Using Magnetic Resonance Imaging for determining Tumor Size: A Meta-Analysis

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ABSTRACT The classical way to measure the size of a tumor is CT scanning. MRI scanning offers an alternative which is less harmful to the patient. Relevant studies have been selected in which MRI is used to measure a tumor, and these studies were used to calculate an overall sensitivity and specificity, using both a classic statistics as a Bayesian approach. MRI scanning appears to have a sensitivity and specificity of 90% and 74%, which is higher than CT scanning. However, as there are many ways to perform CT scanning it is difficult to directly compare the two methods.

Introduction

The TNM Classification of Malignant Tumors is a widely accepted method for classifying malignant tumors in patients. The letters 'T', 'N' and 'M' correspond to the size of the primary tumor, the degree of spread to regional lymph nodes and the presence of metastasis. Determining the TNM classification for a cancer patient is an essential step in the treatment process.

The 'T' in the TNM classification (the size of the primary tumor) is usually determined through Computed Tomography (CT) scans. Due to the use of X-rays these CT scans have a potentially carcinogeneous effect on the patient, and subsequent checkup scans to see how the treatment progresses only increases this effect. Magnetic Resonance Imaging (MRI) scans do not use X-rays and therefore do not cause any potential damage to the patient.

Several studies have researched the usability of MRI to determine the size of the primary tumor, but the sensitivity and specificity vary largely between individual studies. General consensus about the true values of the sensitivity and specificity, and how they compare to classical CT scanning, is still missing. These values are determined in this study.

Methods

We have used Pubmed to search for studies in which the T stage of the TNM classification was determined using MRI scans. The real value of the T stage had to be confirmed by pathology, thus creating information about the amount of patients that were correctly classified by MRI methods. Due to the fast increase in MRI technology accuracy, none of these studies were allowed to be older than 10 years. For each of these studies we calculated sensitivity, specificity and confidence intervals. We also searched Pubmed for studies assessing the sensitivity and specificity of classical CT scanning techniques in determining tumor size.

We compared the calculated sensitivity and specificity, and their confidence intervals with the values obtained by Bayesian analysis. The non-Bayes parameters have been produced by Microsoft Excel 2007 and R (version 2.6.0). To perform the Bayesian analysis we used the WinBUGS (version 3.0.3) program; we assumed the sensitivity and specificity to follow a normal distribution. The R code and the WinBUGS models are listed in appendices A and B.

Results

Our Pubmed searches returned 35 relevant studies, of which 24 studies were rejected after careful examination of their content. Most of the studies were rejected on basis of not using

pathology to determine the real size of the primary tumor, but to use CT/PET scans instead. We used the remaining 11 studies as input for our research. The results of these 11 studies, with their sensitivity and specificity, are listed in Table 1, together with the polled overall sensitivity and specificity obtained by maximizing the loglikelihood.

Study	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)
1	33	0,643 (0,479-0,806)	0,895 (0,790-0,999)
2	36	0.969 (0,912-1.026)	0,810 (0,681-0,938)
3	22	0.833 (0,678-0,989)	0,600 (0,395-0,805)
4	29	0.929 (0,835-1,022)	0,957 (0,882-1.031)
5	38	0,778 (0,646-0,910)	0,636 (0,483-0,789)
6	20	0,950 (0,854-1.046)	0,909 (0,783-1.035)
7	29	0,818 (0,678-0,959)	0,278 (0.115-0.441)
8	26	0,967 (0,898-1.036)	0,667 (0,485-0,848)
9	50	0,909 (0,829-1.036)	0,353 (0,220-0,485)
10	232	0,909 (0,872-0,946)	0,696 (0,637-0,756)
11	13	0,875 (0,695-1.055)	0,900 (0,737-1.063)
Overall polled means:		**0,915 (0,892-0,938)**	**0,754 (0,720-0,787)**

Table 1 – Baseline results from studies included in our analysis

The Bayesian analyses produce a sensitivity of 0,902 (0,832-0,968) and a specificity of 0,731 (0,556-0,876). See Appendix B for the models used to obtain these values.

