising organs [8]. In the mid-20th century, both Pinkel and Freirich [8,9] conducted investigations to compare therapeutic dose ranges and maximum tolerated doses calculated based on body weight and BSA for humans and animals. Though the effective doses of some anti-cancer drugs were found to be more similar among mammals when calculated per unit surface area, there were still large differences across different drug types and species. Based on these findings, BSA was deemed reasonable and began being recommended for use in prescribing chemotherapy dosages by paediatricians and medical oncologists, rather than either being fixed or based on body weight [10,11]. This remains the primary method of dose prescription to this day, for example within chemotherapy dosing in many clinical trials and is also the indicated method for dose calculation in drug package inserts or summary of product information data sheets. However, the continued use of BSA-based dosing remains controversial with methods of calculation not representative of patient variability and thus not truly individualised to patients. Inaccurate dose calculation for an individual may affect efficacy or tolerability as a result [12–15]. Consequently, the need for improved methods of dose calculation and prescription have increased in recent years and remains a significant challenge within oncology [13,16].

In this opinion piece, we discuss the limitations of BSA-based dosing methods and how advanced body measurement techniques, which account for the effects of obesity and describe morphological variations that cannot be identified by traditional anthropometrics, can provide oncology practitioners with improved tools for calculating individualised cytotoxic chemotherapy dosages for patients, regardless of their body type.

2. Dose Individualisation

The optimum cytotoxic drug dosage should provide patients with the maximal anti-cancer effect, alongside acceptable levels of toxicity. For most cancer types, there is a plateau in the dose –response curve for cytotoxic chemotherapy, meaning that any increase in dosage above a certain level will lead to greater levels of toxicity but no additional effect of treatment on the tumour [2,17]. For this reason, the avoidance of excessive toxicity caused by overdosing is regarded as the most important side-effect to control within cytotoxic chemotherapy, with high-dose chemotherapy dose-regimens reserved for acute leukaemia and aggressive lymphomas. However, inadvertent underdosing has been shown to be more common, affecting as many as 30% of patients receiving a standard chemotherapy regimen [3]. This could potentially lead to a reduced effectiveness of the treatment and

response or survival rates. It has been suggested that an underlying issue of clinical trials used to determine the dose of cytotoxic drugs is that the primary consideration is the prevention of toxicity rather than identifying the dose that produces the greatest anti-cancer effect [3].

An alternative proposed method of optimising chemotherapy treatment in individual patients is to adjust successive doses throughout a course of treatment based on their levels of myelosuppression, known as 'toxicity-adjusting dosing' [2,18]. Though this method seeks to account for known interpatient variations in cytotoxic drug clearance, it is still more likely that doses will be reduced, dose intervals increased, or courses of treatment skipped entirely than it is to increase the dose intensity in cases where treatment is well tolerated and there is no significant toxicity. Relative dose intensity (RDI) is defined as the ratio of delivered dose intensity (per unit body surface area per unit time (mg/m^2 per week)) to the planned dose intensity for a chemotherapy regimen [19], with an RDI value of less than 85% considered a clinically significant reduction in dosage compared to planned therapy [20,21]. Though it has been shown that patients who receive higher dose intensities typically achieve better disease-free, progression-free, and overall survival than patients that receive lower dose intensities than planned [22], significant numbers of patients are frequently given less than 85% of the suggested dose [23]. For this reason, the desire among oncology practitioners would be to have a method that enables them to prescribe the correct individualised dosage at the start of treatment, rather than finding the correct dose by the third or fourth cycle through trial and error, resulting in a suboptimal therapeutic effect.

3. Limitations of BSA Dosing

A primary limitation of BSA-based dosing is that surface area cannot be measured directly using traditional anthropometric techniques but must be estimated using simple regression formulae. More than 20 of these formulae exist in previous literature, typically based on non-linear functions of simple body measures—body weight and height (Table 1). One of the earliest of these formulae was developed in 1916 by DuBois and DuBois [24] and remains the standard approach used to estimate BSA within current clinical practice. This formula was originally developed based on a sample of eight patients, who were cast in paper moulds to measure their surface area. However, though the DuBois formula has been found to have the least errors of all the developed formulae, it has still been described as only providing a rough approximation of BSA [9]. Like the DuBois formula, most of the other developed formulae were developed using small, homogenous samples of patients, in terms of their sex, body type and ethnicity. As a result, estimations of BSA calculated using the different formulae can differ by as much as 0.5 m^2 for the same individual and exhibit relative errors from direct measures of BSA, ranging between 9.83% and 43.27% [16]. An example of the differences in estimated BSA values for a typical male patient (height: 164.9 cm, weight: 97.8 kg, body mass index (*BMI*): 36.2 kg/m^2) are shown in Table 1. The range of BSA values estimated for this individual is 0.41 m^2. Recent studies have suggested that the differences in estimated BSA made by these existing formulae are so great that, in certain cases, they may considerably affect patients' mortality if they are inadvertently underdosed [16]. These errors in BSA estimation are even greater in severely underweight or overweight patients who differ from a "standard physique". For example, it has been suggested that the DuBois formula has a systematic negative bias and may be invalid when BSA is below 1.3 m^2. For obese patients (*BMI*) > 30), there is often confusion as to whether actual or ideal body weight should be used to calculate BSA. The choice of which body weight measure to use can be significant since the calculated drug dosage can increase by up to 30% if body weight is used rather than ideal body weight. Without evidence-based recommendations on this issue, practitioners may use either actual or ideal weight or take an average between the two measures. The common practice of either dose banding or rounding of chemotherapy may reduce error when the variation is small from BSA calculation. However, as practice normally allows 5–7% variance with rounding and

banding, this will not account for greater inaccuracies [2,25,26]. It has long been recognised that the current methods of calculating chemotherapy dosages using estimates of BSA are inaccurate [2,4] but the development of more effective dose calculation methods for cytotoxic drugs used in anti-cancer treatment, as well as other pharmaceutical agents within other medical fields, is now a research priority.

