ORIGINAL ARTICLE

Optimal MRI interval for detection of asymptomatic recurrence in surgically treated early cervical cancer by use of a mathematical model

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Abstract

Introduction: Applications of mathematical modeling may provide an insight into the timing of surveillance modalities. We aimed to determine the optimal magnetic resonance imaging (MRI) interval for the detection of surgically treated early cervical cancer asymptomatic recurrence by using a mathematical model for volumetric tumor growth time.

Methods: We assumed that tumor volume increases by a factor equal to the basis of natural logarithms (e~2.718) at constant time intervals. Using a mathematical formula, the tumor volume (V) was converted to diameter (D), which could be expressed as a function of time (t), given an initial diameter Di (corresponding to initial volume Vi) and a constant DT, where DT is the time required for volumetric tumor growth by a factor (e). Three different DTs were used for demonstration of the model, i.e. 20, 100 and 400 days.

Results: Assuming complete surgical clearance, a worst-case scenario for a 20-day DT indicated that a 20 μm cervical tumor would need at least 12 months to reach 10 mm in diameter, which would be detected with an annual surveillance interval MRI. Over a 5-year (60 months) follow-up, nearly five surveillance MRIs would be required if the threshold of 10 mm was desired. For a 100-day DT over a 5-year (60 months) follow-up, a single only MRI would be required, if the threshold of 10 mm was desired. In the case of an indolent tumor (DT is 400 days), the model would not recommend a surveillance MRI to detect asymptomatic recurrence. A positive linear association between optimal MRI intervals and volumetric tumor DTs was demonstrated.

Conclusion: In the absence of evidence, we postulate annual MRI scanning is probably the shortest interval, which can be clinically useful for optimization of routine surveillance follow-up protocols in surgically treated early cervical cancer. This mathematical model requires proper verification in prospective clinical studies. Hippokratia 2016, 20(1): 4-8

Keywords: Cervical cancer, mathematical model, optimal MRI interval, tumor growth

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Introduction

Most patients with early stage cervical cancer [International Federation of Gynecology and Obstetrics (FIGO) Stage IA1-IB1] are successfully treated with surgery only and chemo-radiotherapy in the case of locally advanced disease. Approximately 11-17% will develop recurrence following surgical management[1]. Recurrence typically occurs early in the course of the disease with almost 70% of cases occurring within two years of treatment completion[2]. The main aim of postoperative surveillance is the detection of recurrence at a time, amenable to curative salvage treatment, in order to positively impact survival[3]. The type of routine surveillance strategy has been the subject of great debate[4]. The routine follow-up of patients consists of clinical history, physical examination, vault cytology and radiological imaging, depending on the surveillance policy of the institution. Typically, women who are disease free at the end of their primary treatment are followed up every three months within the first two years, every six months for the next three years and annually thereafter until year ten, at the discretion of the physician[5]. Imaging is undertaken only if strongly indicated by clinical symptoms or signs. The ability of magnetic resonance imaging (MRI) to delineate the tumor extent with high precision has significantly improved the quantitative assessment of tumor volume including cervical cancer[6].

The doubling time (DT) is one way of modeling how fast cancer cells grow and depends onthe tumor type, grade,and location. A single cell needs 30 doublings to

reach a noticeable size (1cm)-10^6 cells. Tumor DT varies from 8 to 600 days, averaging 100 to 120 days. DTs have been reported for lung cancer[7], breast cancer[8], and malignant melanomas[9]. However, no studies have reported on DT for cervical cancer. Volumetric DT is a concept applicable to cervical cancer due to its irregular shape. Sequential tumor volumetry using MRI can help distinguish aggressive cancer from slow-growing tumours[10]. Introducing an interval MRI to assess the tumor DT would help predict the time of asymptomatic recurrence.

No strictly defined follow-up protocols are available for women after they complete primary treatment for early cervical cancer[11]. In addition, no randomized controlled trial (RCT) had looked at outcomes following treatment of early detected asymptomatic recurrence. Recent evidence from retrospective studies supports a better prognosis for the asymptomatic patients, which would necessitate some type of surveillance program[12]. In the absence of evidence to define the best surveillance protocol in early cervical cancer, we aimed to develop a mathematical model in order to provide a scientific base to a prospective study comparing MRI at said intervals to routine follow-up protocols for the detection of asymptomatic recurrence.

