Research Article

MR diffusion and MR dynamic contrast enhanced sequences in characterization of ovarian tumors

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Abstract

Objective: To test and compare the sensitivity and accuracy of diffusion weighted imaging (DWI) and MR perfusion in women having ovarian tumors. **Patients and Methods:** Fifty women with ovarian masses were collected after meeting the inclusion criteria depending on gray scale sonographic findings which suggested the presence of ovarian masses. Conventional MRI, Diffusion weighted imaging (DWI) and MR perfusion (MRP) were done for all patient cohort after the approval of ethical committee of our institution. The sensitivity and accuracy of the techniques were compared. **Results:** The surgical and pathological reports of our patients proved non tumorous lesion in three patients. They proved benign ovarian tumors in 18/47 (38.3%) patients, borderline tumors in 4/47 (8.5%) patients and malignant ovarian tumors in 25/47 (53.2 %) patients. According to conventional MRI ovarian tumors could be diagnosed with sensitivity 92 %, specificity 61.11%, PPV 76.7 %, NPV 84.6% and accuracy 79.1 %. DWI and MR perfusion showed the same results where they showed sensitivity 98 %, specificity 83%, PPV 90 % , NPV 98 % and accuracy 93% with ADC cut off value $1x10^{-3}$ mm^2/sec. **Conclusion:** Diffusion weighted imaging and MR perfusion are useful in diagnosis of ovarian tumors with approximately the same sensitivity and positive impact on the operative management.

Key Words: MRI ovarian cancer, MR diffusion, MR perfusion, ovarian tumors characterization

Introduction

Ovarian tumors are the fifth commonest tumor in women and the leading indication for gynecologic surgery. The therapeutic strategy depends on whether the tumor is benign, borderline or malignant.[1, 2,3]

Late diagnosis of ovarian cancer is due to lack of specific symptoms.[4, 5]

MRI diffusion weighted imaging (DWI) and MRI perfusion (MRP) increased the technical capabilities for preoperative characterization of ovarian masses.[6.7]

The fast "wash-in" of contrast coupled with the rapid "wash-out" through tumors more than normal tissue allows a functional analysis of the tumor microcirculation.[3, 8]

Multi-parametric calculations of permeability and perfusion are used to characterize the tumor vasculature within a tumor “microenvironment” The malignant lesions enhance in contrast quickly and have more intense signals, compared to benign lesions.[9, 10, 11]

DWI is a non-invasive imaging modality depends on the Brownian motion of water molecules in tissues. Diffusion-weighted imaging provides qualitative and quantitative information about tissue cellularity. [12]

Aim of the work

The aim of this study is to evaluate the benefit of application of diffusion weighted imaging (DWI) and MR perfusion (MRP) in characterization of ovarian tumors.

Patients and method

Study design and population

This study was a prospective study. The study population comprised 50 consecutive women who were suspected to have ovarian neoplastic mass. Patients were collected between January 2018 and December 2018. They underwent

MRI imaging after meeting the inclusion criteria. All patients signed a written informed consent before MRI examination.

Inclusion and exclusion criteria

All patients included in this study had previous trans-abdominal or trans-vaginal real time ultrasonography with diagnosis of complex ovarian lesions, cystic lesion with solid vegetation or thick septa or soft tissue component (figure 2), solid ovarian lesions (figure 3) or suspicious adnexal lesions. Patients with simple cystic ovarian lesions, ovarian lesions with pure fatty component, impaired renal functions or general contra-indications to MRI as the presence of any paramagnetic substances such as pacemakers, metallic clips or claustrophobic patients were excluded from the study.

Methods

MRI technique

MR imaging was performed using 1.5 Tesla MR Scanner (Ingenia, Philips Healthcare, Netherlands). All patients were imaged in the supine position using pelvic phased array coil. The MRI examination was conducted on the female pelvis including conventional MRI sequences; Axial, sagittal and coronal T2WIs using the following parameters (TR 5000/TE 110 ms, echo train length 13–15, slice thickness 5–7 mm, gap 1–2 mm, Field of view 24–38 cm, excitations (NSA) 3 and matrix 304 · 512). Followed by axial T1WI spin echo MR images (TR 162, TE 10–14 ms, slice thickness 5–7 mm, gap 1–2 mm, field of view 24–38 cm, flip angle of 90_, excitations (NSA) 1–2 and matrix 256 · 256).