Table 1. Previously developed body surface area (BSA) estimation formulae and estimated BSA values for a typical male patient.

Authors (Year)	Formula	Estimated BSA Values (m^2)
Meeh (1879) [27]	$0.1053 \times W^{2/3}$	2.24
DuBois and DuBois (1916) [24]	$0.007184 \times W^{0.425} \times H^{0.725}$	2.04
Faber and Melcher (1921) [28]	$0.00785 \times W^{0.425} \times H^{0.725}$	2.23
Takahira (1925) [29]	$0.007246 \times W^{0.425} \times H^{0.725}$	2.06
Breitmann (1932) [30]	$0.0087 \times (W + H) - 0.26$	2.03
Boyd (1935) [31]	$0.0003207 \times (W \times 1000)^{0.7285 - 0.0188 \times \log_{10}(W \times 1000)} \times H^{0.3}$	2.18
Stevenson (1937) [32]	$0.0128 \times W + 0.0061 \times H - 0.1529$	2.10
Sendroy and Cecchini (1954) [33]	$0.0097 \times (W + H) - 0.545$	2.00
Banerjee and Sen (1955) [34]	$0.007466 \times W^{0.425} \times H^{0.725}$	2.12
Choi (1956) [35]	Men : $0.005902 \times W^{0.407} \times H^{0.776}$ Women : $0.008692 \times W^{0.442} \times H^{0.678}$	2.00 -
Mehra (1958) [36]	$0.01131 \times W^{0.4092} \times H^{0.6468}$	2.00
Banerjee and Bhattacharya (1961) [37]	$0.007 \times W^{0.425} \times H^{0.725}$	1.99
Fujimoto et al. (1968) [38]	$0.008883 \times W^{0.444} \times H^{0.663}$	2.01
Gehan and George (1970) [39]	$0.0235 \times W^{0.51456} \times H^{0.42246}$	2.15
Haycock et al. (1978) [40]	$0.024265 \times W^{0.5378} \times H^{0.3964}$	2.16
Mosteller (1987) [41]	$\sqrt{W \times H / 3600}$	2.12
Mattar (1989) [42]	$(W + H - 60)/100$	2.03
Nwoye (1989) [43]	$0.001315 \times W^{0.262} \times H^{1.2139}$	2.15
Shuter and Aslani (2000) [44]	$0.00949 \times W^{0.441} \times H^{0.655}$	2.03
Livingston and Lee (2001) [45]	$0.1173 \times W^{0.6466}$	2.27
Tikuisis et al. (2001) [46]	Men : $0.01281 \times W^{0.44} \times H^{0.6}$ Women : $0.01474 \times W^{0.47} \times H^{0.55}$	2.06 -
Nwoye and Al-Sheri (2003) [47]	$0.02036 \times W^{0.427} \times H^{0.516}$	2.01
Yu, Lo, Chiou (2003) [48]	$0.015925 \times (W \times H)^{0.5}$	2.02
Schlich et al. (2010) [49]	Men : $0.000579479 \times W^{0.38} \times H^{1.24}$ Women : $0.000975482 \times W^{0.46} \times H^{1.08}$	1.86 -
Yu, Lin, Yang (2010) [50]	$0.00713989 \times W^{0.404} \times H^{0.7437}$	2.03
Kühnapfel et al. (2017) [51]	General : $0.0151 \times H^{0.5751} \times W^{0.4259}$ Sub − group : $0.0151 \times H^{0.8516} \times H^{0.3262} \times exp(-0.0120 \times Sex) \times exp(0.0036 \times BMI)$	2.00 1.98

W indicates weight in kilograms, and *H* indicates height in centimetres. Estimated BSA values are for a typical male patient (height: 164.9 cm, weight: 97.8 kg, body mass index (*BMI*): 36.2 kg/m^2).

Another issue in using BSA to determine the correct chemotherapy dosage is that several factors cause interpatient variation in drug clearance, including the effects of obesity and variations in body composition, which simple measures of body size—height,

weight (*BMI*) and BSA—do not account for. Measures of overall body mass and size assume both homogenous body composition and drug distribution throughout the body. However, using these measures in isolation, especially in atypical populations, should be performed with caution since it is now widely acknowledged that they are unable to distinguish between fat and lean tissue, or provide information regarding the distribution of mass around the body [52]. The combination of these factors can reduce the confidence of practitioners when determining individualised chemotherapy dosages for people of atypical body types, particularly as they try to limit the risk of over-dosing and consequent excess toxicity, or under-dosing, leaving patients at risk of reduced anti-cancer effects from their treatment. It has been recommended that further research is needed to explore the use of body composition parameters, such as lean body mass and fat-free mass, when determining chemotherapy dosages, particularly for obese patients [53,54].