Methods

Hypothesis

Recurrence is unlikely immediately after the tumor has been surgically removed, assuming histological clearance. It can occur due to single spread with clonal expansion at the site of seeding, which is best determined by DT. If sequential MRIs were available, the tumor DT could be calculated with ease, albeit it is unethical to justify performing sequential imaging before primary surgery. If the DT is known, assuming that recurrence occurs from a single cell 20 μm, the time for the recurrent tumor to grow to 10 mm can be calculated. This is the minimum size for measurable lesions required by the Revised Response Evaluation Criteria in Solid Tumors (RECIST) assuming that slice thickness is no greater than 5 mm[13]. Knowing the volumetric DT and the time from primary surgery would then allow calculating the time interval from completion of surgery for the recurrent cervical tumor to be visible on a surveillance MRI.

If no tumor is detected with MRI, then the same assumption that a recurrent tumor may be still present but below the 5 mm detection size remains; thus the interval to detect it growing to 10 mm will be the same as above. Hence, one can calculate the number of MRIs required to detect asymptomatic recurrence within a follow-up period of five years. Another assumptionis that volumetric DT remains constant over time. The model can then be applied for patients with surgically treated only, early cervical cancer, assuming they were disease-free at the end of surgery. In this work, the essential assumption of constant volumetric DT is slightly modified in that volumetric tumor growth increases by a factor equal to (e~2.718), which is the base of natural logarithms. This exponential increment has been demonstrated in several physical and biological processes and (e) has been extensively utilized in biological as well as mathematical modeling.

Modeling

The difference between diameter based increment time and volume growth time needs to be highlighted. Collins et al, described how to calculate tumor volume in terms of the number of tumor doublings from a single neoplastic cell origin (with an average diameter of 20 μm) assuming exponential tumor growth[14]. As mentioned, the model is modified according to the assumption that tumor growth by a factor equal to (e~2.718) occurs at constant time intervals and for convenience, this is denoted by DT throughout the entire text.

Assuming DT is a constant volumetric growth time by a factor (e), one might conclude that the time needed for (k) volumetric growths, (each one by a factor of e), is:

$$t = k \cdot DT \quad (1)$$

At that time-point (k growths) the tumor volume becomes:

$$V = V_i \cdot ek \quad (2)$$

or, if the number of growths (k) is required instead, $k = ln(V/V_i)/ln\ (e) \rightarrow k = ln(V/V_i)$

where by V_i, an initial tumor volume, as detected and measured by MRI is denoted. Hence, from (1) and (2), the following relationship may hold for the tumor volume at any time (t) as a function of an initially detected volume V_i, given a constant DT:

$$V = V_i \cdot e^{\,t/DT} \quad (3)$$

The tumor volume (detectable with MRI) as a function of its diameter (D), is:

$$V = \left(\frac{4\pi}{3}\right) \cdot \left(\frac{D}{2}\right)^3 \quad (4)$$

Therefore, at any time-point, the diameter (D) may be expressed as a function of time (t), given an initial diameter Di (corresponding to volume Vi) and a constant DT:

$$V = V_i \cdot e^{t/DT} \Rightarrow \left(\frac{4\pi}{3}\right) \cdot \left(\frac{D}{2}\right)^3 = \left(\frac{4\pi}{3}\right) \cdot \left(\frac{D_i}{2}\right)^3 \cdot e^{t/DT} \Rightarrow D = D_i \cdot e^{t/3 \cdot DT} \quad (5)$$

For example, for a tumor diameter of D =2 cm and an initial diameter of Di =0.002 cm, i.e. 20 μm, the volume ratio V/Vi =(D/Di)3 =109, which corresponds to k = t/DT ~21 volume growths by e.