Diffusion weighted imaging was acquired in the axial plane prior to administration of contrast medium by using a single shot echo-planar imaging sequence with b values (0, 800, 1000) (TR/TE 2871/78, Slice thickness 5 mm, Gap 1 mm), FOV 375 x 312 x 161 mm and matrix 124x105).

MRI perfusion was done for all patients using Gadolinium chelate (Dimegluminegadopentate) that was given at a dose of 0.2 ml per kilogram of body weight by using a power injector (Medrad, spectrissolaris R) at a rate of 2ml/sec, followed by 20 ml of normal saline to flush the tubing. Images were obtained sequentially every 14 seconds beginning 14 seconds (first phase) before the bolus injection. 40 sequential slices were taken with slice thickness 2 mm.

Rapid acquisition (every 14 seconds) was performed for 30 consecutive phases with the whole time of the sequence 7 minutes. The images stack should include part of the soft tissue inside the ovarian lesionand the adjacent external myometrium in optimal plane.

Data processing and image interpretation:

The images were transformed to Philips 881030 Intelli-Space IX/LX Workstation.Each MR sequence findings were evaluated as following:

(A) Analysis of conventional sequences:

Conventional MRI sequences were evaluated for the morphologic features of the lesion including the lesion laterality, size, shape, and complexity of the tumor, T2 signal intensity of the solid part inside the mass and the presence of ascites and peritoneal deposits.

(B) Analysis of MRI perfusion:

For ovarian tumor characterization, two regions of interest (ROI) were placed. One on external myometrium and one on the most enhancing part of solid tissue of the ovarian mass. The most enhanced solid part was determined by the use of maximum enhancement colored generated map by the workstation. The enhancement of the solid tissue was classified by using a time-signal intensity curve classification:

1- A gradual increase in the signal intensity of the solid tissue, without a well-defined shoulder was defined as type 1 curve.
2- A moderate initial increase in the signal intensity of the solid tissue relative to that of myometrium followed by a plateau was defined as type 2 curve.
3- An initial increase in the signal intensity of the solid tissue that was steeper than that of the myometrium was defined as type 3 curve.

Enhancement measures:

Maximum enhancement (SI max): Difference between peak intensity S1 and S0.

Maximum relative enhancement: (MRE) Maximum of all relative enhancements

Wash in rate (WIR): Maximum slope between T0 and the time of peak intensity.

Wash out rate (WOR): Maximum slope between the time of peak intensity T1 and the end of measurement.

Histopathological evaluation
All of the patients underwent surgical management. Twenty seven patients underwent radical hysterectomy with bilateral salpingo-oophorectomy, 5 cases underwent simple oophorectomy, 10 cases underwent ovarian

cystectomy and 8 cases underwent simple oophorectomy. All results were correlated to final post- operative histopathological data.

Statistical analysis
Statistical analysis was performed using the SPSS software for Windows v. 20 (SPSS Inc., Chicago, IL). For comparing quantitative data, Kruskal Wallis test and Mann Whitney tests were performed. For comparing qualitative data, Fisher exact test was performed. Accuracy of the studied diagnostic test in predicting malignancy was represented using the terms sensitivity, specificity, overall accuracy, negative and positive predictive values. A probability value (p=0.05) was considered statistically significant. Receiver operating curve ROC curve was used to determine the cutoff values of the semi- quantitative parameters.

Results
Our study included 50 female patients, three of them found to have non-ovarian tumors on histo-pathological evaluation, two of them were tubo-ovarian abscesses and one was cyst with hemorrhagic infarction. Those three cases were excluded from the study to avoid bias.

Diffusion weighted magnetic resonance imaging was done for all patients before contrast injection. Among our patients 37/47 cases (78.7%) showed diffusion restriction and 10/47 cases (21.3%) showed facilitated diffusion. The cut off value of ADC value below which malignancy is expected is less than $1x10^{-3}$ mm^2/sec. There was statistical significance between ADC value and pathological diagnosis (P value *<0.001).*

Regarding MRP, SImax, MRE%, WIR and WOR were evaluated and correlated to the final histopathological results. There was statistical significance between SI max, WIR & WOR and pathological diagnosis with higher sensitivity specificity and accuracy in relation to WOR.There was no statistical significant difference between MRE% and pathological diagnosis. (Table I).