The sensitivity and specificity for classical CT scanning depends on tissue type. Various values of sensitivity and specificity have been found in literature: 88% and 89% for detecting perineural spread of adenoid cystic carcinoma[1], 66% and 95% for detecting distant metastasis in patients with esophageal or gastric cardia cancer[2] and 69% and 71% for detection lymph node mediastinal spread of lung cancer[3].

Conclusion

The average sensitivity and specificity of produced by both methods are 0,909 and 0,743. These values are not exceptionally good, where especially the specificity is quite low. It will depend upon the sensitivity and specificity of the current standard for determining the T stage whether MRI can be used as an alternative diagnostic tool. If the difference between these two techniques is not significant, the decision will have to be based on monetary costs, or on the amount of health risk to which one is willing to subject a patient.

The calculated non-Bayesian sensitivity and specificity closely resemble the sensitivity and specificity obtained by Bayesian analysis. Also, the non-Bayesian sensitivity and specificity lie within the credible intervals of the Bayesian analysis, and vice versa. Therefore, for this study, we cannot tell which method produces better results. However, the Bayesian credible intervals for sensitivity and specificity are approximately 3 and 5 times wider than the non-Bayes confidence intervals, allowing for much more uncertainty in the results.

The values found for the sensitivity and specificity of CT scanning are all lower than the sensitivity and specificity of MRI based diagnosis. It appears that MRI scanning is better able to detect tumors.

Discussion

The Bayesian analysis yielded larger credible intervals than the confidence intervals produced by classical statistics. Bayesian analysis benefits from larger amounts of data,

while the number of patients in each individual study was not very large. Larger number of patients would have allowed the Bayesian algorithm to produce more narrow credible intervals.

The assumption that the sensitivity and specificity are normally distributed has been made, without testing if this is truly the best distribution to describe our data. Also, the parameters used to describe the normal distribution (0,8 as mean, 1/0.3 as variance) do not resemble the mean and variance as calculated by classical statistics. Although an offset of 10001 into the sample-taking process has been used, it was unknown when the Bayesian probability distribution approached the real distribution closely enough.

The sensitivity and specificity of CT scanning has been taken at random from a few studies into this subject. These values seem to vary greatly with the tissue type and the precise conditions under which the scan was done. As none of this information is available for the MRI scanning used in this research, it is nearly impossible to conclude that the use of an MRI scanner is indeed diagnostically better than CT based scanning.

Bibliography

1 **The Sensitivity and Specificity of high-resolution imaging in evaluating perineural spread of adenoid cystic carcinoma to the skull base**
Hanna E, Vural E, Prokopaksis, E, Carrau R, Snyderman C, Weissman J.
Archives of Otolaryngology – Head and Neck Surgery, 2007 Jun, 133(6): 541 – 545

2 **Detection of distant metastasis in patients with esophageal or gastric cardia cancer: a diagnostic decision analysis**
van Vliet EP, Steyerberg EW, Eijkemans MJ, Kuipers EJ, Siersema PD
British Journal of Cancer, 2007 Oct, 97(7): 868-76

3 **Staging of Lung cancer**
Wynands J, Stroobants S, Dooms C, Vansteenkiste J.
Radiologic Clinic of North America, July 2007, Issue 4: 609-625

Appendix A – The R code

The input in R is colored dark blue, the output given by R is colored light blue and the comments are given in black.