4. Chemotherapy Dosing for Obese Patients

Obesity among patients living with cancer is becoming increasingly common, with one in four UK adults classed as obese [55,56]. It has been linked to an increased risk of developing cancer, as well as outcomes in patients with cancer. For example, obesity is not only a risk factor for developing hormone receptor-positive breast cancer [57], but it has been shown that obese patients have worse overall survival than non-obese patients [58–61]. One possible explanation for this overall decrease in survival is that oncologists intentionally reduce cytotoxic chemotherapy dosages for obese patients according to their 'ideal bodyweight' or at a "capped" BSA of 2 m^2 [14,57]. This practice of 'dose capping' is performed to avoid the dose-limiting toxicity effects of chemotherapy treatment, including febrile neutropenia, which are thought to be caused by administering drug dosages that are calculated using actual bodyweight [62,63].

The effect of obesity on treatment-related toxicity remains debated in the literature. For example, Lote el. al. demonstrated that obese patients receiving uncapped chemotherapy do not experience increased rates of febrile neutropenia or toxicity compared with overweight or normal weight patients with early breast cancer [64,65], while Furlanetto et al. showed increased toxicity rates in obese patients [66]. Protani et al. in their meta-analysis suggests dose capping might in fact contribute to the reduced disease-free and overall survival outcomes for these patients [60,61,67,68]. These and other similar findings investigating other tumour groups [53,69,70] have contributed to the American Society of Clinical Oncology (ASCO) recently publishing guidelines that suggest that obese cancer patients should be treated using standard BSA-based chemotherapy dose prescriptions according to their actual bodyweight and should not be capped [14]. Further research to assess the appropriate dosing strategies for people with elevated body weight that includes pharmacokinetic and outcome data in those who are not dose-capped is needed to provide practitioners with evidence-based guidance for determining chemotherapy dosages for obese patients.

5. Chemotherapy Dosing in Patients with Amputations

Additional controversy exists around dosing in patients with amputations, although this is a less common occurrence than obese patients and is observed within clinical practice in patients with osteosarcoma. Like obesity, patients with limb loss are underrepresented in clinical trials, and no standard practice is described in the literature for chemotherapy dosing in this situation. Case reports of applying "rule of nines" [71], developed for the management of burns patients and the adjustment of chemotherapy doses, indicate that this appears to be inappropriate [72]. Amputated limbs may not contribute significantly to drug pharmacokinetics and therefore dose adjustments to account for this are not evidence based [72,73]. Further research is required to support evidence-based practice for dosing in patients with amputation.

6. Limitations of Traditional Body Measures

Traditional body measures—height, weight, lengths and girths—are utilised extensively within healthcare. However, these relatively simple measures fail to capture the 3D topography of the human body and the instruments used to obtain them in practice are the same as those that have been used since the end of the 19th century [74–77]. Despite their limitations, traditional measures are still relied upon due to their ease-of-use, low-cost and portability, and remain the standard that new measurement devices are evaluated against [78]. Though these simple measures are easy to capture and can be combined to create proxies of weight status, or descriptions of overall body shape, they do not capture the complex 3D variations in human form that result from variations in how mass is distributed around the body. These limitations of traditional body measures become particularly apparent within the context of chemotherapy dose calculation. As discussed, all of the BSA estimation formulae that have developed previously are based on non-linear functions of body weight and height, and so are susceptible to the same limitations as previously described. However, not only are these formulae used to estimate BSA described as 'rough approximations' [9], but the measure of BSA itself only represents a measure of the amount of exposed surface on a given 3D object [79]. This means that two individuals could have the same BSA value but still exhibit considerable differences in their external body shape, which could represent external expressions in their body mass distribution, body composition and consequent drug distribution and elimination processes. All of which have been found to be more meaningful for determining the dosage than measures of body size, such as BSA. The limitations of traditional body measures, which are used within BSA estimation formulae, are a leading source of inaccuracy within the current methods of chemotherapy dose calculation, with practitioners requiring more sophisticated body measurement tools to provide patients with individualised dosages.

7. Advanced Human Body Measurement Techniques

Recently, new measures of human body shape have been investigated that can provide additional information regarding morphological variations between individuals that cannot be obtained using traditional measures [80]. These measures of body shape have been shown to improve predictions of both the amount and distribution of fat within the human torso [81]. Derived indices—such as *BMI* and the waist–hip ratio (WHR)—are the primary method used to conduct clinical and population-level diagnostics of disease risk [82,83], estimate body composition [84–86] and prescribe drug dosages, as in the case of BSA. These derived indices provide simple proxies of fat distribution and body shape, which can be easily obtained and interpreted by practitioners and patients. However, they are also considered a relatively unsophisticated approach to assessing body composition and health risk, reducing the complexity of human form down to a single one-dimensional value. Contemporary studies instead use more direct imaging approaches, such as magnetic resonance imaging (MRI) or computed tomography (CT) scanning to assess fat distribution [87,88]. Despite their high accuracy, MRI and CT are not ideal for routine practice due to their high cost and harmful radiation exposure, making anthropometry the most practical solution.