Regarding the time signal intensity curves of MRP; we found that Curves type 2 and 3 carry malignant probability with accuracy 95%, sensitivity 88% and specificity 92%. NPV 100%
ROC curve analysis was used for prediction of malignancy depending on conventional based diagnosis, DWI diagnosis, MRP and combined conventional MRI with DWI and with MRP.

There was statistical significant difference between the three methods of diagnosis and the pathological diagnosis. However; the AUC, sensitivity, specificity and accuracy were higher on DWI and MRP- based diagnosis than those on conventional based diagnosis. Statistical correlation between results of conventional MRI, DWI and MRP to evaluate, the sensitivity, specificity, PPV, NPP and accuracy. (Table II)

Final pathological diagnosis after surgery revealed that 24/47 cases showed epithelial tumors (6 benign cases, 4 borderline cases and 14 malignant cases), 8/47 cases showed sex cord stromal tumors (5 benign cases and 3 malignant cases) and 15/47 cases showed germ cell tumors (7 benign cases and 8 malignant cases).

Discussion
Adnexal masses are challenging diagnostic problem because of the overlapping imaging features between benign and malignant tumors.[13, 14]

In our study, DWI based diagnosis showed 100% sensitivity while specificity remains low 88%. Such low specificity elicited in our study can be explained by the presence of eight benign masses that mimicked malignancy. These masses included mature cystic teratomas, strumaovarii and benign sclerosing tumor. They all showed restricted diffusion and mean ADC values 0.8 x 10^{-3} mm^2/s, $1x10^{-3}$ mm^2/s and

$0.9x10^{-3}$ mm^2/s respectively presenting false positive cases due to mixed cellularity of the lesions. The mean ADC values for benign lesions were $1.7±0.6 x 10^{-3}$ mm^2/s and for borderline and malignant lesions were $0.9±0.2x10^{-3}$ mm^2/s and 0.8±0.1 respectively. Cutoff value for ADC in malignancy is $\leq 1x10^{-3}$ mm^2/sec. This agreed with Thomassin-Naggara et al., where they attributed the presence of low mean ADC values elicited by benign fibrous tumors as fibromas, Brenner tumors, and cystadeno-fibromas are due to dense network of collagen fibers within the extracellular matrix. [15]

In a study done by Zhang P et al., they show higher sensitivity and specificity of DWI than our study because they excluded endometriomas, mature cystic teratomas and pure cystic adenomas from their study. [16]

In our study, Curve type I was found to be specific for benign ovarian tumors with 100% specificity. Curves type II and III were more in favor of borderline/malignant tumors. From all cases with curve type III, only one case was benign which was pathologically diagnosed as benign sclerosing tumor of the ovary. The explanation for such result is the high vascularity of sclerosing stromal tumors.

In our study, the perfusion parameters that showed highest accuracy were WOR (100%) followed by SImax (97%) then WIR (93%).The cut off value for WOR in our study was >6 (lesions with WOR more than 6 is likely to be malignant). The PPV and NPV were 100%.

In our study, the cut off value of SI max was >1285 (tumors with SImax more than that number is considered malignant). The sensitivity was 100% and specificity was 94%. Those measurements do not agree with Dilks et al. that suggested a threshold value of >250 for prediction of malignancy with a sensitivity and specificity 100%. This difference can be explained by the unequal distribution of cases in our study. WIR showed less sensitivity, specificity, NPV, PPV and accuracy (92%, 94%, 89.5%, 95.8% and 93% respectively) than WOR and SImax. Bernardin et al. applied a cut off value > 9.5 for WIR where lesions with WIR mare than 9. 5 are considered malignant. In our study, the cut off value was higher than that value (>17.9) and this also can be explained by the unequal distribution of cases with increased number of cases with hypervascular nature.[13, 17]

Our study had several limitations. The unequal distribution of pathology included in the study. Some relatively common pathological entities were not included in the study as ovarian metastasis. Also there is small number of cases of ovarian epithelial borderline tumors included in the study. Also, the method of the ROI drawing that may be subject to human error, which may affect the performance.

Conclusion

The application of MR diffusion and MR perfusion are proved accurate in characterization of malignant and benign ovarian tumors. Improvements in evaluation of SI max and WI and WO lead to more accurate evaluation of ovarian tumors with high sensitivity and specificity and reduce false positive results.