Load the csv file into rectal

```
rectal = read.csv("rectal.csv")
```

What is stored in rectal

```
rectal
   studienr TN FP FN  TP
1         1 17  2  5   9
2         2 17  4  0  15
3         3  6  4  2  10
4         4 22  1  0   6
5         5  7  4  6  21
6         6 10  1  0   9
7         7  5 13  2   9
8         8  8  4  0  14
9         9  6 11  3  30
10       10 39 17 16 160
11       11  9  1  0   3
```

Extend rectal

```
rectalx <- rectal
```

CALCULATIONS FOR THE SENSITIVITY

Sensitivity is calculated

```
rectalx$sens = rectalx$TP/(rectalx$TP+rectalx$FN)
```

Sensitivity can be one, this code will perform the 0.5 trick

```
for(i in 1:length(rectalx$sens)) {
      if (rectalx$sens[i] == 1) {
            rectalx$sens[i] =
(rectalx$TP[i]+0.5)/(rectalx$TP[i]+rectalx$FN[i]+1)
      }
}
rectalx$sens
[1] 0.6428571 0.9687500 0.8333333 0.9285714 0.7777778 0.9500000 0.8181818
[8] 0.9666667 0.9090909 0.9090909 0.8750000
```

Standard error calculated

```
rectalx$se_sens = sqrt(rectalx$sens*(1-
rectalx$sens)/(rectalx$TN+rectalx$FP+rectalx$FN+rectalx$TP))
rectalx$se_sens
[1] 0.08341060 0.02899877 0.07945522 0.04782386 0.06744189 0.04873397
[7] 0.07162169 0.03520392 0.04065578 0.01887397 0.09172492
```

Show rectalx

```
rectalx
   studienr TN FP FN  TP      sens    se_sens
1         1 17  2  5   9 0.6428571 0.08341060
2         2 17  4  0  15 0.9687500 0.02899877
```

```
3         3  6  4  2  10 0.8333333 0.07945522
4         4 22  1  0   6 0.9285714 0.04782386
5         5  7  4  6  21 0.7777778 0.06744189
6         6 10  1  0   9 0.9500000 0.04873397
7         7  5 13  2   9 0.8181818 0.07162169
8         8  8  4  0  14 0.9666667 0.03520392
9         9  6 11  3  30 0.9090909 0.04065578
10       10 39 17 16 160 0.9090909 0.01887397
11       11  9  1  0   3 0.8750000 0.09172492
```

Calculating mu

```
mu = sum(rectalx$sens/rectalx$se_sens^2)/sum(1/rectalx$se_sens^2)
mu
0.9150373
```

Calculating the standard error of mu

```
se_mu = sqrt(1/sum(1/rectalx$se_sens^2))
se_mu
0.01186587
```

Calculate the 95% Confidence Intervals

```
sens_perc025 = mu - 1.96 * se_mu
sens_perc025
[1] 0.8917802
sens_perc975 = mu + 1.96 * se_mu
sens_perc975
[1] 0.8917802
```

CALCULATIONS FOR THE SPECIFICITY

Calculated specificity

```
rectalx$spec = rectalx$TN/(rectalx$TN+rectalx$FP)
rectalx$spec
 [1] 0.8947368 0.8095238 0.6000000 0.9565217 0.6363636 0.9090909 0.2777778
 [8] 0.6666667 0.3529412 0.6964286 0.9000000
```

Calculated standard error specificity

```
rectalx$se_spec = sqrt(rectalx$spec*(1-
rectalx$spec)/(rectalx$TN+rectalx$FP+rectalx$FN+rectalx$TP))
rectalx$se_spec
 [1] 0.05342308 0.06544612 0.10444659 0.03786906 0.07803592 0.06428243
 [7] 0.08317354 0.09245003 0.06758309 0.03018733 0.08320503
```

```
rectalx
```

Show rectalx

```
   studienr TN FP FN  TP      sens    se_sens      spec    se_spec
1         1 17  2  5   9 0.6428571 0.08341060 0.8947368 0.05342308
2         2 17  4  0  15 0.9687500 0.02899877 0.8095238 0.06544612
3         3  6  4  2  10 0.8333333 0.07945522 0.6000000 0.10444659
4         4 22  1  0   6 0.9285714 0.04782386 0.9565217 0.03786906
5         5  7  4  6  21 0.7777778 0.06744189 0.6363636 0.07803592
6         6 10  1  0   9 0.9500000 0.04873397 0.9090909 0.06428243
7         7  5 13  2   9 0.8181818 0.07162169 0.2777778 0.08317354
8         8  8  4  0  14 0.9666667 0.03520392 0.6666667 0.09245003
9         9  6 11  3  30 0.9090909 0.04065578 0.3529412 0.06758309
10       10 39 17 16 160 0.9090909 0.01887397 0.6964286 0.03018733
11       11  9  1  0   3 0.8750000 0.09172492 0.9000000 0.08320503
```