From equation (5), by solving for (t), one might extract a relationship of the time (t) required to obtain any preset diameter (Do), as a function of assumed DT. There-

fore, the following series of algebraic relationships holds, using neperian logarithms on both parts of equation5:

$$D_o = D_i \cdot e^{1/3 \cdot DT} \Rightarrow \left(\frac{D_o}{D_i}\right) = e^{1/3 \cdot DT} \Rightarrow \ln\left(\frac{D_o}{D_i}\right) = \ln\left(e^{1/3 \cdot DT}\right) \Rightarrow$$
$$\Rightarrow 1/3 \cdot DT = \ln\left(\frac{D_o}{D_i}\right) \Rightarrow t = 3 \cdot DT \cdot \ln\left(\frac{D_o}{D_i}\right) \quad (6)$$

The choice of Do at 10mm was made as this size would model asymptomatic recurrence. Three volumetric DTs were utilized for demonstration of the formula; 20, 100 and 400 days. In the absence of available literature regarding growth rates for cervical cancer, we referenced data for various histological types such as squamous cell carcinoma (SCC) and adenocarcinoma (AC). Histology appears to influence tumor growth. In lung cancer, DTs can be as low as 20 days for SCC and 400 days and beyond for AC[15]. In cervical cancer, AC may have a poorer prognosis than SCC with higher recurrence rates[16]. The average DT for cancer is 100 days[17]. Utilizing the shortest and longest half-lives for early cervical cancer growth rate would model the worst and best-case scenarios respectively.

Results

Assuming complete surgical clearance of an early stage cervical cancer and that recurrence occurs from a single cell, 20 μm in diameter, for a DT of 20 days, an interval of ≥12 months is required to reach 10 mm. Therefore, over a 5-year (60 months) follow-up, almost five MRIs would be required if a threshold of 10 mm was desired (Figure 1).

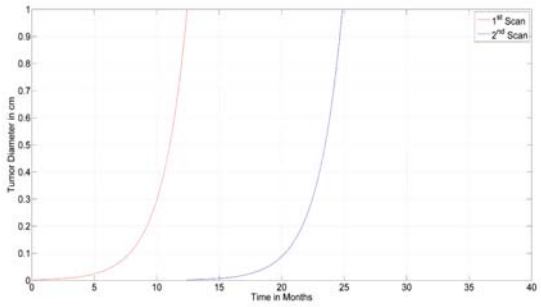

Figure 1: Time to detection of surgically treated early stage cervical cancer asymptomatic recurrenceassuming a 20-day growing time by a factor equal to e (high-risk tumor). An optimal surveillance magnetic resonance imaging (MRI) aims to detect a 10 mm diameter recurrent tumor growing from an initial diameter 0.00002 m (20 μm).

A 20 μm single cervical cancer cell with a DT of 100 days will need almost 62 months to reach 10 mm in diameter. This suggests that a single MRI would be only required over a 5-year follow-up period if a threshold of 10 mm was desired (Figure 2). Likewise, if a tumor is indolent (DT is 400 days), it would take an estimated 250 months (>21 years) for the first surveillance MRI to detect asymptomatic recurrence (Figure 3).

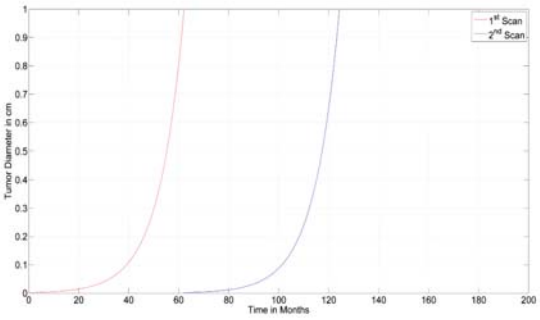

Figure 2: Time to detection of surgically treated early stage cervical cancer asymptomatic recurrence a 100-day growing time by a factor equal to e (medium risk tumor). An optimal surveillance magnetic resonance imaging (MRI) aims to detect a 10 mm diameter recurrent tumor growing from an initial diameter 0.00002 m (20 μm).