Table I: ROC curve analysis for prediction of malignancy according to MR perfusion measurements in correlation with histopathological diagnosis:

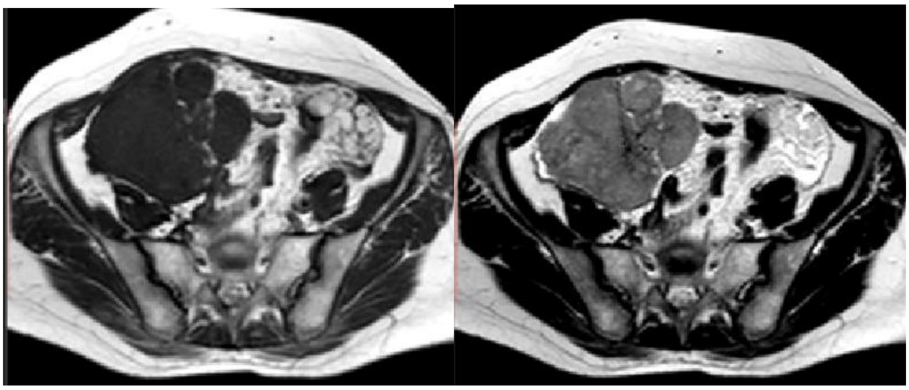
	SI max	WIR	WOR
Sensitivity	100	92	100
Specificity	94.44	94.44	100
PPV	96.2	95.8	100
NPV	100	89.5	100
Accuracy	97.67	93.02	100

Table II: ROC curve analysis for prediction of malignancy among various MRI techniques in correlation to the final histopathological diagnosis:

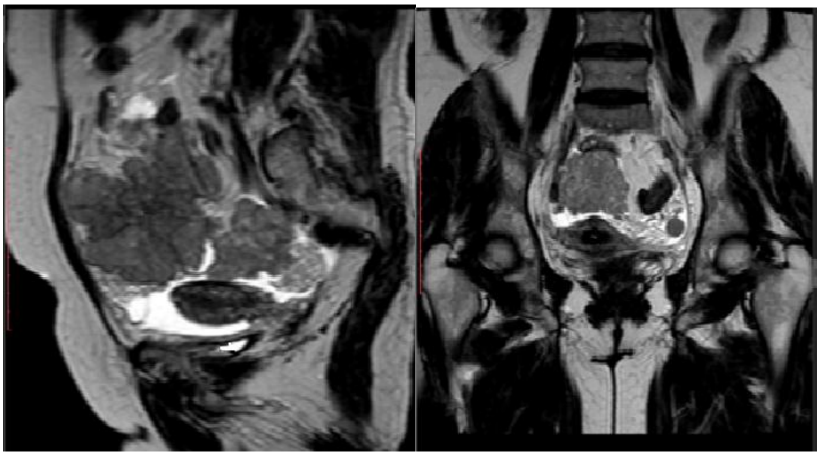
	Conventional MRI	DWI	MRP	Combined conventional+ DWI OR Conventional+ MRI perfusion
Sensitivity	92%	98%	98%	97%
Specificity	61.11%	83%	83%	92%
PPV	76.7%	90%	90%	90%
NPV	84.6%	98%	98%	98%
Accuracy	79.1%	93%	93%	93%

Figures:

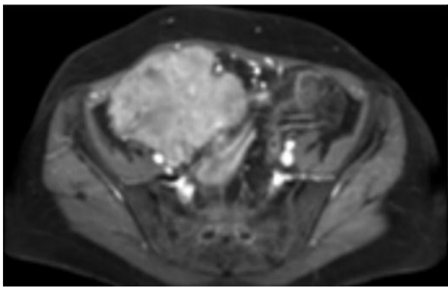
Figure 1: Female patient 53 years old presented with pelvic pain and pelvi-abdominal swelling. US revealed right heterogeneous mass with cystic breakdown. Ascites was noted.Axial T1WI (a), axial T2WI (b), sagittal T2WI (c) and coronal T2WI (d) show a large rather defined heterogeneous solid lesion with cystic components. It attains hypointense signal at T1WI and isointense at T2WI. It shows pelvic ascites and omental deposits. Post contrast axial T1 fat sat (e) demonstrates moderate enhancement of the lesion.Perfusion weighted images shows early and more intense increasing enhancement than the myometrium.Type 3 curve (j).MRI perfusion parameters: The wash in rate and the washout rate are more rapid than the myometrium (i). MRE%: 150%, Tmax: 70sec, WIR: 8.Color map shows the areas of maximum enhancement (h).Laparotomy with radical hysterectomy and bilateral salpingo-oophorectomy were done. Pathology revealed ovarian clear cell carcinoma.