More sophisticated measures of body shape could surpass the use of body girths in obesity assessment and health monitoring, providing finer morphological distinctions in body characteristics [52,77,80]. The reason for this being that shape measures can identify scale-invariant variations in external human form [89] and complement existing anthropometrics when estimating body composition [81,90]. Modern three-dimensional (3D) imaging systems have been used increasingly to investigate new measures of body shape [77,90–92], and novel body shape indices, such as the surface-based body shape index (SBSI) [93]. Recently, researchers have used 3D imaging devices to assess the validity of existing BSA estimation formulae, as well as suggest improvements to parameters within these formulae [16,46,51,94]. These studies reported the excellent reliability of 3D-imaging-derived BSA measurements and demonstrated the inaccuracies of existing BSA estimation formulae. However, none of these previous studies investigated the use of 3D imaging

technology to calculate BSA and subsequent chemotherapy dosages in practice compared to existing BSA estimation formulae. Therefore, future studies that investigate how alterations in dosage relate to error in BSA measurement to inform the future development of improved dose calculation methods are needed. Previously, instrumented booth 3D imaging devices have been too large and expensive to be feasibly used in practice, typically costing more than USD 100,000 and measuring approximately 2.0 m in width and 3.0 m in height. However, recent developments in low-cost, smartphone-based systems that can acquire 3D imaging data have led to increased accessibility of this technology [95]. For example, Size Stream LLC has developed a smartphone-based application, which enables 3D imaging data to be collected anywhere, with no hardware installation requirements or additional costs above that of the price of a standard smartphone [96]. Further research investigating the use of advanced body measures within chemotherapy dosing must ensure that any measurement device is quick and easy-to-use, compact and low-cost to enable all practitioners to acquire this information without relying on expensive, non-portable 3D imaging devices. Advanced body measurement techniques using modern digital technology, such as smartphone-based 3D imaging devices, enables the surface area of the entire body, or of individual body segments to be measured from a single image, offering a potentially viable alternative method of calculating chemotherapy dosing.

8. Conclusions

Despite recent developments in targeted, hormonal and immunotherapies, conventional cytotoxic chemotherapy will continue to play an important role in the management and treatment of patients diagnosed with cancer. However, existing body-surface-area-based dosing strategies have limited validity, particularly with modern populations that tend to display higher *BMI* values. Inaccuracies in estimations from developed formulae can be so large that they could significantly affect patients' morbidity and mortality, particularly in severely underweight or overweight patients that differ from a standard physique. Advanced methods of human measurement and analysis can extract more meaningful information about morphological variation, which cannot be identified by traditional techniques, and represent a viable alternative method for practitioners to calculate individualised chemotherapy dosages. Investigations to develop improved methods for determining cytotoxic chemotherapy dosage for people with atypical body types using advanced body measurement techniques compared to traditional methods are currently ongoing. The long-term goal of this research is to reduce incidences of incorrect dosing and its negative effects on treatment, which remains a research priority.

Author Contributions: Conceptualization, M.T. and N.M.; writing—original draft preparation, M.T.; writing—review and editing, M.T., N.M., R.A. and A.M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Reading, B.D.; Freeman, B. Simple formula for the surface area of the body and a simple model for anthropometry. *Clin. Anat.* **2005**, *18*, 126–130. [CrossRef]
2. Gurney, H. Dose calculation of anticancer drugs: A review of the current practice and introduction of an alternative. *JCO* **1996**, *14*, 2590–2611. [CrossRef] [PubMed]
3. Gurney, H. How to calculate the dose of chemotherapy. *Br. J. Cancer* **2002**, *86*, 1297. [CrossRef] [PubMed]
4. Ratain, M.J. Body-surface area as a basis for dosing of anticancer agents: Science, myth, or habit? *J. Clin. Oncol.* **1998**, *16*, 2297–2298. [CrossRef]