Calculate the mu

```
mu_spec = sum(rectalx$spec/rectalx$se_spec^2)/sum(1/rectalx$se_spec^2)
mu_spec
[1] 0.753612
```

Calculate the standard error of the mu

```
se_mu_spec = sqrt(1/sum(1/rectalx$se_spec^2))
se_mu_spec
[1] 0.01689982
```

Calculate the 95% Confidence Intervals

```
spec_perc025 = mu_spec - 1.96 * se_mu_spec
spec_perc025
[1] 0.7204884
spec_perc975 = mu_spec + 1.96 * se_mu_spec
spec_perc975
[1] 0.7867357
```

Appendix B – The OpenBUGS Model

In dark blue the comments in OpenBUGS, in light blue the input in OpenBUGS

```
# Meta-analysis of SENSITIVITY
model{

  for (i in 1:N) {
    a[i]  ~ dnorm(alpha,tau)  # the logit-sensitivity in study i is sampled
                              # from a normal distribution with mean alpha
                              # and variance 1/tau

    p[i] <- exp(a[i])/(1+exp(a[i])) # calculate the sensitivity in study i
    nn[i] <- tp[i]+fn[i]            # number of observations in study i

    tp[i]~dbin(p[i],nn[i])          # given the sensitivity, the number of
                                    # positive outcomes is binomially
                                    # distributed
   }
   sig <- 1/tau                     # sig is inverse of tau
   pi <- exp(alpha)/(1+exp(alpha)) # pi is the average sensitivity, the
                                    # ultimate statistic of interest

# prior distribution for the two parameters in this model:
# alpha is the average logit-transformed sensitivity, tau is 1/variance of
# the sensitivities

   alpha~dnorm(0.00,1.0E-3)   # logit-sens may vary between minus and plus
                              # infinity, thus a normal distribution seems
                              # okay

   tau ~dgamma(0.01,0.01)     # variance >0, thus tau=1/variance >0
                              # the gamma-distribution seems more
                              # appropriate
}

# data
list(N=11,fn=c(5,0,2,0,6,0,2,0,3,16,0),tp=c(9,15,10,6,21,9,9,14,30,160,3))

# initial parameters
list(alpha=0.8,tau=0.3)
```

 # Meta-analysis of SPECIFICITY

```
model{

  for (i in 1:N) {
    a[i]  ~ dnorm(alpha,tau)  # the logit-specificity in study i is sampled #
                              from a normal distribution with mean alpha
                              # and variance 1/tau

    p[i] <- exp(a[i])/(1+exp(a[i])) # calculate the specificity in study i
    nn[i] <- fp[i]+tn[i]            # number of observations in study i

    tn[i]~dbin(p[i],nn[i])    # given the specificity, the number of
                              # positive outcomes is binomially distributed
  }
  sig <- 1/tau                       # sig is inverse of tau
  pi <- exp(alpha)/(1+exp(alpha))    # pi is the average specificity, the
                                    # ultimate statistic of interest

# prior distribution for the two parameters in this model:
# alpha is the average logit-transformed specificity, tau is 1/variance of
# the specificities

  alpha~dnorm(0.00,1.0E-3)   # logit-sens may vary between minus and plus
                             # infinity, thus a normal distribution seems
                             # okay

  tau ~dgamma(0.01,0.01)     # variance >0, thus tau=1/variance >0
                             # the gamma-distribution seems more
                             # appropriate
}

# data
list(N=11,tn=c(17,17,6,22,7,10,5,8,6,39,9),fp=c(2,4,4,1,4,1,13,4,11,17,1))

# initial parameters
list(alpha=0.8,tau=0.3)
```