(a) (b)



(c) (d)



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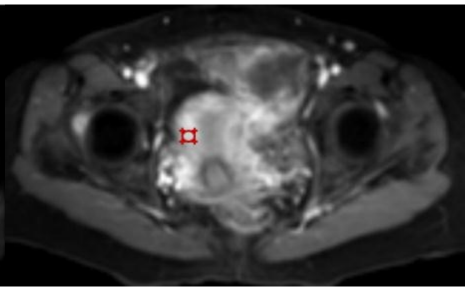
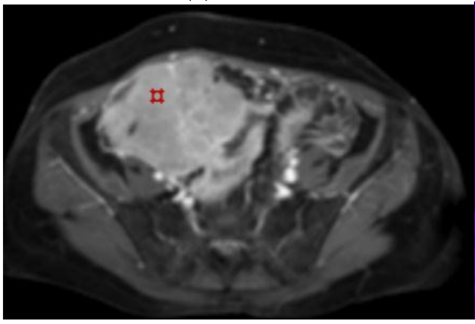
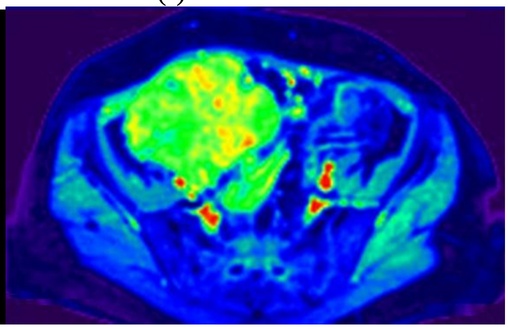


(f)



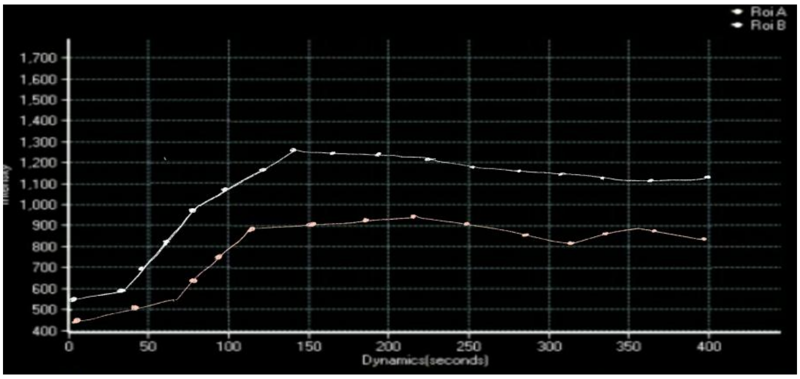
(g)



(h)

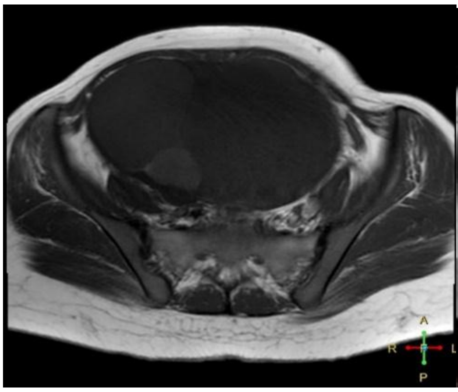
Maximum Enhancement (%):	150.0
Maximum Relative Enhancement (%):	70.0
T0 (s):	36.3
Time To Peak (s):	133.2
Wash in Rate (l/s):	8.0
Wash out Rate (l/s):	0.69
Brevity of Enhancement (s):	139.2
Area under the curve:	103390.1

(i)