5. Kaestner, S.A.; Sewell, G.J. Chemotherapy Dosing Part I: Scientific Basis for Current Practice and Use of Body Surface Area. *Clin. Oncol. (R. Coll. Radiol.)* **2006**, *19*, 23–37. [CrossRef]
6. Kaestner, S.A.; Sewell, G.J. Chemotherapy Dosing Part II: Alternative Approaches and Future Prospects. *Clin. Oncol. (R. Coll. Radiol.)* **2007**, *19*, 99–107. [CrossRef]
7. Palumbo, M.; Kavan, P.; Miller, W.; Panasci, L.; Assouline, S.; Johnson, N.; Cohen, V.; Patenaude, F.; Pollak, M.; Jagoe, R.; et al. Systemic cancer therapy: Achievements and challenges that lie ahead. *Front. Pharmacol.* **2013**, *4*, 57. [CrossRef] [PubMed]
8. Pinkel, D. The use of body surface area as a criterion of drug dosage in cancer chemotherapy. *Cancer Res.* **1958**, *18*, 853–856. [PubMed]
9. Freireich, E.J.; Gehan, E.A.; Rall, D.P.; Schmidt, L.H.; Skipper, H.E. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. *Cancer Chemother. Rep.* **1966**, *50*, 219–244.
10. Pinkel, D. Cancer chemotherapy and body surface area. *J. Clin. Oncol.* **1998**, *16*, 3714–3715. [CrossRef] [PubMed]
11. Farber, S.; Pinkel, D.; Sears, E.M.; Toch, R. Advances in chemotherapy of cancer in man. *Adv. Cancer Res.* **1956**, *4*, 1–71. [CrossRef]
12. Baker, S.D.; Verweij, J.; Rowinsky, E.K.; Donehower, R.C.; Schellens, J.H.M.; Grochow, L.B.; Sparreboom, A. Role of body surface area in dosing of investigational anticancer agents in adults, 1991–2001. *J. Natl. Cancer Inst.* **2002**, *94*, 1883–1888. [CrossRef] [PubMed]
13. Beumer, J.H.; Chu, E.; Salamone, S.J. Body-surface area-based chemotherapy dosing: Appropriate in the 21st century? *J. Clin. Oncol.* **2012**, *30*, 3896–3897. [CrossRef] [PubMed]
14. Griggs, J.J.; Mangu, P.B.; Anderson, H.; Balaban, E.P.; Dignam, J.J.; Hryniuk, W.M.; Morrison, V.A.; Pini, T.M.; Runowicz, C.D.; Rosner, G.L.; et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J. Clin. Oncol.* **2012**, *30*, 1553–1561. [CrossRef] [PubMed]
15. Miller, A.A.; Rosner, G.L.; Egorin, M.J.; Hollis, D.; Lichtman, S.M.; Ratain, M.J. Prospective evaluation of body surface area as a determinant of paclitaxel pharmacokinetics and pharmacodynamics in women with solid tumors: Cancer and Leukemia Group B Study 9763. *Clin. Cancer Res.* **2004**, *10*, 8325–8331. [CrossRef]
16. Redlarski, G.; Palkowski, A.; Krawczuk, M. Body surface area formulae: An alarming ambiguity. *Sci. Rep.* **2016**, *6*, 27966. [CrossRef]
17. Stadtmauer, E.A.; O'Neill, A.; Goldstein, L.J.; Crilley, P.A.; Mangan, K.F.; Ingle, J.N.; Brodsky, I.; Martino, S.; Lazarus, H.M.; Erban, J.K.; et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Philadelphia Bone Marrow Transplant Group. *N. Engl. J. Med.* **2000**, *342*, 1069–1076. [CrossRef]
18. Bergh, J.; Wiklund, T.; Erikstein, B.; Lidbrink, E.; Lindman, H.; Malmström, P.; Kellokumpu-Lehtinen, P.; Bengtsson, N.O.; Söderlund, G.; Anker, G.; et al. Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: A randomised trial. Scandinavian Breast Group 9401 study. *Lancet* **2000**, *356*, 1384–1391. [CrossRef] [PubMed]
19. Havrilesky, L.J.; Reiner, M.; Morrow, P.K.; Watson, H.; Crawford, J. A review of relative dose intensity and survival in patients with metastatic solid tumors. *Crit. Rev. Oncol. Hematol.* **2015**, *93*, 203–210. [CrossRef]
20. Lyman, G.H.; Dale, D.C.; Crawford, J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices. *J. Clin. Oncol.* **2003**, *21*, 4524–4531. [CrossRef]
21. Lyman, G.H.; Dale, D.C.; Friedberg, J.; Crawford, J.; Fisher, R.I. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: A nationwide study. *J. Clin. Oncol.* **2004**, *22*, 4302–4311. [CrossRef]
22. Nielson, C.M.; Bylsma, L.C.; Fryzek, J.P.; Saad, H.A.; Crawford, J. Relative Dose Intensity of Chemotherapy and Survival in Patients with Advanced Stage Solid Tumor Cancer: A Systematic Review and Meta-Analysis. *Oncologist* **2021**, *26*, e1609–e1618. [CrossRef]
23. Wonders, K.Y.; Schmitz, K.; Harness, J. Dose Delays, Dose Reductions, and Relative Total Dose Intensity in Patients With Advanced Cancer Who Exercised During Neoadjuvant Chemotherapy Treatment. *Integr. Cancer Ther.* **2023**, *22*, 15347354231168368. [CrossRef]
24. Du Bois, D.; Du Bois, E.F. Clinical calorimetry: Tenth paper a formula to estimate the approximate surface area if height and weight be known. *Arch. Intern. Med.* **1916**, *17*, 863–871. [CrossRef]
25. Reilly, J.J.; Workman, P. Is body composition an important variable in the pharmacokinetics of anticancer drugs? A review and suggestions for further research. *Cancer Chemother. Pharmacol.* **1994**, *34*, 3–13. [CrossRef] [PubMed]
26. Veal, G.J.; Coulthard, S.A.; Boddy, A.V. Chemotherapy individualization. *Investig. New Drugs* **2003**, *21*, 149–156. [CrossRef] [PubMed]
27. Meeh, K.V. Ober flachenmessungen des menschlichen korpers. *Z. Biol.* **1879**, *15*, 425–458.
28. Faber, H.K.; Melcher, M.S. A modification of the Du Bois height-weight formula for surface areas of newborn infants. *Proc. Soc. Exp. Biol. Med.* **1921**, *19*, 53–54. [CrossRef]
29. Takahira, H. Metabolism of the Japanese. In *No. 1 in Imperial Government Institute of Nutrition Report 1*; Rept. Imper. Govt. Inst. For Nutrition: Tokyo, Japan, 1925; pp. 61–95.
30. Breitman, M. Eine vereinfachte Methodik der K6rperoberflfichenbestimmung. *Scitti Biol.* **1932**, *7*, 395–399.
31. Boyd, E. *The Growth of the Surface Area of the Human Body*; University of Minnesota Press: Minneapolis, MN, USA, 1935.