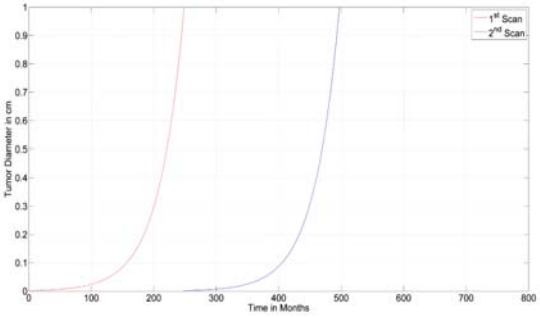

Figure 3: Time to detection of surgically treated early stage cervical cancer asymptomatic recurrence assuming a 400-day growing time by a factor equal to e (indolent tumor). An optimal surveillance magnetic resonance imaging (MRI) aims to detect a 10 mm diameter recurrent tumor growing from an initial diameter 0.00002 m (20 μm).

From equation (6) and assuming Do =1o mm and Di =20 μm (0.00002 m), the time required to reach an endpoint diameter might be modeled, at least in theory, as a linear function of DT, which can be depicted in a linear graph (Figure 4).

Discussion

Surveillance studies to detect recurrence in cervical cancer are not consistently evidence based[18]. Although imaging surveillance modalities show promise, they have not been prospectively evaluated. Nonetheless, MRI has shown increased specificity in the detection of recurrent disease[19]. On this background, the most important finding of our model is that, for surgically treated patients, an annual interval MRI post completion of surgery should even detect the most rapidly growing cervical tumor (worst-case scenario), based on known tumor growth biology. Given that recurrence occurs mostly within two years of treatment completion, our worst-case scenario would employ a total of two MRIs, at 12-month intervals to detect asymptomatic recurrence. In a more conservative scenario, based on average DTs (DT=100 days), a single only

MRI at five years of follow-up would not be unreasonable. In the case of an indolent tumor, surveillance MRI would not be of any value over a 10-year follow-up period. On the contrary, if a slow-growing tumor requires 21 years to recur to a detectable size, this would explain the concept of late-onset recurrence and perhaps question the duration of the follow-up. The model would only be applicable to patients with intention-to-treat surgery without the need for further oncologic treatment. The introduction of chemo-radiotherapy might affect biological events and thus alter DTs. In that respect, it would have been impossible to model for the effects of adjuvant therapy on tumor growth. However, the timing intervals would still remain valid for the worst-case scenario.

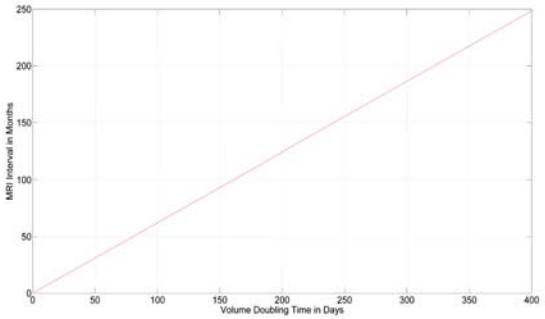

Figure 4: Graph demonstrating a linear relation between optimal magnetic resonance imaging (MRI) interval post completion of surgery and volumetric tumor growing times by a factor equal to e for surgically treated early stage cervical cancers.

This model would neither substitute traditional clinical follow-up nor prove the superiority of MRI over other surveillance modalities. As prospective studies are awaited, comments regarding the sensitivity and positive predictive value of MRI compared to clinical evaluation for detection of recurrence could not be made.

Our model requires internal and external validation. The expressed hypothesis of optimal intervals should only be tested in the context of RCTs or at least prospective cohort studies, given that heterogeneity of histological subtypes, biological behavior and the additional impact of prognostic factorsmay differentiate clinical reality from hypothesized mathematical outcomes. To avoid introducing bias, the model focused solely on the tumor DT, albeit the impact of prognostic factors including tumor size, grade, and depth of stromal invasion, lymphovascular invasion and margins status must be appreciated. Nevertheless, it can be potentially informative to follow-up protocols inclusive of MRI as an additional surveillance test[20].