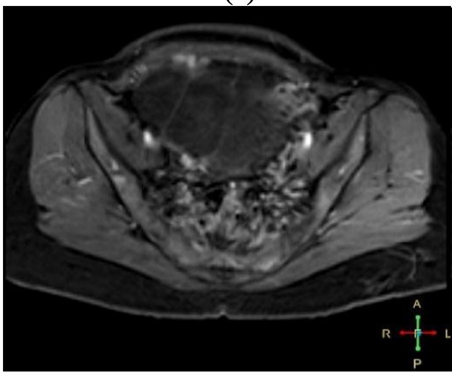
(j)

Figure 2: Female patient 28 years old complaining of abdominal swelling. US revealed large complex adnexal mass with thick septations and solid component.Axial T1WI (a) and T2WI (B) show a well-defined right adnexal lesion, dominantly cystic with thick septations (more than 3mm) with a small posterior solid component on the right side. It attains iso- intense signal on T1WI andT2WI. Post-Gad. Sequential images (c&d) show mildly enhanced septae. Perfusion weighted images show slow rising enhancement.Type 1 curve (h).MRI perfusion parameters (g): Hight T_{max} suggests benign nature. MRE%: 85 %, T_{max}: 268 sec, WIR: 13.3.Color map shows the areas of maximum enhancement (f). Laparotomy was done with surgical removal of the lesion. Pathology revealed Struma ovarii (benign ovarian cyst contains thyroid tissue).

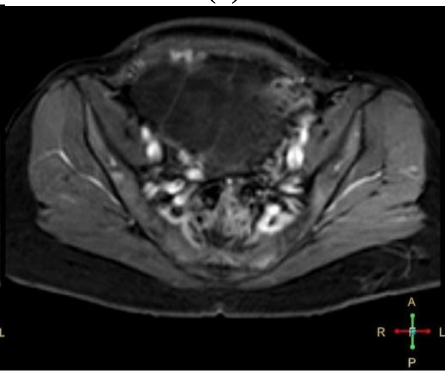


(a)

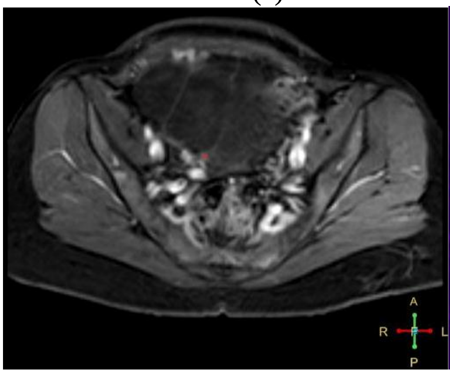
(b)



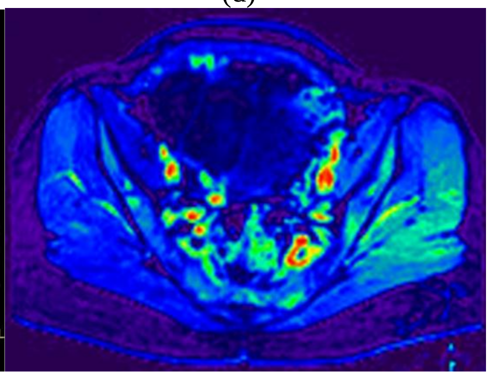
(c)



(d)



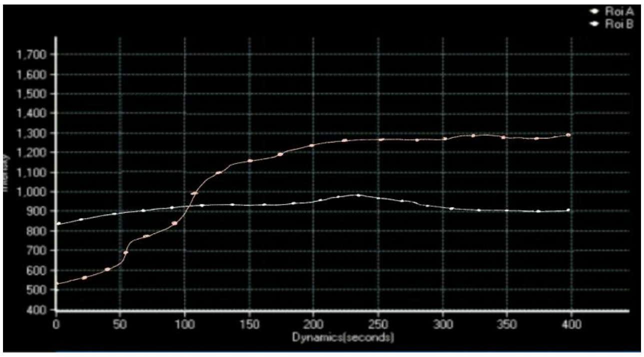
(e)



(f)

Maximum Enhancement (%):	268.0
Maximum Relative Enhancement (%):	85.0
T0 (s):	33.2
Time To Peak (s):	320.2
Wash in Rate (l/s):	13.3
Wash out Rate (l/s):	.....
Brevity of Enhancement (s):	.....
Area under the curve:	121245.5

(g)



(h)

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