32. Stevenson, P.H. Height-weight-surface formula for the estimation of surface area in Chinese subjects. *Chin. J. Physiol.* **1937**, *12*, 327–330.
33. Sendroy, J.J.; Cecchini, L.P. Determination of human body surface area from height and weight. *J. Appl. Physiol.* **1954**, *7*, 1–12. [CrossRef] [PubMed]
34. Banerjee, S.; Sen, R. Determination of the Surface Area of the Body of Indians. *J. Appl. Physiol.* **1955**, *7*, 585–588. [CrossRef]
35. Choi, W.R. The Body Surface Area of Koreans. Ph.D. Thesis, Seoul National University, Seoul, Republic of Korea, 1956.
36. Mehra, N.C. Body Surface Area of Indians. *J. Appl. Physiol.* **1958**, *12*, 34–36. [CrossRef]
37. Banerjee, S.; Ashim, K.B. Determination of body surface area in Indian Hindu children. *J. Appl. Physiol.* **1961**, *16*, 969–970. [CrossRef]
38. Fujimoto, S.; Watanabe, T.; Sakamoto, A.; Yukawa, K.; Morimoto, K. Studies on the physical surface area of Japanese. 18. Calculation formulas in three stages over all ages. *Nihon Eiseigaku Zasshi* **1968**, *23*, 443–450. [CrossRef]
39. Gehan, E.; George, S. Estimation of Human Body Surface Area from Height and Weight. *Cancer Chemother. Rep. Part 1* **1970**, *54*, 225–235.
40. Haycock, G.B.; Schwartz, G.J.; Wisotsky, D.H. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. *J. Pediatr.* **1978**, *93*, 62–66. [CrossRef]
41. Mosteller, R.D. Simplified calculation of body-surface area. *N. Engl. J. Med.* **1987**, *317*, 1098. [CrossRef] [PubMed]
42. Mattar, J.A. A simple calculation to estimate body surface area in adults and its correlation with the Du Bois formula. *Crit. Care Med.* **1989**, *17*, 846–847. [CrossRef]
43. Nwoye, L.O. Body surface area of Africans: A study based on direct measurements of Nigerian males. *Hum. Biol.* **1989**, *61*, 439–457.
44. Shuter, B.; Aslani, A. Body surface area: Du Bois and Du Bois revisited. *Eur. J. Appl. Physiol.* **2000**, *82*, 250–254. [CrossRef]
45. Livingston, E.H.; Lee, S. Body surface area prediction in normal-weight and obese patients. *Am. J. Physiol. Endocrinol. Metab.* **2001**, *281*, E586–E591. [CrossRef] [PubMed]
46. Tikuisis, P.; Meunier, P.; Jubenville, C.E. Human body surface area: Measurement and prediction using three dimensional body scans. *Eur. J. Appl. Physiol.* **2001**, *85*, 264–271. [CrossRef]
47. Nwoye, L.O.; Al-Shehri, M.A. A formula for the estimation of the body surface area of Saudi male adults. *Saudi Med. J.* **2003**, *24*, 1341–1346. [PubMed]
48. Yu, C.; Lo, Y.; Chiou, W. The 3D scanner for measuring body surface area: A simplified calculation in the Chinese adult. *Appl. Ergon.* **2003**, *34*, 273. [CrossRef]
49. Schlich, E.; Schumm, M.; Schlich, M. 3D-Body-Scan als anthropometrisches Verfahren zur Bestimmung der spezifischen Körperoberfläche. *Wiss. Forsch.* **2010**, *4*, 178–183.
50. Yu, C.; Lin, C.; Yang, Y. Human body surface area database and estimation formula. *Burns* **2010**, *36*, 616–629. [CrossRef] [PubMed]
51. Kühnapfel, A.; Ahnert, P.; Loeffler, M.; Scholz, M. Body surface assessment with 3D laser-based anthropometry: Reliability, validation, and improvement of empirical surface formulae. *Eur. J. Appl. Physiol.* **2017**, *117*, 371–380. [CrossRef] [PubMed]
52. Wells, J.C.K.; Treleaven, P.; Cole, T.J. BMI compared with 3-dimensional body shape: The UK National Sizing Survey. *Am. J. Clin. Nutr.* **2007**, *85*, 419–425. [CrossRef]
53. Stocker, G.; Hacker, U.T.; Fiteni, F.; John Mahachie, J.; Roth, A.D.; Van Cutsem, E.; Peeters, M.; Lordick, F.; Mauer, M. Clinical consequences of chemotherapy dose reduction in obese patients with stage III colon cancer: A retrospective analysis from the PETACC 3 study. *Eur. J. Cancer* **2018**, *99*, 49–57. [CrossRef] [PubMed]
54. Drami, I.; Pring, E.T.; Gould, L.; Malietzis, G.; Naghibi, M.; Athanasiou, T.; Glynne-Jones, R.; Jenkins, J.T. Body Composition and Dose-limiting Toxicity in Colorectal Cancer Chemotherapy Treatment; a Systematic Review of the Literature. Could Muscle Mass be the New Body Surface Area in Chemotherapy Dosing? *Clin. Oncol.* **2021**, *33*, e540–e552. [CrossRef] [PubMed]
55. Statistics on Obesity, Physical Activity and Diet (Replaced by Statistics on Public Health). Available online: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet (accessed on 5 December 2023).
56. Obesity, Weight and Cancer. Available online: https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/obesity-weight-and-cancer (accessed on 5 December 2023).
57. Sinicrope, F.A.; Dannenberg, A.J. Obesity and Breast Cancer Prognosis: Weight of the Evidence. *JCO* **2011**, *29*, 4–7. [CrossRef]
58. Copson, E.R.; Cutress, R.I.; Maishman, T.; Eccles, B.K.; Gerty, S.; Stanton, L.; Altman, D.G.; Durcan, L.; Wong, C.; Simmonds, P.D.; et al. Obesity and the outcome of young breast cancer patients in the UK: The POSH study. *Ann. Oncol.* **2015**, *26*, 101–112. [CrossRef] [PubMed]
59. Chan, D.S.M.; Vieira, A.R.; Aune, D.; Bandera, E.V.; Greenwood, D.C.; McTiernan, A.; Navarro Rosenblatt, D.; Thune, I.; Vieira, R.; Norat, T. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann. Oncol.* **2014**, *25*, 1901–1914. [CrossRef] [PubMed]
60. Rosner, G.L.; Hargis, J.B.; Hollis, D.R.; Budman, D.R.; Weiss, R.B.; Henderson, I.C.; Schilsky, R.L. Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: Results from cancer and leukemia group B study 8541. *JCO* **1996**, *14*, 3000–3008. [CrossRef]
61. Griggs, J.J.; Sorbero, M.E.S.; Lyman, G.H. Undertreatment of obese women receiving breast cancer chemotherapy. *Arch. Intern. Med.* **2005**, *165*, 1267–1273. [CrossRef]