A recent meta-analysis aimed to determine the optimal recommended program for the follow-up of women who are disease free after completing primary therapy for cervical cancer[5]. The review provided the core for the publication of an evidence-based clinical practice guideline by the Gynecology Cancer Disease Site Group, which mostly included patients treated for early stage cervical cancer. A subgroup of women had completed primary treatment for early cervical cancer by surgery alone, which was indeed the group addressed in our model. The role of MRI in predefined follow-up protocols was acknowledged, and prompt prospective evaluation was proposed. In the Elit et al meta-analysis, the median time to recurrence ranged from seven to 36 months, for those with asymptomatic recurrence[5]. At least nine follow-ups were scheduled over a period of five years for that subgroup of patients.

It is important to note that our model was based on the assumption that DT remains constant over the life cycle of a tumor. A small number of methodologies, including kinetic models, have described the DT concept. Nevertheless, they contain variables that are difficult to measure in the clinical setting[21]. Application of artificial intelligence may be advantageous by use of non-linear network interactions[22]. In practice, the clinically observed DT (in the order of 100 days or more) is much longer than the potential DT, as the growth of a tumor is influenced by cell loss secondary to apoptosis, exfoliation, and necrosis[17]. Mean potential DTs decrease with increasing stage[23].

A UK survey investigating routine surveillance follow-up of women with cervical cancer, which focused on recurrent disease, confirmed the existing diversity regarding surveillance practice patterns[11]. Interestingly, only 21% of the respondents would use routine imaging for detection of recurrence. The lack of evidence is a reasonable response to not routinely using MRI for surveillance, although this low level of MRI usage in follow-up protocols would make hinder the development of appropriate studies. MRI might sound costly but once proven non-inferior to clinical follow-up, it would prove cost-effective by saving medical man-hour and reducing anxiety for patients. Therefore, we performed this study to establish the concept why this is feasible.

In an attempt to mimic asymptomatic recurrence, we have modeled a single scenario, based on a tumor size of 10 mm, which is in agreement with the RECIST criteria for measurable lesions. We used three different DTs to demonstrate reproducibility of the model. In cervical cancer, it appears that AC and SCC -the major histological subtypes- behave differently with the majority of studies, in contrast to lung cancer, supporting a more aggressive AC behavior. However, for surgically only treated patients, the low recurrence and high overall survival rates might not relate to histological types[24]. In the absence of data, we assumed that all recurrences, including central, locoregional and distant recurrences are morphologically identical, arising from the same cancer cell-primary tumor; hence the DTs are not different. Equally, we assumed a higher than simply doubling tumor growth rate (e).This exponential behavior appears more appropriate since it is commonly demonstrated in many physical and/or biological processes. We implemented the concept of worst and best-case scenarios and demonstrated the time required for a tumor to reach the end-point diameter, should the DT become available (Figure 4). This linear association concurs with our results and can assist with estimation of time to recurrence in other solid tumors.

The model is not without limitations. Calculations are still based on geometrical considerations assuming that DT remains constant. The assumption of volumetric cancer growth by a factor e remains to be additionally supported by recorded data. To minimize bias, in addition to prognostic factors, parameters such as metastatic potential, tumor-host interactions or tumor vascular supply are not included in the model as they are difficult to quantify.We acknowledge the fact that, in the absence of RCTs, it is challenging to proclaim survival benefits from early detection of asymptomatic recurrence. The belief that the longer a cancer is allowed to grow, the more deadly it becomes, has become common sense among the lay public. Therefore, from a patient perspective, the information derived from this study can potentially help reassuring those women who would discontinue routine follow-up out of fear of recurrence.

In conclusion, this work is only based on a mathematical simulation, which requires proper verification in clinical studies. Despite several limitations, the model provides an insight into how clinicians might optimizefollow-up surveillance protocols for surgically treated early-stage cervical cancer. Given the low risk of recurrence for this disease entity, follow-up procedures should probably be tailored towards different prognostic factors, reflecting various tumor DTs (Figure 4), until prospective randomized studies become available.

Conflict of interest

The authors declare no conflict of interest

Acknowledgements

We would like to thank Mr Krishnayan Haldar for constructive discussions.This work was presented as a poster presentation at ESGO 19, Nice, France, in October 2015.

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