62. Lyman, G.H.; Lyman, C.H.; Agboola, O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist* **2005**, *10*, 427–437. [CrossRef]
63. Kuderer, N.M.; Dale, D.C.; Crawford, J.; Cosler, L.E.; Lyman, G.H. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* **2006**, *106*, 2258–2266. [CrossRef] [PubMed]
64. Lote, H.; Sharp, A.; Redana, S.; Papadimitraki, E.; Capelan, M.; Ring, A. Febrile Neutropenia Rates According to Body Mass Index and Dose Capping in Women Receiving Chemotherapy for Early Breast Cancer. *Clin. Oncol. (R. Coll. Radiol.)* **2016**, *28*, 597–603. [CrossRef] [PubMed]
65. Carroll, J.P.; Protani, M.M.; Nguyen, L.; Cheng, M.E.; Fay, M.; Saleem, M.; Pillay, P.S.; Walpole, E.; Martin, J.H. Toxicity and tolerability of adjuvant breast cancer chemotherapy in obese women. *Med. Oncol.* **2014**, *31*, 881. [CrossRef]
66. Furlanetto, J.; Eiermann, W.; Marmé, F.; Reimer, T.; Reinisch, M.; Schmatloch, S.; Stickeler, E.; Thomssen, C.; Untch, M.; Denkert, C.; et al. Higher rate of severe toxicities in obese patients receiving dose-dense (dd) chemotherapy according to unadjusted body surface area: Results of the prospectively randomized GAIN study. *Ann. Oncol.* **2016**, *27*, 2053–2059. [CrossRef]
67. Protani, M.; Coory, M.; Martin, J.H. Effect of obesity on survival of women with breast cancer: Systematic review and meta-analysis. *Breast Cancer Res. Treat.* **2010**, *123*, 627–635. [CrossRef] [PubMed]
68. Carroll, J.; Protani, M.; Walpole, E.; Martin, J.H. Effect of obesity on toxicity in women treated with adjuvant chemotherapy for early-stage breast cancer: A systematic review. *Breast Cancer Res. Treat.* **2012**, *136*, 323–330. [CrossRef] [PubMed]
69. Morrison, V.A.; McCall, L.; Muss, H.B.; Jatoi, A.; Cohen, H.J.; Cirrincione, C.T.; Ligibel, J.A.; Lafky, J.M.; Hurria, A. The impact of actual body weight-based chemotherapy dosing and body size on adverse events and outcome in older patients with breast cancer: Results from Cancer and Leukemia Group B (CALGB) trial 49907 (Alliance A151436). *J. Geriatr. Oncol.* **2018**, *9*, 228–234. [CrossRef] [PubMed]
70. Lyman, G.H.; Sparreboom, A. Chemotherapy dosing in overweight and obese patients with cancer. *Nat. Rev. Clin. Oncol.* **2013**, *10*, 451–459. [CrossRef] [PubMed]
71. Knaysi, G.A.; Crikelair, G.F.; Cosman, B. The role of nines: Its history and accuracy. *Plast. Reconstr. Surg.* **1968**, *41*, 560–563. [CrossRef]
72. Owen, D.; O'Reilly, E.M.; Ang, C.; Ma, J.; Do, R.K.G.; Abou-Alfa, G.K. Optimal chemotherapy dosing in a bilateral lower extremities amputee with metastatic pancreatic adenocarcinoma. *Gastrointest. Cancer Res.* **2013**, *6*, 93–94. [PubMed]
73. Hutson, P.R. Using body surface area adjustments in amputees. *Am. J. Hosp. Pharm.* **1985**, *42*, 1048–1049. [CrossRef] [PubMed]
74. Simmons, K.P.; Istook, C.L. Body measurement techniques. *J. Fash. Mark. Manag.* **2003**, *7*, 306–332.
75. Bragança, S.; Arezes, P.; Carvalho, M.; Ashdown, S.P. Current state of the art and enduring issues in anthropometric data collection. *Dyna* **2016**, *83*, 22–30.
76. Tsang, B.; Chan, C.K.; Taylor, G.; Tsangc, B.; Taylor, K.C. Kinanthropometry study of the physique of disciplined personnel. *Int. J. Cloth. Sci. Technol.* **2000**, *12*, 144–160.
77. Löffler-Wirth, H.; Willscher, E.; Ahnert, P.; Wirkner, K.; Engel, C.; Loeffler, M.; Binder, H. Novel anthropometry based on 3D-bodyscans applied to a large population based cohort. *PLoS ONE* **2016**, *11*, e0159887. [CrossRef] [PubMed]
78. Bretschneider, T.; Koop, U.; Schreiner, V.; Wenck, H.; Jaspers, S. Validation of the body scanner as a measuring tool for a rapid quantification of body shape. *Ski. Res. Technol.* **2009**, *15*, 364–369.
79. Oxford Dictionaries. In *Concise Oxford English Dictionary*; Oxford University Press: Oxford, UK, 2008.
80. Thelwell, M.; Bullas, A.; Kühnapfel, A.; Hart, J.; Ahnert, P.; Wheat, J.; Loeffler, M.; Scholz, M.; Choppin, S. Modelling of human torso shape variation inferred by geometric morphometrics. *PLoS ONE* **2022**, *17*, e0265255. [CrossRef]
81. Choppin, S.; Bullas, A.; Thelwell, M. Torso Shape Improves the Prediction of Body Fat Magnitude and Distribution. *Int. J. Environ. Res. Public Health* **2022**, *19*, 8302. [CrossRef] [PubMed]
82. Wells, J.C.K.; Ruto, A.; Treleaven, P. Whole-body three-dimensional photonic scanning: A new technique for obesity research and clinical practice. *Int. J. Obes.* **2008**, *32*, 232–238. [CrossRef]
83. Kühnapfel, A.; Ahnert, P.; Loeffler, M.; Broda, A.; Scholz, M. Reliability of 3D laser-based anthropometry and comparison with classical anthropometry. *Sci. Rep.* **2016**, *6*, 26672. [CrossRef] [PubMed]
84. Duren, D.L.; Sherwood, R.J.; Czerwinski, S.A.; Lee, M.; Choh, A.C.; Siervogel, R.M.; Chumlea, W.C. Body composition methods: Comparisons and interpretation. *J. Diabetes Sci. Technol.* **2008**, *2*, 1139–1146. [CrossRef] [PubMed]
85. Lee, J.J. Assessment of Body Composition: Total, Central, and Regional Adiposity via Stereovision Body Imaging. Ph.D. Thesis, The University of Texas, Austin, TX, USA, 2014.
86. Hume, P.A.; Ackland, T. Physical and Clinical Assessment of Nutritional Status. In *Nutrition in the Prevention and Treatment of Disease*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 71–84.
87. Deurenberg, P.; Schutz, Y. Body composition: Overview of methods and future directions of research. *Ann. Nutr. Metab.* **1995**, *39*, 325–333. [CrossRef] [PubMed]
88. Wells, J.C.K.; Fewtrell, M.S. Measuring body composition. *Arch. Dis. Child.* **2006**, *91*, 612–617. [CrossRef]
89. Thelwell, M.; Chiu, C.Y.; Bullas, A.; Hart, J.; Wheat, J.; Choppin, S. How shape-based anthropometry can complement traditional anthropometric techniques: A cross-sectional study. *Sci. Rep.* **2020**, *10*, 12125.
90. Ng, B.K.; Sommer, M.J.; Wong, M.C.; Pagano, I.; Nie, Y.; Fan, B.; Kennedy, S.; Bourgeois, B.; Kelly, N.; Liu, Y.E.; et al. Detailed 3-dimensional body shape features predict body composition, blood metabolites, and functional strength: The Shape Up! Studies. *Am. J. Clin. Nutr.* **2019**, *110*, 1316–1326. [CrossRef] [PubMed]

91. Heymsfield, S.B.; Bourgeois, B.; Ng, B.K.; Sommer, M.J.; Li, X.; Shepherd, J.A. Digital anthropometry: A critical review. *Eur. J. Clin. Nutr.* **2018**, *72*, 680–687. [CrossRef] [PubMed]
92. Pleuss, J.D.; Talty, K.; Morse, S.; Kuiper, P.; Scioletti, M.; Heymsfield, S.B.; Thomas, D.M. A machine learning approach relating 3D body scans to body composition in humans. *Eur. J. Clin. Nutr.* **2019**, *73*, 200–208. [CrossRef] [PubMed]
93. Rahman, S.A.; Adjeroh, D. Surface-based body shape index and its relationship with all-cause mortality. *PLoS ONE* **2015**, *10*, e0144639. [CrossRef] [PubMed]
94. Redlarski, G.; Krawczuk, M.; Palkowski, A. Evaluation of Body Surface Area Formulae Based on 3D Body Scans. In Proceedings of the 3DBODY TECH 2017—8th International Conference and Exhibition on 3D Body Scanning and Processing Technologies, Montreal, QC, Canada, 11–12 October 2017. [CrossRef]
95. Bullas, A.M.; Greenwood, R.; Thelwell, M.; Choppin, S. A Review of Commercially Available 3D Surface Imaging Systems for Body Composition Estimation. *Appl. Sci.* **2022**, *12*, 8815. [CrossRef]
96. Size Stream—Our Technology. Available online: https://www.sizestream.com/technology (accessed on 5 January 2024).